Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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1. BACKGROUND

1.1 Introduction
This overview represents the updated European Association of Urology (EAU) guidelines for Non-muscle-invasive Bladder Cancer (CIS, Ta, T1). The information presented is limited to urothelial carcinoma, if not specified otherwise. Aim is to provide practical guidance on the clinical management of non-muscle-invasive bladder cancer with a focus on clinical presentation and recommendations.

The EAU Guidelines Panel on Non-muscle-invasive Bladder Cancer consists of an international multidisciplinary group of clinicians, including a pathologist and a statistician.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients - also taking personal values and preferences and individual circumstances of patients into account.

Separate EAU guidelines documents are available addressing upper urinary tract tumours (1), muscle-invasive bladder cancer (2), and primary urethral carcinomas (3).

1.2 Methodology

1.2.1 Data Identification
The systematic literature search for each section of the Non-muscle-invasive Bladder Cancer Guidelines was performed by the panel members. For identification of original and review articles, Medline, Web of Science, and Embase databases were used. For the current update, all articles published between 2010 and 2012 on non-muscle-invasive bladder cancer were considered. Focus of the searches was identification of all level 1 scientific papers (randomised controlled trials (RCTs), systematic reviews (SRs), and meta-analyses of RCTs) in accordance with the EAU guidelines methodology.

1.2.2 Level of evidence and grade of recommendation
References in the text have been assessed according to their level of scientific evidence (LE), and guideline recommendations have been graded follow the listings in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (4). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (4).

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (5-7).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.
Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (4).

1.3 Publication history
The first European Association of Urology (EAU) Guidelines on Bladder Cancer were published in 2000 (8). In 2004 it was decided to develop separate guidelines for muscle-invasive and infiltrative bladder cancer and a separate scientific publication on upper urinary tract tumours was presented (9), which was updated and has been included in the EAU Guidelines compilation print since 2011 (10). The complete updates of guidelines for non-muscle-invasive bladder cancer were prepared in 2006, 2008 and 2011 (11-14). Since 2011 the EAU Guidelines on TaT1 tumours and CIS were integrated in one guidelines document (14).

Several scientific summaries have been published in the EAU scientific journal, European Urology (9,15-19). A quick reference document (pocket guidelines) is available presenting the main findings of the Non-muscle-invasive Bladder Cancer Guidelines. This document follows the updating cycle of the underlying large texts.

All material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of translations and republications produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

1.3.1 Summary of changes
For all chapters the literature has been assessed.

Chapter 4 - Classification: a clear definition of non-muscle-invasive bladder cancer is presented. Since appropriate classification and grading directly influences treatment decisions, additional information on pathological parameters has been added.

Chapter 5 - Diagnosis: an illustration on bladder diagram to facilitate the description of cystoscopy finding has been added. The new data on endoscopic diagnosis and pathological evaluation of the tissue included in this section resulted in a number of changes in the recommendations.

Chapter 6 - Predicting disease recurrence and progression: the new stratification of patients into 3 risk groups facilitating treatment recommendation is presented.

Chapter 7 - Adjuvant treatment: updated information on intravesical chemo- and immunotherapy is provided. The definition and stratification of BCG toxicity and side-effects is provided in an overview table. The definition of BCG failures has been specified.

Chapter 8: Radical cystectomy for NMIBC: the indication criteria were updated.

1.4 Potential conflict of interest statement
The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/.

1.5 References


2. EPIDEMIOLOGY

Bladder Cancer (BC) is the most common malignancy of the urinary tract and the seventh most common cancer in men and the 17th in women. The worldwide age standardised incidence rate is 9 per 100,000 for men and 2 per 100,000 for women (2008 data) (1). In the European Union (EU) age standardised incidence rate is 27 per 100,000 for men and six per 100,000 for women (1).

Incidence varies between regions and countries; in Europe, the highest age standardised incidence rate has been reported in Spain (41.5 in men and 4.8 in women) and the lowest in Finland (18.1 in men and 4.3 in women) (1). The variations can partly be attributed to different methodology and quality of data collection, thus warranting care in the interpretation of results (2,3).

The world global age standardised mortality rate is 3 for men versus 1 per 100,000 for women. In the EU, age standardised mortality rate is 8 for men and 3 per 100,000 for women, respectively (1). In 2008 BC was the eighth most common cause of cancer-specific mortality in Europe (1).

The incidence of BC has decreased in some registries possibly reflecting decreased impact of causative agents, mainly smoking and occupational exposure (4). The mortality of BC has also decreased, possibly reflecting increased standard of care (5).

Approximately 75% of patients with BC present with a disease that is confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). These categories are grouped as non-muscle-invasive bladder tumours. Non-muscle invasive BC (NMIBC) has a high prevalence due to low progression rates and long-term survival in many cases; patients with muscle-invasive BC (MIBC) are at higher risk of cancer-specific mortality (3). The prevalence of BC is among the highest of all urological malignancies (1).

3. RISK FACTORS

Increasing evidence suggests that genetic predisposition has a significant influence on bladder cancer incidence, especially via its impact on susceptibility to other risk factors (3,6). Tobacco smoking is the most important risk factor for BC, accounting for ~50% of cases (3,7) (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting in the modern era for ~10% of all cases. Such occupational exposure occurs mainly in industrial branches processing paint, dye, metal and petroleum products (3,8-10) (LE: 3).

Although the significance of the amount of fluid intake is uncertain, chlorination of drinking water and subsequent levels of trihalomethanes is potentially carcinogenic, and exposure to arsenic in drinking water increases BC risk (3,11) (LE: 3). The relation between personal hair dye use and BC risk remains uncertain; increased risk has been suggested in users of permanent hair dyes with NAT2 slow acetylation phenotype) (12,13).

The exposure to ionizing radiation is connected with increased risk of BC (LE: 3). It is suggested that cyclophosphamide and pioglitazone are weakly associated with BC risk (3). Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is a cause of bladder cancer, particularly squamous cell carcinoma (3) (LE: 3).

4. CLASSIFICATION

4.1 Definition of non-muscle-invasive bladder cancer
A papillary tumour confined to the mucosa is classified as stage Ta according to the Tumour, Node, Metastasis (TNM) classification system. Tumours that have invaded the lamina propria are classified as stage T1. Ta and T1 tumours can be removed by transurethral resection (TUR), and therefore they are grouped under the heading of NMIBC for therapeutic purposes. Also included under this heading are flat, high-grade tumours that are confined to the mucosa, and classified as CIS (Tis). However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions. Therefore, the terms NMIBC and superficial BC are suboptimal descriptions. The latter term should no longer be used. Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.
4.2  Tumour, Node, Metastasis Classification (TNM)
The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) has been widely accepted. This version was updated in 2009, but it has no changes for bladder tumours (Table 3) (14).

Table 3: 2009 TNM classification of urinary bladder cancer

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Ta</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T2a</td>
</tr>
<tr>
<td>T2b</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T3a</td>
</tr>
<tr>
<td>T3b</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>T4a</td>
</tr>
<tr>
<td>T4b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

4.3  Histological grading of non-muscle-invasive bladder urothelial carcinomas
In 1998, a new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification) and published by the WHO in 2004 (15,16) (Table 4). Its major contribution is a detailed histological description of the various grades, which uses specific cytological and architectural criteria. A website (www.pathology.jhu.edu/bladder) that illustrates examples of the various grades has been developed to further improve accuracy in using the system.
Table 4: WHO grading in 1973 and in 2004 (15,16)

<table>
<thead>
<tr>
<th>1973 WHO grading</th>
<th>Urothelial papilloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>well differentiated</td>
</tr>
<tr>
<td>Grade 2</td>
<td>moderately differentiated</td>
</tr>
<tr>
<td>Grade 3</td>
<td>poorly differentiated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2004 WHO grading</th>
<th>Flat lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperplasia (flat lesion without atypia or papillary aspects)</td>
</tr>
<tr>
<td></td>
<td>Reactive atypia (flat lesion with atypia)</td>
</tr>
<tr>
<td></td>
<td>Atypia of unknown significance</td>
</tr>
<tr>
<td></td>
<td>Urothelial dysplasia</td>
</tr>
<tr>
<td></td>
<td>Urothelial CIS</td>
</tr>
<tr>
<td></td>
<td>Papillary lesions</td>
</tr>
<tr>
<td></td>
<td>Urothelial papilloma (completely benign lesion)</td>
</tr>
<tr>
<td></td>
<td>Papillary urothelial neoplasm of low malignant potential</td>
</tr>
<tr>
<td></td>
<td>Low-grade papillary urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>High-grade papillary urothelial carcinoma</td>
</tr>
</tbody>
</table>

The 2004 WHO classification of the flat lesions includes urothelial hyperplasia, reactive urothelial atypia, atypia of unknown significance, dysplasia, and CIS. Among non-invasive papillary urothelial lesions, the 2004 WHO grading differentiates between papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas.

Papillary urothelial neoplasms of low malignant potential (PUNLMPs) are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur.

The intermediate grade (Grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated (17–19) (Figure 1). The published comparisons, however, have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification (20,21).

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one of the systems, however, have yielded controversial results (17–20,22–24). The majority of clinical trials published to date on TaT1 bladder tumours have been performed using the 1973 WHO classification, and therefore, the following guidelines are based on this version. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications should be used.

Figure 1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications (19)*

<table>
<thead>
<tr>
<th>PUNLMP</th>
<th>Low grade</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
</tbody>
</table>

1973 WHO Grade 1 carcinomas have been reassigned to PUNLMP and Low-grade carcinomas in 2004 WHO classification, and Grade 2 carcinomas to Low-grade and High-grade carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to High-grade carcinomas. Reproduced with permission from Elsevier.

4.4 Inter- and intraobserver variability in staging and grading

Despite well-defined criteria for the diagnosis of urothelial carcinoma, there is significant variability among pathologists for diagnosis of CIS, for which agreement is achieved in only 70–78% of cases (25,26) (LE: 2a). There is interobserver variability in classification of stage T1 versus Ta tumours and tumour grading in both 1997 and 2004 classifications. The general conformity in staging and grading is between 50 and 60% (20,25–29) (LE: 2a).
4.5 **Further promising pathological parameters**

Some novel parameters based on pathological investigation of resected tissue have been evaluated and considered for subclassification and prognostic purposes.

In patients with T1 tumours, the depth and extent of invasion into the lamina propria (T1 substaging) can be evaluated. The prognostic value of this evaluation has been demonstrated by some retrospective cohort studies (30-33) (LE: 3). The presence of lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours (34) (LE: 3). It must be presented in pathological reports.

Detection of the micropapillary variant of urothelial carcinoma represents a poor prognostic factor even if it is non-muscle invasive at the time of diagnosis (35,36) (LE: 3). In micropapillary urothelial tumours with T1 invasion, some cases with distant metastases have been confirmed (35). Moreover, the risk of understaging in these tumours is substantial (37).

Rare cases of non-invasive squamous cell carcinoma in the bladder with poor prognosis have been described (38). Novel molecular markers, particularly FGFR3 mutation status, are promising but need further evaluation (17,33,39-41).

4.6 **Specific character of CIS and its clinical classification**

CIS is a flat, high-grade, non-invasive urothelial carcinoma. Macroscopically, CIS can be missed at cystoscopy or be considered as an inflammatory lesion if it is not biopsied. It is often multifocal and can occur not only in the bladder but also in the upper urinary tract, prostatic ducts, and prostatic urethra (42).

CIS is classified into one of four different clinical types (43):

- **Primary**: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- **Secondary**: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- **Concurrent**: CIS in the presence of any other urothelial tumour in the bladder;
- **Recurrent**: Repeat occurrence of isolated CIS after initial successful response to intravesical treatment.

5. **DIAGNOSIS**

5.1 **Patient history**

Patient history should be taken and recorded for all important information with possible connection to BC, including risk factors and history of suspect symptoms.

5.2 **Symptoms**

Haematuria is the most common finding in NMIBC. Ta, T1 tumours do not cause bladder pain and rarely present with lower urinary tract symptoms (LUTS). In patients who do complain of these symptoms, particularly in those with irritative LUTS refractory to symptomatic treatment, CIS might be suspected.

5.3 **Physical examination**

Physical examination does not reveal NMIBC.

5.4 **Imaging**

5.4.1 **Intravenous urography and computed tomography**

Intravenous urography (IVU) is used to detect filling defects in the calyces, renal pelvis and ureters, and hydronephrosis, which can indicate the presence of a ureteral tumour. Large exophytic tumours may be seen as filling defects in the bladder. The necessity to perform routine IVU once a bladder tumour has been detected is questioned because of the low incidence of significant findings obtained with this method (44-46) (LE: 2a). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (45) (LE: 2b). The risk of tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours (47) (LE: 2b).

In most centres, computed tomography (CT) urography is used as an alternative to conventional IVU (48). Especially in muscle-invasive tumours of the bladder and upper urinary tract tumours, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs). However, CT urography has the disadvantage of higher radiation exposure compared to IVU.
5.4.2 Ultrasonography
Ultrasonography (US) is often used as the initial tool to assess the urinary tract. This is not only because it avoids the use of contrast agents, but also because sensitive transducers have improved imaging of the upper urinary tract and bladder.

Transabdominal US permits characterisation of renal masses, detection of hydroureterism, and visualisation of intraluminal masses in the bladder. It can be as accurate as IVU for diagnosis of upper urinary tract obstruction (44) (LE: 3). US is therefore a useful tool for detection of obstruction in patients with haematuria, however, it cannot exclude the presence of upper tract tumours.

CIS cannot be diagnosed with imaging methods (IVU, CT urography or US).

5.5 Urinary cytology
Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in high-grade tumours but low sensitivity in low-grade tumours. As a result of loss of cell cohesion in the epithelial lining of the bladder in CIS, there is a larger number of floating cells in the urine, as well as a high degree of anaplasia. The sensitivity of cytology for CIS detection is 28-100% (49) (LE: 2b). Cytology is thus useful when a high-grade malignancy or CIS is present. However, urinary cytology often is negative in the presence of low-grade cancer. Positive voided urinary cytology can indicate a urothelial tumour anywhere in the urinary tract, from the calyx to the ureters, bladder, and proximal urethra. Negative cytology, however, does not exclude the presence of a tumour in the urinary tract.

Cytological interpretation is user-dependent (50). Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations. In experienced hands however, the specificity exceeds 90% (51) (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.

5.6 Urinary molecular marker tests
There are specified general requirements for good bladder cancer markers (51):

- The test must be as technically simple as possible (preferably a point-of-care test, with readily available results, easy to perform, with a short learning curve);
- Low cost;
- Good reliability and reproducibility;
- For individual patient populations and clinical situations, the test should have a high specificity to avoid unnecessary workup because of false-positive results, and high sensitivity to avoid the risk of missing a tumour;
- For clinical settings, it is of utmost importance to detect high-risk urothelial cancer before it escapes curative treatment.

Driven by the low sensitivity of urine cytology, extensive laboratory research has developed numerous urinary tests for BC detection (51-57). Considering the frequency of cystoscopy for follow-up, markers for recurrent urothelial cancer would be especially useful.

Numerous reviews of urinary markers have appeared in recent years (51-53,55-65). None of these markers have been accepted as standard diagnostic or follow-up procedures in routine urology or in guidelines. Some urine tests that have been evaluated in several laboratories/centres and in studies with sufficient numbers of patients are listed in Table 5. Sensitivity and specificity should be used to compare studies on urine tests because they remain constant, whereas positive and negative predictive values vary between populations with different numbers of positive and negative events (54,57).

The following conclusions can be drawn about the existing tests. Sensitivity is usually higher at the cost of lower specificity than urine cytology (51-57) (LE: 3). Benign conditions and BCG influence many urinary marker tests (51-65) (LE: 3). Sensitivity and specificity of a urinary marker test depend on the clinical context of the patient (screening, primary detection, follow-up (high risk), and follow-up (low/intermediate risk)) (54-57) (LE: 3). For example, sensitivity of a given urinary marker is higher for detection of a primary lesion than a recurrent lesion (54) (LE: 3). Patient selection explains the wide range in performance of the markers listed in Table 5.

Unlike other urine tests, some false-positive results of UroVysion and microsatellite analysis can be attributed to occult disease and thus identify those patients who are more likely to experience subsequent recurrence. It might also be useful to predict response to intravesical therapy (66-68) (LE: 3). Microsatellite analysis is the most promising of the methods listed in Table 5 (69-71).
Table 5: Summary of main urinary markers

<table>
<thead>
<tr>
<th>Markers (or test specifications)</th>
<th>Overall sensitivity (%)</th>
<th>Overall specificity (%)</th>
<th>Sensitivity for high-grade tumours (%)</th>
<th>Point-of-care test</th>
<th>Level of evidence (LE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UroVysion</td>
<td>30-86</td>
<td>63-95</td>
<td>66-70</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Microsatellite analysis</td>
<td>58-92</td>
<td>73-100</td>
<td>90-92</td>
<td>No</td>
<td>1b</td>
</tr>
<tr>
<td>Immunocyt/uCyt +</td>
<td>52-100</td>
<td>63-75</td>
<td>62-92</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear matrix protein 22</td>
<td>47-100</td>
<td>55-98</td>
<td>75-83</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>BTA stat</td>
<td>29-83</td>
<td>56-86</td>
<td>62-75</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>BTA TRAK</td>
<td>53-91</td>
<td>28-83</td>
<td>74-77</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Cytokeratins</td>
<td>12-88</td>
<td>73-95</td>
<td>33-100</td>
<td>No</td>
<td>3</td>
</tr>
</tbody>
</table>

BTA = bladder tumour antigen.

5.7 Practical application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered:

- Screening of the population at risk of BC. The application of haematuria dipstick, NMP22 or UroVysion in BC screening in high-risk populations has been reported (72,73). The low incidence of BC in the general population and the short lead time impair feasibility and cost-effectiveness (57,72-74). Routine application of screening is not recommended.

- Exploration of patients after haematuria or other symptoms suggestive of BC (primary detection). It is generally accepted that none of the tests can replace cystoscopy. However, urinary cytology or markers can be used as an adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, sensitivity for high-grade tumours and specificity are particularly important. Urinary cytology is highly specific but urinary markers lack this high specificity and are not recommended for primary detection. Future studies should explore the feasibility of urine markers preceding/replacing cystoscopy in patients with microscopic haematuria.

- Facilitate surveillance of NMIBC (54,59,75,76).
  
  a. Follow-up of high-risk NMIBC: High-risk tumours should be detected early in follow-up, and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology. Specificity is more important than sensitivity in this subset of patients, because the urinary markers are used as an adjunct to cystoscopy. A urinary marker other than cytology is not recommended for high-risk NMIBC surveillance.

  b. Follow-up low/intermediate risk NMIBC: To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low grade/risk recurrences. Several urinary markers are better but still do not detect half of the low-grade tumours that are detected by cystoscopy (54,57) (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow-up or help to lower cystoscopic frequency in routine fashion. One prospective randomised study confirmed that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy (77) (LE: 1b). It supports the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy. (77).

5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies (78).

Cystoscopy is initially performed in the office. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance, especially in men (79). Careful inspection of the whole urothelial lining in the bladder should be performed to prevent missing the tumour.

If a bladder tumour has been visualised in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo TUR (80).
A careful description of the findings is necessary. It should include the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended (Figure 2).

Figure 2: Bladder diagram

5.9 Transurethral resection of Ta, T1 bladder tumours

The goal of the TURB in Ta, T1 BC is to make the correct diagnosis and remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC.

TUR of the bladder (TURB) should be performed systematically as follows:

- Procedure is initiated with careful bimanual palpation under general or spinal anaesthesia;
- Insertion of the resectoscope, in men under visual guidance, with inspection of the whole urethra;
- Inspection of the whole urothelial lining of the bladder;
- Biopsy from prostatic urethra (if indicated, see lower);
- Cold-cup bladder biopsies (if indicated, see lower);
- Resection of the tumour.

The strategy of resection depends on the size of the lesion. Small tumours (<1 cm) can be resected en bloc, which includes the entire tumour and part of the underlying bladder wall. Larger tumours should be resected separately in fractions, including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. This approach provides good information about the vertical and horizontal extent of the tumour and helps to improve resection completeness (81) (LE: 3). Deep resection is not necessary in small, apparently low-grade lesions with a previous history of low-grade Ta (G1) tumour.

- In patients with palpable lesions before TURB, bimanual palpation should be repeated after resection
- The protocol is formulated, which must describe all previous steps of the procedure, as well as extent and completeness of resection
- An order form for pathological evaluation is prepared.

The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately, to enable him/her to make a correct diagnosis. Cauterisation should be avoided as much as possible during TURB to prevent tissue destruction.

Complete and correct TURB is essential to achieve a good prognosis (82). It has been confirmed that absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease.
and early recurrence (83) (LE: 2b).

Training in the methods of TURB should be included in teaching programmes. It has been shown that surgical experience can improve TURB results (84).

5.10 Office-based fulguration
In patients with a history of small, low-grade (WHO 2004 classification)/G1 (1973 classification) Ta tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option (85) (LE: 3).

5.11 Bladder- and prostatic urethral biopsies
CIS can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it might not be visible at all.

When abnormal areas of urothelium are seen, it is advised to take cold-cup biopsies or biopsies with a resection loop. Biopsies from normal-looking mucosa, so-called random (mapping) biopsies, should be performed in patients with positive urinary cytology and absence of visible bladder tumour, in addition to upper tract work-up/diagnostics. It is recommended to take biopsies from the trigone, bladder dome, and from the right, left, anterior and posterior bladder walls.

In patients with TaT1 tumours, mapping/random biopsies are not routinely recommended. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) (86) (LE: 2a). Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers as specified previously.

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou et al. (87) showed that in 128 men with T1G3 BC, the incidence of CIS in prostatic urethra was 11.7% (LE:2b). The risk of prostatic urethra or duct involvement seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours (88,89) (LE: 3). When bladder CIS is suspected, or cytology is positive with no evidence of bladder tumour, or abnormalities of prostatic urethra are visible, prostatic urethral biopsies are recommended (87). The biopsy is taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock positions) using a resection loop. In primary NMIBC when stromal invasion is not suspected, a cold-cup biopsy with forceps can be performed (90).

5.12 New TURB techniques
5.12.1 New resection techniques
Compared to monopolar resection, the bipolar electrocautery system may reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) (91) (LE: 3). This benefit however must be confirmed by a prospective trial.

5.12.2 New methods of tumour visualisation
As a standard procedure, cystoscopy and TUR are performed using white light. However, the use of white light can lead to missing lesions that are present but not visible, which is why new technologies are being developed.

5.12.2.1 Photodynamic diagnosis (fluorescence cystoscopy)
Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for detection of malignant tumours, particularly for CIS (92,93) (LE: 2a). In the systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for both patient (92% versus 71%) and biopsy (93% versus 65%) level analyses (93).

PDD had lower specificity than white light endoscopy (63% versus 81%) (93). False-positivity can be induced by inflammation or recent TUR, and during the first 3 months after BCG instillation (94,95) (LE: 3).

Prospective randomised studies evaluating the impact of ALA fluorescence-guided TURB on disease recurrence rate have shown controversial results (93,96,97).

A large, multicentre, prospective randomised trial that compared HAL fluorescence-guided TURB with standard TURB reported an absolute reduction of no more than 9% in the recurrence rate within 9 months in the HAL arm. Median time to recurrence improved from 9.4 months in the white light arm to 16.4 months in the HAL arm after mean follow-up of 53 and 55 months, respectively (98,99) (LE: 1b).

The value of fluorescence cystoscopy for improvement of the outcome in relation to progression rate or survival remains to be demonstrated.

In summary, PDD improves tumour detection rate, particularly in CIS. HAL but not ALA fluorescence-guided TURB was shown to have a beneficial effect on disease recurrence rate.
Photodynamic diagnosis is recommended in patients who are suspected of harbouring a high-grade tumour, for example, for biopsy guidance in patients with positive cytology or with a history of high-grade tumour. The additional costs of the equipment and instillation for PDD should be taken into account.

5.12.2.2 Narrow band imaging
In narrow band imaging (NBI) the contrast between normal urothelium and hypervascular cancer tissue is enhanced by filtering white light into two bandwidths of 415 and 540 nm, which are absorbed by haemoglobin. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection (100) (LE: 3). These findings should be confirmed in large multi-institutional studies.

5.13 Second resection
The significant risk of residual tumour after initial TURB of Ta, T1 lesions has been demonstrated (82,101) (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-53% of patients (101-106). Moreover, the tumour is often understaged by initial resection. The likelihood that a T1 tumour has been understaged and muscle-invasive disease detected by second resection ranges from 4 to 25%. This risk has increased up to 50% in some radical cystectomy series, although these studies have only enrolled selected patients (102,107-109) (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; therefore, correct staging is important. It has been demonstrated that a second TURB can increase the recurrence-free survival (104,105) (LE: 2a).

A second TURB is recommended in the following situations:
• After incomplete initial TUR;
• If there was no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS;
• In all T1 tumours;
• In all G3 tumours, except primary CIS.

There is no consensus about the strategy and timing of second TURB. Most authors recommend resection at 2-6 weeks after initial TURB. The procedure should include resection of the primary tumour site.

5.14 Pathological report
Pathological investigation of the specimen obtained by TURB and biopsies is an essential step in the diagnosis and treatment decision making of bladder cancer. High quality of resected and submitted tissue is essential for correct pathological assessment. The presence of sufficient muscle is necessary for correct assignment of pT category. Individual biopsies and portions of the tumour should be submitted in separate containers, and labelled individually. Pathologists should obtain from urologists order forms with sufficient clinical information regarding each sample, including the location of each sample.

The pathological report should specify (110):
• location of the evaluated sample (information obtained from the urologist order form);
• grade of each lesion;
• depth of tumour invasion (stage);
• presence of CIS;
• presence of detrusor muscle in the specimen;
• presence of lymphovascular invasion (LVI);
• presence of aberrant histology.

Close cooperation between urologists and pathologists is recommended.
## 5.15 Guidelines for primary assessment of non-muscle-invasive bladder cancers

<table>
<thead>
<tr>
<th>Initial diagnosis</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient history should be taken and recorded regarding all important information with possible connection to bladder cancer, including risk factors and history of suspect symptoms.</td>
<td>A</td>
</tr>
<tr>
<td>Renal and bladder US may be used during initial work-up in patients with haematuria.</td>
<td>C</td>
</tr>
<tr>
<td>At the time of initial diagnosis of bladder cancer, CT urography or IVU should be performed only in selected cases (e.g., tumours located in the trigone).</td>
<td>B</td>
</tr>
<tr>
<td>Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or any other non-invasive test.</td>
<td>A</td>
</tr>
<tr>
<td>Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.</td>
<td>C</td>
</tr>
<tr>
<td>Voided urine cytology is advocated to predict high-grade tumour before TUR.</td>
<td>C</td>
</tr>
<tr>
<td>Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.</td>
<td>C</td>
</tr>
</tbody>
</table>

### TURB

<table>
<thead>
<tr>
<th>TURB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TURB should be performed systematically in individual steps: bimanual palpation under anaesthesia; insertion of the resectoscope, under visual control with inspection of the whole urethra; inspection of the whole urothelial lining of the bladder; biopsy from prostatic urethra (if indicated); cold-cup bladder biopsies (if indicated); resection of the tumour; bimanual palpation after resection; protocol formulation; formulation of order form for pathological evaluation.</td>
<td>C</td>
</tr>
<tr>
<td>Perform resection in one piece for small papillary tumours (&lt; 1 cm), including part from the underlying bladder wall.</td>
<td>B</td>
</tr>
<tr>
<td>Perform resection in fractions (including muscle tissue) for tumours &gt; 1 cm in diameter.</td>
<td>B</td>
</tr>
<tr>
<td>Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.</td>
<td>C</td>
</tr>
<tr>
<td>Biopsy of the prostatic urethra should be taken from abnormal areas and from the precollicular area (between 5 and 7 o’clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.</td>
<td>C</td>
</tr>
<tr>
<td>If equipment is available, fluorescence-guided (PDD) biopsy should be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion).</td>
<td>B</td>
</tr>
<tr>
<td>The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately.</td>
<td>C</td>
</tr>
</tbody>
</table>

### A second TURB is recommended in the following situations:
- after incomplete initial TURB;
- if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS;
- in all T1 tumours;
- in all G3 tumours, except primary CIS.

<table>
<thead>
<tr>
<th>Classification and pathological report</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of tumour invasion is classified according to TNM system.</td>
<td>A</td>
</tr>
<tr>
<td>For histological classification, 1973 and 2004 WHO grading systems are used. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications should be used.</td>
<td>A</td>
</tr>
<tr>
<td>Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.</td>
<td>A</td>
</tr>
<tr>
<td>The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.</td>
<td>A</td>
</tr>
<tr>
<td>The pathological report should specify the presence of LVI or aberrant histology.</td>
<td>C</td>
</tr>
</tbody>
</table>
6. PREDICTING DISEASE RECURRENTCE AND PROGRESSION

6.1 Ta, T1 tumours

The classic way to categorise patients with Ta, T1 tumours with or without concomitant CIS is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Using such a technique, it has been proposed to divide patients into low-, intermediate- and high-risk groups (111). When using these risk groups, however, no distinction is usually drawn between the risk of disease recurrence and disease progression. Although prognostic factors may indicate a high risk of recurrence, the risk of progression might still be low, while other tumours might have a high risk of both recurrence and progression.

In order to predict separately the short-term and long-term risks of disease recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group (GUCG) has developed a scoring system and risk tables (112). The basis for these tables is the EORTC database, which provides individual patient data for 2,596 patients diagnosed with TaT1 tumours, who were randomised in seven EORTC-GUCG trials. Patients with CIS alone were not included. Seventy-eight percent of patients received intravesical treatment, mostly chemotherapy. However, they did not undergo a second TUR or receive maintenance BCG. The scoring system is based on the six most significant clinical and pathological factors:

- number of tumours;
- tumour size;
- prior recurrence rate;
- T category;
- presence of concurrent CIS;
- tumour grade.

Table 6 illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 7 shows the total scores stratified, as in the original article (112), into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years.

Table 6: Weighting used to calculate disease recurrence and progression scores

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumour diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 cm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Prior recurrence rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≤1 recurrence/year</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 recurrence/year</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Concurrent CIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Grade (WHO 1973)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>0-17</td>
<td>0-23</td>
</tr>
</tbody>
</table>
Table 7: Probability of recurrence and disease progression according to total score

<table>
<thead>
<tr>
<th>Recurrence score</th>
<th>Probability of recurrence at 1 year % (95% CI)</th>
<th>Probability of recurrence at 5 years % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15 (10-19)</td>
<td>31 (24-37)</td>
</tr>
<tr>
<td>1-4</td>
<td>24 (21-26)</td>
<td>46 (42-49)</td>
</tr>
<tr>
<td>5-9</td>
<td>38 (35-41)</td>
<td>62 (58-65)</td>
</tr>
<tr>
<td>10-17</td>
<td>61 (55-67)</td>
<td>78 (73-84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression score</th>
<th>Probability of progression at 1 year % (95% CI)</th>
<th>Probability of progression at 5 years % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2 (0-0.7)</td>
<td>0.8 (0-1.7)</td>
</tr>
<tr>
<td>2-6</td>
<td>1 (0.4-1.6)</td>
<td>6 (5-8)</td>
</tr>
<tr>
<td>7-13</td>
<td>5 (4-7)</td>
<td>17 (14-20)</td>
</tr>
<tr>
<td>14-23</td>
<td>17 (10-24)</td>
<td>45 (35-55)</td>
</tr>
</tbody>
</table>

Note: Electronic calculators for Tables 6 and 7, which have been updated for the iPhone, iPad and Android phones and tablets, are available at http://www.eortc.be/tools/bladdercalculator/.

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received 12 instillations during 5-6 months. No immediate postoperative instillation or second TUR was performed in these patients. The scoring system is based on evaluation of seven prognostic factors:

- sex;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- tumour grade.

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients (113). The lower risks in the CUETO tables may be attributed to using BCG, which is a more effective instillation therapy. Validations of the EORTC scoring system using the CUETO patients treated with BCG and in an independent patient population with long-term follow-up has confirmed its prognostic value (114,115) (LE: 2a).

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received 12 instillations during 5-6 months. No immediate postoperative instillation or second TUR was performed in these patients. The scoring system is based on evaluation of seven prognostic factors:

- sex;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- tumour grade.

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients (113). The lower risks in the CUETO tables may be attributed to using BCG, which is a more effective instillation therapy. Validations of the EORTC scoring system using the CUETO patients treated with BCG and in an independent patient population with long-term follow-up has confirmed its prognostic value (114,115) (LE: 2a).

Further prognostic factors have been described in selected patient populations. Female sex and CIS in the prostatic urethra are important prognostic factors in T1G3 patients treated with an induction course of BCG (87) (LE: 2b). Recurrence at 3 months was the most important predictor of progression in T1G2 tumours treated with TURB (116) (LE: 2b). The prognostic value of pathological factors, particularly T1 substaging, has been discussed elsewhere (see Chapter 4.4).

More work is required to determine the role of molecular markers in improving the predictive accuracy of the currently existing risk tables (114,117).

### 6.2 Carcinoma in situ

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease (118) (LE: 3). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease and specify the most dangerous cases. Publications are based on retrospective analyses of small series of patients, and their conclusions are not homogeneous. Some studies have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS (119,120), in extended CIS (121) and in CIS in the prostatic urethra (87) (LE: 3).

Various publications have shown that the response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by bladder cancer (113-116). Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders (122-124) (LE: 2a).
6.3 **Recommendation for patients’ stratification in risk groups**

Based on available prognostic factors and particularly data from the EORTC risk tables, the Guidelines Panel recommends stratification of patients into three risk groups that will facilitate treatment recommendations. Their definition, which takes into account the EORTC risk tables probabilities of recurrence and especially progression, can be found in Table 8. The recommendation is similar but not identical to that provided by the International Bladder Cancer Group (125).

For individual prediction of the risk of tumour recurrence and progression at different intervals after TURB, application of EORTC risk tables and calculator is strongly recommended.

**Table 8: Risk group stratification**

<table>
<thead>
<tr>
<th>Low-risk tumours</th>
<th>Primary, solitary, Ta, G1 (low grade), &lt; 3 cm, no CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-risk tumours</td>
<td>All tumours not defined in the two adjacent categories (between the category of low and high risk)</td>
</tr>
<tr>
<td>High-risk tumours</td>
<td>Any of the following: • T1 tumour • G3 (high grade) tumour • CIS • Multiple and recurrent and large (&gt; 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)</td>
</tr>
</tbody>
</table>

6.3.1 **Recommendations for stratification of NMIBC**

| Stratify patients into three risk groups according to Table 8. | B |
| Application of EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB. | B |

7. **ADJUVANT TREATMENT**

7.1 **Intravesical chemotherapy**

Although state-of-the-art TUR by itself can eradicate a Ta, T1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that TUR is incomplete or provokes recurrences in a high percentage of patients (82). It is therefore necessary to consider adjuvant therapy in all patients.

7.1.1 **One, immediate, postoperative intravesical instillation of chemotherapy**

Early single instillation has been shown to function by the destruction of circulating tumour cells resulting from TUR, and by an ablative effect (chemoablation) on residual tumour cells at the resection site and on small overlooked tumours (126-129) (LE: 3).

In a meta-analysis of 1,476 patients, one immediate instillation of chemotherapy after TUR significantly reduced recurrence rate by 11.7% compared to TUR alone (130) (LE: 1a). The majority of patients (> 80%) in the meta-analysis had a single tumour. A similar efficacy was reported in two more recent studies (131,132), with subgroup analyses suggesting that immediate instillation is most effective in tumour types with the lowest tendency towards recurrence, that is, in single primary or small tumours. Mitomycin C, epirubicin, and doxorubicin have all shown a beneficial effect, with no efficacy comparisons made between the drugs (130) (LE: 1a).

There is evidence from one subgroup analysis and one combined analysis that immediate instillation might have an impact on recurrence even when further adjuvant instillations are given (133,134) (LE: 2a).

Prevention of tumour cell implantation should be initiated within the first hours after cell seeding. Within a few hours, the cells are implanted firmly and are covered by extracellular matrix (127,136-138) (LE: 3).
3). In all single instillation studies, the instillation was administered within 24 h. To maximise the efficacy of immediate instillation, one should devise flexible practices that allow the instillation to be given as early as possible, that is, in the recovery room or even in the operating theatre.

Immediate instillation of postoperative chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation, which is most likely to appear in extensive TUR procedures, and in situations with bleeding that requires bladder irrigation. Clear instructions should be given to the nursing staff to control the free flow of the bladder catheter at the end of the instillation. Severe complications have been reported in patients with drug extravasation (139).

7.1.2 Additional adjuvant intravesical chemotherapy instillations
The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 7 and 8), a single immediate instillation reduces the risk of recurrence and is considered as the standard treatment (130) (LE: 1a). No further treatment should be given in these patients before subsequent recurrence. For other patients, however, a single immediate instillation remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 7 and 8).

A large meta-analysis of 3,703 patients from 11 randomised trials showed a highly significant 44% reduction in the odds of recurrence at 1 year in favour of chemotherapy over TUR alone (140). This corresponds to an absolute difference of 13–14% in the number of patients with recurrence. Contrary to chemotherapy, two meta-analyses have demonstrated that BCG therapy may reduce the risk tumour progression (141,142) (LE: 1a) (see section 7.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than regimens with mitomycin C (MMC) or epirubicin (143-145) (see section 7.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy does (145) (LE: 1a).

It is still controversial for how long and how frequently chemotherapy instillations should be given. From a systematic review of the literature of RCTs, which compared different schedules of intravesical chemotherapy instillations, one can only conclude that the ideal duration and intensity of the schedule remains undefined because of conflicting data (146). The available evidence does not support any treatment longer than 1 year (LE: 3).

7.1.3 Options for improving efficacy of intravesical chemotherapy
Some promising data have been presented about enhancing the efficacy of MMC using microwave-induced hyperthermia (Synergo) or electromotive drug administration (EMDA) in patients with high-risk tumours. The current evidence, however, is limited. The number of patients in the prospective series applying the microwave-induced hyperthermia was small and data on progression were inconclusive. In one study of 212 patients comparing BCG with sequential BCG and electromotive MMC, a significant benefit was found in favour of the electromotive arm regarding recurrence and progression (147,148) (LE: 2b). Still, both treatment modalities are considered to be experimental.

One RCT using MMC has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduces the recurrence rate (149) (LE: 1b). Another trial reported that a 1-h instillation of MMC is better than 30 min, but no efficacy comparisons are available for 1- and 2-h instillations (150) (LE: 3).

Another RCT using epirubicin has documented that concentration is more important than treatment duration (151) (LE: 1b). In view of these data, which need confirmation, it seems advisable to ask the patient not to drink on the morning before instillation, and to dissolve the drug in a buffered solution at optimal pH.

7.2 Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy
7.2.1 Efficacy of BCG
Five meta-analyses have confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy for prevention of recurrence of non-muscle-invasive tumours (143,152-155) (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have been conducted. BCG was compared with combination of epirubicin and interferon (156), MMC (157) or epirubicin alone (144). All of these studies have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). It has been shown that the effect was long lasting (144,157) and was also observed in a separate analysis of patients with intermediate-risk tumours (144).

One meta-analysis (143) has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC versus BCG. In the trials with BCG maintenance, a 32% reduction in the risk of recurrence for BCG compared to MMC was found (P < 0.0001), whereas there was a 28% increase in the risk of recurrence (P = 0.006) for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses have demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression (141,142) (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4,863 patients (81.6% with papillary tumours and 18.4% with primary or concurrent CIS) enrolled in 24
RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, in 260 out of 2,658 patients (9.8%) treated with BCG, tumours progressed compared to 304 out of 2,205 (13.8%) in the control groups (TUR alone, TUR plus intravesical chemotherapy, or TUR plus other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment ($P = 0.0001$). The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS (142). A recent RCT with long-term observation has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin (144) (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death (143).

The conflicting results in the outcomes of the studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. The majority of studies were however able to show a reduction in the risk of progression in high- and intermediate-risk tumours if BCG was applied including a maintenance schedule.

Two other meta-analyses have suggested a possible bias in favour of BCG by the inclusion of patients who were previously treated with intravesical chemotherapy (158,159). In the most recent meta-analysis, however, BCG maintenance was more effective than MMC also in patients who were previously treated with chemotherapy (143) (LE: 1a).

### 7.2.2 Optimal BCG schedule

Induction BCG instillations are classically given according to the empirical 6-weekly schedule that was introduced by Morales in 1976 (160). For optimal efficacy, BCG must be given in a maintenance schedule (141-143,155) (LE: 1a). In the EORTC-GU group meta-analysis, only patients who received maintenance BCG benefited. Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 27 over 3 years (161). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective (142). In their meta-analysis, Böhle et al. concluded that at least 1 year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression (141,155) (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown (162). However, in an RCT of 1,355 patients, the EORTC has recently shown that when BCG is given at full dose, 3 years maintenance reduces the recurrence rate as compared to 1 year in high-risk but not in intermediate-risk patients. There were no differences in progression or overall survival (159) (LE: 1b). The benefit of the two additional years of maintenance in the high-risk patients should be weighed against its added costs and inconveniences.

### 7.2.3 BCG toxicity

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy (145) (LE: 1a). Serious side effects however are encountered in < 5% of patients and can be treated effectively in almost all cases (163) (LE: 1b). It has been shown that maintenance schedule is not associated with increased risk of side effects comparing to induction course (163).

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected.

BCG should not be administered (absolute contraindications):
- during the first 2 weeks after TUR;
- in patients with macroscopic haematuria;
- after traumatic catheterisation;
- in patients with symptomatic urinary tract infection.

The presence of leukocyturia or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases (164,165) (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus (HIV) infection) (166), although some small studies have shown similar efficacy and no increase in complications comparing to non-immuno-compromised patients (167,168) (LE: 3).

The management of side effects after BCG should reflect their type and grade. Recommendations for individual situations have been provided by the International Bladder Cancer Group (IBCG) and by a Spanish group (169,170) (Table 9).
### Table 9: Management options for side effects associated with intravesical BCG (169,171,172)

#### Management options for local side effects (modified from IBCG group)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms of cystitis</strong></td>
<td>Phenazopyridine, propantheline bromide, or NSAIDs</td>
</tr>
<tr>
<td>If symptoms improve within a few days: continue instillations.</td>
<td></td>
</tr>
<tr>
<td>If symptoms persist or worsen:</td>
<td>a. Postpone the instillations</td>
</tr>
<tr>
<td></td>
<td>b. Perform a urine culture</td>
</tr>
<tr>
<td></td>
<td>c. Start empirical antibiotic treatment</td>
</tr>
<tr>
<td>If symptoms persist even with antibiotic treatment:</td>
<td>d. With positive culture: antibiotic treatment according to sensitivity.</td>
</tr>
<tr>
<td></td>
<td>e. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (to repeat cycle if necessary) (173).</td>
</tr>
<tr>
<td>If symptoms persist:</td>
<td>anti-tuberculosis drugs + corticosteroids.</td>
</tr>
<tr>
<td>If no response to treatment and/or contracted bladder:</td>
<td>radical cystectomy.</td>
</tr>
<tr>
<td><strong>Haematuria</strong></td>
<td>Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.</td>
</tr>
<tr>
<td>If haematuria persists,</td>
<td>perform cystoscopy to evaluate presence of bladder tumour.</td>
</tr>
<tr>
<td><strong>Symptomatic granulomatous prostatitis</strong></td>
<td>Symptoms rarely present: perform urine culture.</td>
</tr>
<tr>
<td>Quinolones.</td>
<td></td>
</tr>
<tr>
<td>If quinolones are not effective:</td>
<td>isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.</td>
</tr>
<tr>
<td>Cessation of intravesical therapy.</td>
<td></td>
</tr>
<tr>
<td><strong>Epididymo-orchitis</strong> (172)</td>
<td>Perform urine culture and administer quinolones.</td>
</tr>
<tr>
<td>Cessation of intravesical therapy.</td>
<td></td>
</tr>
<tr>
<td>Orchidectomy if abscess or no response to treatment.</td>
<td></td>
</tr>
</tbody>
</table>

#### Management options for systemic side effects

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>General malaise, fever</td>
<td>Generally resolve within 48 h, with or without antipyretics.</td>
</tr>
<tr>
<td>Arthralgia and/or arthritis</td>
<td>Rare complication and considered autoimmune reaction.</td>
</tr>
<tr>
<td>Arthralgia: treatment with NSAIDs.</td>
<td></td>
</tr>
<tr>
<td>Arthritis: NSAIDs and if no/partial response proceed to corticosteroids, high-dose quinolones or antituberculous drugs (171).</td>
<td></td>
</tr>
<tr>
<td>Persistent high-grade fever (&gt; 38.5°C for &gt; 48 h)</td>
<td>Permanent discontinuation of BCG instillations.</td>
</tr>
<tr>
<td>Immediate evaluation: urine culture, blood tests, chest X-ray.</td>
<td></td>
</tr>
<tr>
<td>Prompt treatment with ≥ 2 antimicrobial agents while diagnostic evaluation is conducted.</td>
<td></td>
</tr>
<tr>
<td>Consultation with an infectious diseases specialist.</td>
<td></td>
</tr>
<tr>
<td><strong>BCG sepsis</strong></td>
<td>Prevention: initiate BCG at least 2 weeks post TURBT (if no signs and symptoms of haematuria).</td>
</tr>
<tr>
<td>Cessation of BCG</td>
<td></td>
</tr>
<tr>
<td>For severe infection:</td>
<td>- High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months.</td>
</tr>
<tr>
<td>- Early, high-dose corticosteroids as long as symptoms persist.</td>
<td>Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.</td>
</tr>
<tr>
<td><strong>Allergic reactions</strong></td>
<td>Antihistamines and anti-inflammatory agents.</td>
</tr>
<tr>
<td>Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.</td>
<td>Delay therapy until reactions resolve.</td>
</tr>
</tbody>
</table>
7.2.4 **Optimal dose of BCG**

To reduce BCG toxicity, instillation of a reduced dose was proposed. Comparing one-third dose to full-dose BCG in 500 patients, CUETO found no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours (LE: 1b). Although fewer patients have reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar in the standard- and reduced-dose groups. The same Spanish group has shown in a prospective RCT that one-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy for prevention of recurrence with no decrease in toxicity (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full dose BCG, however, the former was associated with a higher recurrence rate, especially when it was given only for 1 year (LE: 1b).

7.2.5 **BCG strain**

There is no conclusive evidence that there may be a difference in clinical efficacy between various BCG strains.

7.2.6 **Indications for BCG**

Although BCG is a very effective treatment, there is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patient’s risk (Table 8):

- BCG does not alter the natural course of low-risk tumours (Table 8), and could be considered as overtreatment for this patient category.
- In patients with high-risk tumours, for whom radical cystectomy is not carried out, 1-3 years full-dose maintenance BCG is indicated. The additional beneficial effect of the second and third years of maintenance on recurrence in high-risk patients should be weighed against its added costs and inconveniences.
- In intermediate-risk patients, full-dose BCG with 1 year maintenance is more effective than chemotherapy for prevention of recurrence; however, it has more side effects than chemotherapy. For this reason both BCG with maintenance and intravesical chemotherapy remain an option. The final choice should reflect the individual patient’s risk of recurrence and progression as well as efficacy and side effects of each treatment modality.

7.3 **Specific aspects of treatment of CIS**

7.3.1 **Treatment strategy**

If concurrent CIS is found in association with MIBC, therapy is determined according to the invasive tumour. The detection of CIS with TaT1 tumours increases the risk of recurrence and progression of TaT1 tumours (112,113) and further treatment is mandatory. The treatment strategy is generally based on the criteria that are summarised in Chapters 7.1, 7.2, 7.4 and 8.

CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy (LE: 4). No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (radical cystectomy) should be done. There has been a lack of randomised trials of instillation therapy and early radical cystectomy as immediate primary treatment. Tumour-specific survival rates after early radical cystectomy for CIS are excellent, but as many as 40-50% of patients might be overtreated (177) (LE: 3).

7.3.2 **Cohort studies**

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG (118-121,178) (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence (121,161,178,179) (LE: 3).

7.3.3 **Prospective randomised trials**

Unfortunately, there have been few randomised trials in patients with CIS alone. Thus, the power to detect differences in treatment results has been low and the reliability of the conclusions is limited (177).

A meta-analysis of clinical trials that has compared intravesical BCG to intravesical chemotherapy (MMC, epirubicin, or adriamycin) in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG (OR = 0.41, P = 0.0001). In trials that have compared BCG with MMC, the long-term benefit of BCG was smaller, but BCG was superior to MMC in trials with BCG maintenance (OR = 0.57, P = 0.04) (180) (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different
immunotherapy (OR = 0.65, 95% CI = 0.36-1.16, P = 0.10) (LE: 1b). There has been no single trial that has demonstrated superiority of combined BCG and MMC over BCG alone (181).

In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1a).

7.3.4 Treatment of extravesical CIS
Patients with CIS are at high risk of extravesical involvement: in the upper urinary tract and in the prostatic urethra. Solsona et al. have found that 87 of 138 patients (63%) with CIS developed extravesical involvement initially or during follow-up (182). Patients with extravesical involvement had worse survival than those with bladder CIS alone (182) (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts (177). These situations should be distinguished from tumour invasion into the prostatic stroma, which is staged as T4a, and for which immediate radical cystoprostatectomy is mandatory.

Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. TUR of the prostate can improve contact of BCG with the prostatic urethra (78,177,183) (LE: 3).

In patients with prostatic duct involvement, there are promising results, but only from short series, so the data are insufficient to provide clear treatment recommendations (184). No conclusive results have been obtained with conservative therapy, therefore, radical surgery should be considered (183) (LE: 3).

Treatment of CIS that involves the upper urinary tract is discussed in the Guidelines on Urothelial Carcinomas of the Upper Urinary Tract.

7.4 Treatment of failure of intravesical therapy

7.4.1 Failure of intravesical chemotherapy
Patients with non-muscle-invasive recurrence of BC after chemotherapy regimen can profit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation (143) (LE: 1a).

7.4.2 Recurrence and failure after intravesical BCG immunotherapy

Table 10: Categories of unsuccessful treatment with intravesical BCG

<table>
<thead>
<tr>
<th>BCG failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Whenever a muscle-invasive tumour is detected during follow-up.</td>
<td></td>
</tr>
</tbody>
</table>

BCG-refractory tumour:

1. If high-grade, non-muscle-invasive papillary tumour is present at 3 months (185). Further conservative treatment with BCG is connected with increased risk of progression (122,186) (LE: 3).

2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases (42) LE: 3).

3. If high-grade tumour appears during BCG therapy.*

High grade recurrence after BCG. Recurrence of high grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (187) (LE: 3).*

<table>
<thead>
<tr>
<th>BCG intolerance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe side effects that prevent further BCG instillation before completing induction (170).</td>
<td></td>
</tr>
</tbody>
</table>

* Patients with low-grade recurrence during or after BCG treatment are not considered as BCG failure.

7.4.3 Treatment of BCG failure and recurrences after BCG

Treatment recommendations are provided in Table 11. They reflect categories mentioned in the previous paragraph and tumour characteristics at the time of recurrence.

Patients with BCG failure are unlikely to respond to further BCG therapy; therefore, radical cystectomy is the preferred option. The results of various studies suggest that repeat BCG therapy is appropriate for non-high-grade and even for some high-grade recurrent tumours (188,189) LE: 3).

Additionally, there are several bladder preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy (190). Changing from BCG to these options can yield responses in selected cases with BCG treatment failure for NMIBC (188, 191-199) (LE: 3). However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time (122,185,186) (LE: 3).
7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS

The type of intravesical therapy should be based on the risk groups shown in Tables 8 and 11. A

One immediate chemotherapy instillation is recommended in tumours presumed to be at low or intermediate risk. A

In patients with low-risk Ta tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment. A

In patients with intermediate-risk Ta T1 tumours, one immediate instillation of chemotherapy should be followed by 1 year full-dose BCG treatment, or by further instillation of chemotherapy for a maximum of 1 year. A

In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated. A

In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG is an option. C

In patients at highest risk of tumour progression (Table 11), immediate radical cystectomy should be considered. C

In BCG refractory tumours, radical cystectomy is indicated. B

Intravesical chemotherapy.

One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intraperitoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation). C

The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined and should not exceed 1 year. C

If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug during instillation by reducing fluid intake. B

The length of individual instillation should be 1-2 hours. C

BCG intravesical immunotherapy.

Absolute contraindications of BCG intravesical instillation are: during the first 2 weeks after TUR; in patients with macroscopic haematuria; after traumatic catheterization; and in patients with symptomatic urinary tract infection. C

The management of side effects after BCG intravesical instillation should reflect their type and grade (Table 9). C

8. RADICAL CYSTECTOMY FOR NON-MUSCLE-INVASIVE BLADDER CANCER

If cystectomy is indicated before pathologically confirmed progression into muscle-invasive tumour, immediate (immediately after NMIBC diagnosis) and early (after BCG failure) radical cystectomy can be distinguished. There are several reasons to consider radical cystectomy for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27-51% of patients being upstaged to muscle-invasive tumour at radical cystectomy (90,108,200-211) (LE: 3).
- Some patients with non-muscle invasive tumours experience disease progression in muscle-invasive disease (Table 7).
- It has been shown retrospectively that patients with high-risk NMIBC who undergo early rather than delayed cystectomy for tumour relapse after initial treatment with TURB and BCG have a better survival rate (212) (LE: 3).

Potential benefit of radical cystectomy must be weighed against the risk, morbidity, and impact on quality of life of radical cystectomy. It is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression. These are (35,87,112,113) (LE: 3):

- multiple and/ or large (> 3 cm) T1, high-grade (G3) tumours;
- T1, high-grade (G3) tumours with concurrent CIS;
- recurrent T1, high-grade (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- micropapillary variant of urothelial carcinoma.
It is recommended to discuss immediate radical cystectomy and conservative treatment with BCG instillation. Patients should be informed about the benefits and risks of both approaches. Individual factors like gender and age of the patient should be considered because of worse prognosis between females and life-long risk of progression after BCG in high risk tumours.

Radical cystectomy is strongly recommended in patients with BCG refractory tumours, as mentioned above. Delay of radical cystectomy might lead to decreased disease-specific survival (213) (LE: 3). In patients in whom radical cystectomy is performed at the time of pathological non-muscle-invasive disease, the 5-year disease-free survival rate exceeds 80% (214-219) (LE: 3).

Table 11: Treatment recommendations in TaT1 tumours according to risk stratification

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Definition</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk tumours</td>
<td>Primary, solitary, Ta, G1, &lt; 3 cm, no CIS</td>
<td>One immediate instillation of chemotherapy</td>
</tr>
<tr>
<td>Intermediate-risk tumours</td>
<td>All cases between categories of low and high risk</td>
<td>One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1 year full-dose BCG</td>
</tr>
</tbody>
</table>
| High-risk tumours           | Any of the following:  
  • T1 tumours  
  • G3 tumours  
  • CIS  
  • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented) | Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest risk tumours) |
| Subgroup of highest-risk tumours | T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, micropapillary variant of urothelial carcinoma | Cystectomy should be considered                                    |

Table 12: Treatment recommendations for BCG failure and recurrences after BCG

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment recommendation</th>
<th>GR</th>
</tr>
</thead>
</table>
| BCG refractory tumour                 | 1. Radical cystectomy  
  2. Bladder-preserving strategies in patients not suitable for cystectomy           | B  |
| High-grade recurrence after BCG       | 1. Radical cystectomy  
  2. Repeat BCG course  
  3. Bladder-preserving strategies                                                   | C  |
| Non-high-grade recurrence after BCG for primary intermediate-risk tumour | 1. Repeat BCG or intravesical chemotherapy  
  2. Radical cystectomy                                                             | C  |
9. FOLLOW-UP OF PATIENTS WITH NON-MUSCLE-INVASIVE BLADDER TUMOURS

As a result of the risk of recurrence and progression, patients with TaT1 bladder tumours and with CIS need to be followed up; however, the frequency and duration of cystoscopy and imaging should reflect the individual patient’s degree of risk. Using risk tables (see Tables 6 and 7), we are able to predict the short- and long-term risks of recurrence and progression in individual patients, and can adapt the follow-up schedule accordingly (112). When planning the follow-up schedule and methods the following aspects should be considered:

- The prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and low grade. Small, non-invasive (Ta), low-grade papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy (220-227) (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden (85) (LE: 3). Some authors have even defended temporary surveillance in selected cases (226-228) (LE: 3).
- The first cystoscopy after TUR at 3 months is a very important prognostic indicator for recurrence and progression (112,116,122,229-231) (LE: 1a). The first cystoscopy should thus always be performed 3 months after TUR in all patients with TaT1 BC.
- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low (230) (LE: 3). Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered (231).
- In tumours originally at intermediate or high risk, recurrences after 10 years tumour-free interval are not unusual (232) (LE: 3). Therefore, lifelong follow-up is recommended (231).
- The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours (47) (LE: 3).
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy (77) (LE: 1b). It supports the adjunctive role of urine tests during follow-up.

No non-invasive method has been proposed that can replace endoscopy, therefore, follow-up is based on regular cystoscopy (Section 5.8). There has been a lack of randomised studies that have investigated the possibility of safely reducing the frequency of follow-up cystoscopy. The following recommendations are therefore based mostly on retrospective experience.

9.1 Guidelines for follow-up in patients after TURB of NMIBC

<table>
<thead>
<tr>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The follow-up of TaT1 tumours is based on regular cystoscopy.</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.</td>
<td>C</td>
</tr>
<tr>
<td>Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.</td>
<td>C</td>
</tr>
<tr>
<td>Patients with intermediate-risk TaT1 tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.</td>
<td>C</td>
</tr>
<tr>
<td>Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.</td>
<td>C</td>
</tr>
<tr>
<td>Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.</td>
<td>B</td>
</tr>
<tr>
<td>During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.</td>
<td>B</td>
</tr>
</tbody>
</table>
10. REFERENCES


    http://www.uicc.org/tnm/


http://www.ncbi.nlm.nih.gov/pubmed/16600720


**11. ABBREVIATIONS USED IN THE TEXT**

*This list is not comprehensive for the most common abbreviations.*

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ALA</td>
<td>5-aminolaevulinic acid</td>
</tr>
<tr>
<td>ASR</td>
<td>age standardised incidence rate</td>
</tr>
<tr>
<td>BCG</td>
<td>bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>BTA</td>
<td>bladder tumour antigen</td>
</tr>
<tr>
<td>CIS</td>
<td>carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CUETO Club</td>
<td>Urológico Español de Tratamiento Oncológico (Spanish Oncology Group)</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EORTC-GUCG</td>
<td>EORTC Genito-Urinary Cancer Group</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridisation</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
</tr>
<tr>
<td>HAL</td>
<td>hexaminolaevulinic acid</td>
</tr>
<tr>
<td>ISUP</td>
<td>International Society of Urological Pathology</td>
</tr>
<tr>
<td>IVU</td>
<td>intravenous urography</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>MMC</td>
<td>mitomycin C</td>
</tr>
<tr>
<td>NMIBC</td>
<td>non-muscle-invasive bladder cancer</td>
</tr>
<tr>
<td>NVP</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>PDD</td>
<td>photodynamic diagnosis</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>papillary urothelial neoplasms of low malignant potential</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>TCC</td>
<td>transitional cell carcinoma</td>
</tr>
<tr>
<td>TNM</td>
<td>tumour, node, metastasis</td>
</tr>
<tr>
<td>TUR</td>
<td>transurethral resection</td>
</tr>
<tr>
<td>UICC</td>
<td>Union International Contre le Cancer</td>
</tr>
<tr>
<td>US</td>
<td>ultrasonography</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

**Conflict of interest**

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Urothelial Carcinomas of the Upper Urinary Tract


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            3.8.1.2.1 Ureteroscopy  
            3.8.1.2.2 Segmental resection  
            3.8.1.2.3 Percutaneous access  
         3.8.1.3 Adjuvant topical agents  
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         3.8.2.1 Nephroureterectomy  
         3.8.2.2 Chemotherapy  
         3.8.2.3 Radiotherapy  
   3.9 Follow-up  
4. **CONCLUSIONS**  
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6. **ABBREVIATIONS USED IN THE TEXT**
1. INTRODUCTION

The last European Association of Urology (EAU) guidelines on upper urinary tract tumours known as upper tract urothelial carcinomas (UTUCs) were published in 2011 (1). The EAU Guidelines Working Panel for UTUCs has prepared the current guidelines to provide evidence-based information for the clinical management of these rare tumours and to help clinicians incorporate these recommendations into their practice. The current update is based on a structured literature search.

2. METHODOLOGY

2.1 Data identification
A Medline search was performed on urothelial malignancies and UTUC management using combinations of the following terms: urinary tract cancer; urothelial carcinomas; upper urinary tract; urothelial carcinoma; renal pelvis; ureter; chemotherapy; nephroureterectomy; adjuvant treatment; neoadjuvant treatment; recurrence; risk factors; nomogram; and survival. The publications concerning UTUCs were mostly retrospective, including some large multicentre studies. Due to the scarcity of randomised data, articles were selected for these guidelines based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were included selectively if they were historically relevant or if data were scarce in recent publications. To facilitate evaluation of the quality of information provided, levels of evidence (LE) and grades of recommendation (GR) were inserted according to general principles of evidence-based medicine (EBM) (2).

2.2 Publication history
A first guidelines publication on upper urinary tract tumours was presented in 2004 (3). This document was updated and included in the EAU Guidelines compilation print in 2011. The current 2013 publication presents a limited update of the 2011 document.

This document was peer reviewed prior to publication.

2.3 Potential conflict of interest statement
The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

3. EVIDENCE SYNTHESIS

3.1 Epidemiology
Urothelial carcinomas are the fourth most common tumours after prostate (or breast), lung and colorectal cancer (4,5). They can be located in the lower urinary tract (bladder and urethra) or upper urinary tract (pyelocaliceal cavities and ureter). Bladder tumours account for 90-95% of urothelial carcinomas and are the most common malignancy of the urinary tract (1,5). However, UTUCs are uncommon and account for only 5-10% of urothelial carcinomas (4,6). The estimated annual incidence of UTUCs in western countries is about two new cases per 100,000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present (7). Recurrence of disease in the bladder occurs in 22-47% of UTUC patients (8-10), whereas recurrence in the contralateral upper tract is observed in 2-6% (11,12).

The natural history of UTUCs differs from that of bladder cancer: 60% of UTUCs are invasive at diagnosis compared with only 15-25% of bladder tumours (13,14). UTUCs have a peak incidence in people in their 70s and 80s, and they are three times more prevalent in men than in women (15,16).

There are familial/hereditary cases of UTUCs linked to hereditary non-polyposis colorectal carcinoma (HNPCC) (17). Among patients with UTUCs, HNPPC cases can be screened during a medical interview (18). There is a suspicion of hereditary UTUC if the patient is < 60 years of age, has a personal history of an HNPPC-associated cancer, a first-degree relative aged < 50 years with HNPPC-associated cancer, or two first-degree relatives with HNPPC-associated cancer (18). These patients should undergo DNA sequencing to identify hereditary cancers that have been misclassified as sporadic cancers by insufficient clinical data (19).
The presence of other HNPCC-associated cancers should also be evaluated. These patients should be closely monitored, and genetic counselling is advocated (17,19).

3.2 Risk factors

Many environmental factors contribute to the development of UTUCs (20,21). Some are similar to those associated with bladder cancer, whereas others are more specific for UTUC. Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Exposure to tobacco increases the relative risk of developing UTUC from 2.5 to 7 (20,21). UTUC “amino tumours” are related to occupational exposure to certain aromatic amines. These aromatic hydrocarbons are used in many industries (e.g., dyes, textiles, rubber, chemicals, petrochemicals, and coal). They are responsible for the carcinogenicity of certain chemicals, including benzidine and β-naphthalene. These two chemicals have been banned since the 1960s in most industrialised countries. In most cases, UTUCs are secondary to an amino tumour of the bladder. The average duration of exposure needed to develop a UTUC is approximately 7 years, with a latency period of about 20 years following the termination of exposure. The estimated risk (odds ratio) of developing UC after exposure to aromatic amines is 8.3 (21,22).

Upper urinary tract tumours resulting from phenacetin consumption almost disappeared after the product was banned in the 1970s (21).

Although the incidence of Balkan endemic nephropathy is also on the decline, roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the pathophysiology and induction, respectively, of this nephropathy (23-26). Several studies have revealed the carcinogenic potential of aristolochic acid contained in Aristolochia fangchi and Aristolochia clematitis (plants endemic to the Balkans). This acid contains a set of highly toxic nitrophenolate derivatives that exhibit a powerful mutagenic action due to their ability to make up covalent links with cell DNA. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139. This mutation is very rare in the non-exposed population and is predominant in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC (21,23,24).

A high incidence of UTUC has also been described in Taiwan, especially in the population on the southwest coast of the island, and represents 20-25% of UCs in the region (21,24). The association of UTUC with blackfoot disease and arsenic exposure remains unclear in this patient population (21,24).

Differences in the ability to counteract carcinogens may contribute to host susceptibility and the risk of developing UC. Although it is not unusual that a genotype confers protection for an organ and increases the risk for another, UTUC may share some risk factors or molecular disruption pathways with bladder UC, but each has its own specific features. Certain genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, thus, there is variability in inter-individual susceptibility to the risk factors just mentioned. Only two polymorphisms specific to UTUC have been reported so far (27,28). A variant allele, SULT1A1*2, which reduces sulfotransferase activity, and a polymorphism located at the T allele of rs9642880 on chromosome 8q24 enhance the risk of developing UTUC.

3.3 Histology and classification

3.3.1 Histological types

More than 95% of UCs are derived from the urothelium and correspond to UTUCs or bladder tumours (13,29). With regard to UTUCs, morphological variants have been described that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours, and such UCs are associated with one of the following variants: micropapillary, clear cell, neuroendocrine, and lymphoepithelial (29,30).

Collecting-duct carcinoma has similar characteristics to UTUC because of its common embryologic origin (31). Upper urinary tract tumours with pure non-urothelial histology are exceptions (32,33) but a variant can be seen in nearly 25% of cases (34). Squamous cell carcinomas of the upper urinary tract represent < 10% of pyelocaliceal tumours and are even rarer within the ureter. Squamous cell carcinoma of the urinary tract is associated with chronic inflammatory and infectious disease arising from stones in the urinary tract (29,30). Other histological subtypes are adenocarcinomas (< 1%), small cell carcinomas, and sarcomas.

3.3.2 Classification

The classification and morphology of UTUCs are similar to those of bladder carcinomas (13). It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential, low-grade papillary UC, high-grade papillary UC), flat lesions (carcinoma in situ (CIS)), and invasive carcinomas. All variants of urothelial tumours described in the bladder can also be observed in the upper urinary tract (34).

3.3.2.1 Tumour Node Metastasis staging

Table 1 presents the Union Internationale Contre le Cancer (UICC) 2009 Tumour Node Metastasis (TNM) classification used throughout these guidelines (35).
According to the TNM classification, the regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect the N classification.

There is an interest to use a renal pelvic pT3 subclassification to discriminate between microscopic infiltration of the renal parenchyma (pT3a) versus macroscopic infiltration or invasion of peripelvic adipose tissue (pT3b) (34,36). pT3b UTUCs are more likely to have aggressive pathological features and have a higher risk of recurrence (34,36).

Table 1: TNM classification 2009 for UTUC (35)*

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Ta</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>T4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

*All EAU guidelines advocate the TNM system of tumour classification.

3.3.2.2 Tumour grade

Until 2004, the most common classification used was the World Health Organization (WHO) classification of 1973, which distinguished only three grades (G1, G2 and G3) (37). In recent years, molecular biological data have allowed for further distinction between different tumour groups and the development of a new classification system that better reflects the potential growth of these tumours (38). Thus the 2004 WHO classification now takes histological data into account to distinguish among three groups of non-invasive tumours: papillary urothelial neoplasia of low malignant potential; low-grade carcinomas; and high-grade carcinomas. There are almost no tumours of low malignant potential in the upper urinary tract (29,30).

3.4 Symptoms

The diagnosis of UTUC may be fortuitous or related to the exploration of symptoms. The symptoms are generally restricted (39). The most common symptom of UTUC is gross or microscopic haematuria (70-80%) (40). Flank pain occurs in 20-40% of cases, and a lumbar mass is present in 10-20% (41,42). However, systemic symptoms (altered health condition including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt consideration of a more rigorous metastatic evaluation (41,42).

3.5 Diagnosis

3.5.1 Imaging

3.5.1.1 Computed tomography urography

Computed tomography (CT) urography is the imaging technique with the highest diagnostic accuracy for
UTUC and has replaced intravenous excretory urography and ultrasonography as the first-line imaging test for investigating high-risk patients (40). The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99 depending on the technique used (43-50). Attention to technique is therefore very important for optimum results.

Computed tomography urography of the urinary tract acquires at least one image series during the excretory phase, usually 10-15 min, following the administration of intravenous contrast medium (51). Rapid acquisition of thin sections allows high-resolution isotropic images to be produced that can be viewed in multiple planes to assist with diagnosis without degradation of resolution (52,53).

Computed tomography urography can also detect wall thickening of the renal pelvis or ureter, which is a sign of UTUC, even when there is no luminal mass effect, but flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening (54). The secondary sign of hydronephrosis on imaging in the presence of UTUC is associated with advanced pathological disease and poorer oncological outcomes (51,55).

3.5.1.2 Magnetic resonance imaging
Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography usually when radiation or iodinated contrast media are contraindicated (56). The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm (56). Magnetic resonance urography with certain gadolinium-based contrast media is contraindicated in selected patients with severe renal impairment (< 30 ml/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis.

Computed tomography urography is generally preferred to MR urography for diagnosing UTUCs in terms of greater diagnostic accuracy, lower cost, and greater patient acceptability.

3.5.2 Cystoscopy and urinary cytology
Positive urine cytology is highly suggestive of UTUC when bladder cystoscopy is normal and if CIS of the bladder or prostatic urethra has been largely excluded (e.g., by biopsies of any suspicious lesion, possibly guided by photodynamic diagnosis) (13,57). Cytology is less sensitive for UTUC than for bladder tumours, even for high-grade lesions, and it should ideally be performed in situ (i.e., in the renal cavities) (58). Retrograde ureteropyelography (through a ureteral catheter or during ureteroscopy) remains an option for the exclusion of a tumour in the upper urinary tract (44,59). However, urinary cytology of the renal cavities and ureteral lumina should preferably be performed prior to application of larger amounts of contrast agent for retrograde ureteropyelography, because it may deteriorate cytological specimens.

The sensitivity of fluorescence in situ hybridisation (FISH) for the identification of molecular abnormalities characterising UTUCs parallels its performance in bladder cancer; however, the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally-invasive therapy for UTUCs may limit its usefulness (60,61). In addition, FISH appears to have limited value for upper UTUCs surveillance (60,61).

3.5.3 Diagnostic ureteroscopy
Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis and collecting system with a technical success approaching 95%. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate regardless of the size of the sample (62). Undergrading may occur from the diagnostic biopsy, making intensive follow-up a requirement if renal sparing treatments are selected (63). Ureteroscopy also facilitates selective ureteral sampling for cytology in situ (59,64,65).

Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, when conservative treatment is being considered, or in patients with a solitary kidney. If available, ureteroscopy and biopsy should be performed in the preoperative assessment of any UTUC patient. Combining ureteroscopic biopsy grade, diagnostic imaging findings such as hydronephrosis, and urinary cytology may help decision making on radical nephroureterectomy (RNU) versus endoscopic treatment (64,66).

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions. Narrow band imaging appears to be the most promising technique but results are still preliminary (66,67). Table 2 lists the recommendations.
Table 2: Guidelines for the diagnosis of UTUC

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary cytology</td>
<td>A</td>
</tr>
<tr>
<td>Cystoscopy to rule out a concomitant bladder tumour</td>
<td>A</td>
</tr>
<tr>
<td>CT urography</td>
<td>A</td>
</tr>
<tr>
<td>Diagnostic ureteroscopy and biopsy</td>
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<tr>
<td>Retrograde ureteropyelography</td>
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</tbody>
</table>

CT urography = Computed tomography urography

3.6 Prognostic factors
UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 (67,68). This section briefly describes the currently recognised prognostic factors (69).

3.6.1 Tumour stage and grade
According to the most recent classifications, the primary recognised prognostic factors are tumour stage and grade (64,69-71). Extranodal extension appears to be a powerful predictor of clinical outcomes in patients with UTUCs and positive lymph node metastases (72).

3.6.2 Age and sex
Sex is no longer considered an independent prognostic factor that influences UTUC mortality (15,69,73). Conversely, patient age is still considered an independent prognostic factor because older age at the time of RNU is associated with decreased cancer-specific survival (LE: 3) (69,74). However, chronologic age alone should not be an absolute exclusion criterion for the treatment of potentially curable UTUC but rather overall life expectancy. A significant proportion of elderly patients can still be cured with RNU (74). This suggests that chronological age alone is an inadequate indicator of outcomes in older UTUC patients (74,75).

3.6.3 Ethnicity
There are differences in clinicopathological characteristics of tumours between Caucasian and Japanese patients. However, race and ethnicity are not so far recognised as independent factors for survival (LE: 3) (76).

3.6.4 Tumour location
According to the most recent findings, the initial location of the tumour within the upper urinary tract (e.g., ureter vs. renal pelvis) is a prognostic factor (77-79) (LE: 3). There is a prognostic impact of tumour location when adjusted for tumour stage: ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours (69,78-80).

3.6.5 Tobacco consumption
Smoking intensity (long-term exposure) and being a smoker at diagnosis increases the risk for poor oncological outcomes (LE: 3) (81-83).

3.6.6 Lymphovascular invasion
Lymphovascular invasion is present in approximately 20% of UTUCs and an independent predictor of survival (84,85). Lymphovascular invasion status should be systematically included and specifically reported in the pathologic report of all RNU specimens (LE: 3) (84,86).

3.6.7 Surgical margins
Positive surgical margin after RNU appears to be a significant factor for developing subsequent UTUC metastases (LE: 3). Pathologists should look for, and report on, positive margins at the level of ureter transsections, bladder cuff and around the tumour if the tumour is ≥ T2. (87).

3.6.8 Other factors
Extensive tumour necrosis is an independent predictor of clinical outcomes in patients who undergo RNU. Extensive tumour necrosis can be defined as > 10% of the tumour area (LE: 3) (88,89).

The tumour architecture (e.g., papillary vs. sessile) of UTUCs appears to be associated with the prognosis after RNU. A sessile growth pattern is associated with the worst outcomes (LE: 3) (90,91).

The presence of concomitant CIS in patients with organ-confined UTUC is associated with a higher
risk of recurrent disease and cancer-specific mortality (LE: 3) (92,93). Similar to lower tract urothelial carcinoma, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease (94). A previous history of bladder CIS is associated with increased risk of recurrence and death from UTUCs (LE: 3) (95).

The American Society of Anesthesiologists (ASA) score also significantly correlates with cancer-specific survival after RNU (LE: 3) (96) but ECOG performance status correlates only with overall survival (97). Obesity and higher body mass index adversely affect cancer-specific outcomes in patients with UTUCs (LE: 3) (98).

3.6.9 Molecular markers

Several research groups are working on UTUC characteristics and carcinogenesis pathways. Several studies have investigated the prognostic impact of various tissue-based markers that are related to cellular processes such as cell adhesion (E-cadherin and CD24), cell differentiation (Snail and epidermal growth factor receptor) angiogenesis (hypoxia-inducible factor-1α and metalloproteinases), cell proliferation (Ki67), epithelial-mesenchymal transition (snail), mitosis (Aurora-A), apoptosis (Bcl-2 and survivin) and vascular invasion (récepteur d’origine nantais RON) and c-met protein MET) (69,99-102). However, because of the rarity of the disease, the main limitations shared by these studies are their retrospective nature and their small sample size.

Microsatellite instability (MSI) is an independent molecular marker used for tumour prognosis (103). In addition, MSI can help detect germ-line mutations, allowing for the detection of possible hereditary cancers (17).

To date, none of the markers has fulfilled the clinical and statistical criteria necessary to support their introduction in daily clinical decision making.

3.7 Prediction and risk stratification

Available accurate predictive tools are rare in UTUCs.

There are two available models in a preoperative setting: one for the prediction of locally advanced cancer that could guide the extent of lymph node dissection at the time of RNU (104); and one for selection of non-organ-confined UTUCs that are likely to benefit from nephroureterectomy (105).

Additionally there are two nomograms that can predict survival rates in a postoperative setting based on standard pathological features: one coming from an international group (106) and the other one built from a European population only (107).

3.8 Treatment

3.8.1 Localised disease

3.8.1.1 Radical nephroureterectomy

Radical nephroureterectomy with excision of the bladder cuff is the gold standard treatment for UTUC, regardless of the location of the tumour in the upper urinary tract (LE: 3) (14). The RNU procedure must comply with oncological principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection (14). Resection of the distal ureter and its orifice is performed because it is a part of the urinary tract with considerable risk of tumour recurrence. After removal of the proximal part, it is almost impossible to image or approach it by endoscopy during follow-up. Recent publications on survival after RNU have concluded that removal of the distal ureter and bladder cuff is beneficial (108-110).

McDonald et al. presented the pluck technique in 1952, but it was not until 1995 (111) that the usefulness of an endoscopic approach to the distal ureter was emphasised, and then several other alternative techniques were reconsidered to simplify resection of the distal ureter: stripping, transurethral resection of the intramural ureter, and intussusception techniques (11,109). Apart from ureteral stripping, none of these techniques is inferior to excision of the bladder cuff (LE: 3) (74-76,78). Nevertheless, the endoscopic approach is clearly associated with a higher risk of subsequent bladder recurrence (112).

A delay between diagnosis and removal of the tumour may increase the risk of disease progression. However the cut-off has been disputed between 45 days and 3 months and it remains a moot point (LE: 3) (113-115).

Lymph node dissection (LND) associated with RNU is of therapeutic interest and allows for optimal staging of the disease (LE: 3) (116,117). However, the anatomical sites of LND have not yet been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed (118).

Lymph node dissection appears to be unnecessary in cases of TaT1 UTUCs because it was reported to be retrieved in 2.2% T1 versus 16% pT2-4 tumours (117). In addition, a continuous increase in the probability of lymph-node-positive disease related to pT classification has been described (117). However, these data are retrospective; consequently, under-reporting of the true rate of node-positive disease is likely. It is not yet possible to standardise either indication or extent of LND. However, LND can be achieved according to lymphatic drainage as follows: LND medially to the ureter in ureteropelvic tumour, retroperitoneal LND in
case of higher ureteral tumour and/or tumour of the renal pelvis (i.e., right side: border vena cava and left side: border aorta) (116-118).

The laparoscopic RNU has not yet achieved final proof of its safety. There are early reports of retroperitoneal metastatic dissemination and dissemination along the trocar pathway when large tumours were manipulated in a pneumoperitoneal environment (119,120).

Several precautions must be taken when operating with a pneumoperitoneum because it may increase tumour spillage:

• Entering the urinary tract should be avoided.
• Direct contact of the instruments with the tumour should be avoided.
• Laparoscopic RNU must take place in a closed system. Morcellation of the tumour should be avoided, and an endobag is necessary to extract the tumour.
• The kidney and ureter must be removed en bloc with the bladder cuff.
• Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU, until proven otherwise.

Recent data show a tendency towards equivalent oncological outcomes after either laparoscopic or open RNU (121-126). In addition, the laparoscopic approach appears to be superior to open surgery only with regard to functional outcomes (LE: 3) (121-126). Only one prospective randomised study of 80 patients has provided evidence that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC (LE: 2) (127). In addition, it has been demonstrated that oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements (LE: 3) (128). Recommendations are listed in Table 3.

### Table 3: Guidelines for radical management of UTUC: RNU

<table>
<thead>
<tr>
<th>Indications for RNU for UTUC</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of infiltrating UTUC on imaging</td>
<td>B</td>
</tr>
<tr>
<td>High-grade tumour (urinary cytology)</td>
<td>B</td>
</tr>
<tr>
<td>Multifocality (with two functional kidneys)</td>
<td>B</td>
</tr>
<tr>
<td>Non-invasive but large (i.e., &gt; 2 cm) UTUC</td>
<td>B</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Techniques for RNU for UTUC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Open and laparoscopic access are equivalent in terms of efficacy</td>
<td>B</td>
</tr>
<tr>
<td>Bladder cuff removal is imperative</td>
<td>A</td>
</tr>
<tr>
<td>Several techniques for bladder cuff excision are acceptable, except stripping</td>
<td>C</td>
</tr>
<tr>
<td>Lymphadenectomy is recommended in case of invasive UTUC</td>
<td>C</td>
</tr>
<tr>
<td>Postoperative instillation (chemotherapy) is recommended after RNU to avoid bladder recurrence</td>
<td>B</td>
</tr>
</tbody>
</table>

#### 3.8.1.2 Conservative surgery

Conservative surgery for low-risk UTUCs allows preservation of the upper urinary renal unit while sparing the patient the morbidity associated with open radical surgery. Conservative management of UTUCs can be considered in imperative cases (renal insufficiency or solitary functional kidney) or in elective cases (when the contralateral kidney is functional) for low-grade, low-stage tumours (LE: 3) (110,129,130). The choice of technique depends on technical constraints, the anatomical location of the tumour, and the experience of the surgeon.

##### 3.8.1.2.1 Ureteroscopy

Endoscopic ablation can be considered in highly selected cases and in these situations (131-133):

- A flexible rather than a rigid ureteroscope, laser generator (134), and pliers (pluck) for biopsies are available (LE: 3) (132,135).
- The patient is informed of the need for closer, more stringent surveillance.
- A complete resection of the tumour is strongly advocated.

However there is a risk of understaging and undergrading the disease with pure endoscopic management.

##### 3.8.1.2.2 Segmental resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Ureteroureterostomy is indicated for non-invasive, low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means (i.e., size or multiplicity) and for high-grade or invasive tumours when renal sparing surgery
(RSS) for preservation of renal function is a goal (LE: 3). High-grade tumours of the proximal ureter or mid-ureter should undergo RNU with excision of bladder cuff when possible. Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means (i.e., size or multiplicity) and for high-grade, locally-invasive tumours (LE: 3) (136-138). For both ureteroureterostomy and complete distal ureterectomy and neocystostomy it is necessary, however, to ensure that the area of tissue around the tumour is not invaded. Segmental resection of the iliac and lumbar ureter is associated with a failure rate greater than that for the distal pelvic ureter (136-138). Open resection of tumours of the renal pelvis or calices has almost disappeared. Resection of pyelocaliceal tumours is technically difficult, and the recurrence rate is higher than for tumours of the ureter.

### 3.8.1.2.3 Percutaneous access

Percutaneous management can be considered for low-grade or non-invasive UTUCs in the renal cavities (LE: 3) (132,139,140). This treatment option may be offered to patients with low-grade tumours in the lower caliceal system that are inaccessible or difficult to manage by ureteroscopy. A theoretical risk of seeding exists in the puncture tract and in perforations that may occur during the procedure. This approach, however, is being progressively abandoned due to enhanced materials and advances in distal-tip deflection of recent ureteroscopes (132,139,140).

### 3.8.1.3 Adjuvant topical agents

The antegrade instillation of bacillus Calmette-Guérin vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete eradication of the tumour) is technically feasible after conservative treatment of UTUCs or for the treatment of CIS (LE:3) (141). Retrograde instillation through a ureteric stent or with the help of the reflux obtained from a double J stent have also been used (142), but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The medium-term results are similar to those observed for the treatment of bladder tumours but have not been confirmed in long-term studies (LE: 3) (141,142).

One prospective randomised study of 144 patients has provided evidence that a single postoperative dose of intravesical mitomycin reduces the risk (i.e., absolute risk 11%) of a bladder tumour within the first year following RNU (LE: 2) (143). Table 4 lists the recommendations.

#### Table 4: Guidelines for conservative management of UTUC

<table>
<thead>
<tr>
<th>Indications for conservative management of UTUC</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unifocal tumour</td>
<td>B</td>
</tr>
<tr>
<td>Tumour size less than 1 cm</td>
<td>B</td>
</tr>
<tr>
<td>Low-grade tumour (cytology or biopsies)</td>
<td>B</td>
</tr>
<tr>
<td>No evidence of an infiltrative lesion on CT urography</td>
<td>B</td>
</tr>
<tr>
<td>Understanding of close follow-up</td>
<td>B</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Techniques used in conservative management of UTUC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser should be used in case of endoscopic treatment</td>
<td>C</td>
</tr>
<tr>
<td>Flexible ureteroscopy is preferable over rigid ureteroscopy</td>
<td>C</td>
</tr>
<tr>
<td>A percutaneous approach remains an option in small low-grade caliceal tumours unsuitable for ureteroscopic treatment</td>
<td>C</td>
</tr>
<tr>
<td>Ureteroureterostomy is indicated for non-invasive low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means, and for high-grade or invasive tumours when RSS for preservation of renal function is a goal</td>
<td>C</td>
</tr>
<tr>
<td>Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means and for high-grade, locally-invasive tumours</td>
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</tbody>
</table>

#### 3.8.2 Advanced disease

##### 3.8.2.1 Nephroureterectomy

There are no benefits of RNU in metastatic (M+) disease, although it can be considered a palliative option (LE: 3) (14,117).

##### 3.8.2.2 Chemotherapy

UTUCs are urothelial tumours, therefore, platinum-based chemotherapy is expected to produce similar results.
to those seen in bladder cancer. Several platinum-based chemotherapy regimens have been proposed (144). However, adding chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, to a population with already impaired postsurgical renal function may also be related to the reduced survival in these patients (145,146). In addition, not all the patients receive this treatment because of comorbidity and impaired renal function after radical surgery.

Contrary to what has been demonstrated for bladder cancer, there have been no reported effects of neoadjuvant chemotherapy for UTUCs in the only study published to date (147). Although survival data need to mature and longer follow-up is awaited, current preliminary data provide justification for the sustained support of trials using this strategy in UTUCs.

Adjuvant chemotherapy can somehow achieve a recurrence-free rate of up to 50% but has clearly no impact on survival (148,149). Further data are awaited from the ongoing prospective randomised POUT trial (PeriOperative chemotherapy or sUrveillance in upper Tract urothelial cancer) (150). Data are currently insufficient to provide any recommendations.

3.8.2.3 Radiotherapy

Adjuvant radiotherapy may improve local control of the disease (151). When given in combination with cisplatinum, it may result in longer disease-free and overall survival (152) (LE: 3). Radiotherapy appears to be scarcely relevant nowadays both as a unique therapy and associated with chemotherapy as adjuvant therapy (Fig. 1).

Fig. 1: Proposed flowchart for the management of UTUC

MDCT = multidetector computed tomography

3.9 Follow-up

Stringent follow-up of UTUC patients after surgical treatment is mandatory to detect metachronous bladder tumours (in all cases), local recurrence, and distant metastases (in the case of invasive tumours).

When RNU is performed, local recurrence is rare, and the risk of distant metastases is directly related to the risk factors listed previously. The reported recurrence rate within the bladder after treatment of a primary UTUC varies considerably from 22 to 47% (8,10). Thus, the bladder should be observed in all cases.
The surveillance regimen is based on cystoscopy and urinary cytology for at least 5 years (8-10). Bladder recurrence should not be considered as distant recurrence. When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence (129,133,135). Despite notable improvements in endourological technology, the follow-up of patients treated with conservative therapy is difficult, and frequent and repeated endoscopic procedures are necessary.

Table 5 lists the recommended follow-up schedules.

**Table 5: Guidelines for follow-up of UTUC patients after initial treatment**

<table>
<thead>
<tr>
<th>After RNU, over at least 5 years</th>
<th>GR</th>
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<tbody>
<tr>
<td><strong>Non-invasive tumour</strong></td>
<td></td>
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<tr>
<td>Cystoscopy/urinary cytology at 3 months and then yearly</td>
<td>C</td>
</tr>
<tr>
<td>CT every year</td>
<td>C</td>
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<tr>
<td><strong>Invasive tumour</strong></td>
<td></td>
</tr>
<tr>
<td>Cystoscopy/urinary cytology at 3 months and then yearly</td>
<td>C</td>
</tr>
<tr>
<td>CT urography every 6 months over 2 years and then yearly</td>
<td>C</td>
</tr>
<tr>
<td><strong>After conservative management, over at least 5 years</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary cytology and CT urography at 3 and 6 months, and then yearly</td>
<td>C</td>
</tr>
<tr>
<td>Cystoscopy, ureteroscopy and cytology <em>in situ</em> at 3 and 6 months, and then every 6 months over 2 years, and then yearly</td>
<td>C</td>
</tr>
</tbody>
</table>

**4. CONCLUSIONS**

These renewed UTUC guidelines contain information for the diagnosis and treatment of individual patients according to a current, standardised approach. When determining the optimal treatment regimen for their patients, urologists must take into account each individual patient’s specific clinical characteristics with regard to renal function including medical comorbidity; tumour location, grade, and stage; and molecular marker status.

**5. REFERENCES**


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6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

EBM  evidence based medicine
CIS  carcinoma in situ
CT   computed tomography
EAU  European Association of Urology
EBM  evidence-based medicine
ECOG Eastern Cooperative Oncology Group
FISH fluorescence in situ hybridisation
GR   grade of recommendation
HIF  hypoxia-inducible factor
HNPPC hereditary nonpolyposis colorectal carcinoma
LE   level of evidence
CT Urography computed tomographic urography
MRI  magnetic resonance imaging
MSIs microsatellite instabilities
RNU  radical nephroureterectomy
TNM  Tumour Node Metastasis
UTUC upper tract urothelial carcinoma
WHO  World Health Organization
LND  Lymph node dissection

Conflict of interest
All members of the Upper Urinary Tract Urothelial Carcinomas Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Muscle-invasive and Metastatic Bladder Cancer

J.A. Witjes (chair), E. Compérat, N.C. Cowan, M. De Santis, G. Gakis, T. Lebret, M.J. Ribal, A. Sherif

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1. INTRODUCTION

1.1 The guideline

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) has prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice. The EAU Guidelines Panel comprises an international multidisciplinary group of experts from the fields of urology, pathology, radiology and oncology.

It is evident that optimal treatment strategies for MIBC require the involvement of a specialist multidisciplinary team and a model of integrated care to avoid fragmentation of patient care.

The Muscle-invasive and Metastatic Bladder Cancer guidelines are one of four EAU guidelines documents addressing bladder cancer (EAU Guidelines on Non-muscle-invasive (TaT1 and CIS) Bladder Cancer, EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas and EAU Guidelines on Primary Urethral Carcinoma) which, together, present a comprehensive overview of the management of urothelial neoplasms (1-3).

1.2 Methodology

1.2.1 Data identification

Comprehensive literature searches were designed for each section of the MIBC guidelines with the help of an expert external consultant. Following detailed internal discussion, searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline & Embase on the Dialog-Datastar platform. The searches used the controlled terminology of the respective databases. Both Medline and EMTREE were analysed for relevant terms; urinary bladder neoplasms (Medline) and bladder cancer (Embase) were the narrowest single terms available.

Extensive use of free text ensured the sensitivity of the searches, although the subsequent concomitant workload for panel members having to assess the substantial body of literature greatly increased.

Search strategies covered the last 10 years for Medline and for Embase in most cases. Randomised controlled trial (RCT) strategies used were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform. Results of all searches were scan-read by panel members. In many cases there was a high ‘numbers needed to read’ due to the sensitivity of the search.

There is clearly a need for continuous re-evaluation of the information presented in the current guidelines by an expert panel. It must be emphasised that these guidelines contain information for the treatment of an individual patient according to a standardised approach.

The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2 (4). The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

It should be noted, however, that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (5-7).

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

1.2.2 Publication history

The EAU published the first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. As different treatment strategies are employed for these
conditions it was decided to split these topics up, resulting in a first publication of the MIBC guidelines in 2004, with subsequent updates in 2007, 2009, 2010, 2011, 2012 and this 2013 update. A quick reference document presenting the main findings is also available alongside several scientific publications (8-10).

All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.3 Summary of updated information
For this 2013 update, of note are the following changes:

Chapter 2 “Epidemiology and risk factors”;
• Section 2.2.8 Carcinoma in situ has been added.

Chapter 3 “Classification”;
• Sections 3.3, through 3.3.5 were revisited resulting in slightly adapted recommendations in section 3.3.4 (recommendations for the assessment of tumour specimens).
• Section 3.3.5 (pT2 substaging in node-negative disease after cystectomy) has been added.

Chapter 4 “Diagnosis and staging”;
• Sections 4.2.1.2 (CT imaging for local staging of MIBC), 4.2.2 (Imaging of lymph nodes in MIBC) and 4.2.3 (Upper urinary tract urothelial carcinoma) have been added, as well as section 4.2.5 (Future developments).

Chapter 6 “Neoadjuvant Chemotherapy”;
• A new section 6.2 (The role of imaging to assess treatment response) has been included. The text has been updated with new literature resulting in amended conclusions and recommendations (section 6.4).

Chapter 7 “Radical Surgery and Urinary Diversion”
• A new section 7.1.4 (MIBC and comorbidity) on co-morbidities and patient selection for orthotopic diversion has been added.

Chapter 12 “Metastatic disease”;
• New data has been added, in particular to section 12.3 (Standard first-line chemotherapy for “fit” patients).

Chapter 14 “Follow-up”;
• Additional data included on recurrences and secondary urethral tumours.

For all updated sections, the literature has been assessed for currency.

Updates of chapters 5 - 8 - 9 - 10 - 11 and 13 are foreseen for publication in 2014.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

*Modified from Sackett, et al. (4).

Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Modified from Sackett, et al. (4).
2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology
Bladder cancer is the ninth most common cancer diagnosis worldwide, with more than 330,000 new cases each year and more than 130,000 deaths per year, with an estimated male-female ratio of 3.8:1.0 (1). At any point in time, 2.7 million people have a history of urinary bladder cancer (1).

At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC). Among patients treated with radical cystectomy because of MIBC, 57% had muscle invasion at presentation, while 43% were initially diagnosed with NMIBC that progressed despite organ-preserving treatment (2). Approximately one-third of patients diagnosed with MIBC have undetected metastases at the time of treatment for the primary tumour (3), while 25% of patients who undergo radical cystectomy present with lymph node involvement at the time of surgery.
2.2 Risk factors for bladder cancer

2.2.1 Tobacco smoking

Tobacco smoking is the most well-established risk factor for bladder cancer, causing 50-65% of male cases and 20-30% of female cases (4). A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias, and confounding can be ruled out with reasonable confidence (5).

The incidence of bladder cancer is directly related to the duration of smoking and the number of cigarettes smoked per day (6). The risk of bladder cancer is also higher in those who start smoking at a young age or who are exposed to environmental tobacco smoke during childhood (7). A recent meta-analysis looked at 216 observational studies on cigarette smoking and cancer from 1961 to 2003, with reported estimates for current and/or former smokers. The pooled risk estimates for bladder cancer demonstrated a significant association for both current and former smokers. In an analysis of 21 studies, the overall relative risk calculated for current smokers was 2.77 (95% confidence interval [CI], 2.17 to 3.54), while an analysis of 15 studies showed that the overall relative risk calculated for former smokers was 1.72 (95% CI, 1.46 to 2.04) (8). An immediate decrease in the risk of bladder cancer was observed in those who stopped smoking. The reduction was about 40% within 1-4 years of quitting smoking and 60% after 25 years of cessation (6). Encouraging people to stop smoking would result in the incidence of bladder cancer decreasing equally in men and women.

2.2.2 Occupational exposure to chemicals

Occupational exposure is the second most important risk factor for bladder cancer. Work-related cases have accounted for 20-25% of all bladder cancer cases in several series. The substances involved in chemical exposure have been benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4′-methyleneedianiline, and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used (9). The risk of bladder cancer due to occupational exposure to carcinogenic aromatic amines is significantly greater after 10 years or more of exposure; the mean latency period usually exceeds 30 years (10,11). The chemicals involved have contributed minimally to the current incidence of bladder cancer in Western countries because of strict regulations. In fact, there has been a trend towards a decrease in bladder cancer due to occupational exposure, as indicated by a pooled analysis of 11 European case-control studies on bladder cancer between 1976 and 1996 (12).

An example of occupational exposure is that of aromatic amines. These are established carcinogens for urothelium and can be inactivated by a metabolic acetylation pathway. The presence of an NAT2 slow-acetylation genotype has been associated with a higher risk of bladder cancer (13), suggesting that patients who are slow acetylators may be more susceptible to bladder cancer than rapid acetylators. Other risk factors include phenacetin, which the International Agency for Research on Cancer (IARC) included in 1987 among proven human carcinogens. Some studies have suggested that the risk of bladder cancer due to phenacetin is dose-dependent; however, the data concerning its metabolite acetaminophen are controversial (14).

2.2.3 Radiotherapy

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 (15). A recent population cohort study identified 243,082 men treated for prostate cancer between 1988 and 2003 in the Surveillance, Epidemiology and End Results database (SEER) in the USA. The standardised incidence ratios for bladder cancer developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population. The increased risk of bladder cancer in patients undergoing ERBT, BT, or ERBT-BT should be taken into account during follow-up, although the likelihood of mortality was described as very low in a recent study (16). It has recently been proposed that patients who have received radiotherapy for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder and rectal secondary malignancies (17). Nevertheless, since longer follow-up data are not yet available, and as bladder cancer requires a long period to develop, patients treated with radiation and with a long life-expectancy are at highest risk and should be followed up closely (17).

2.2.4 Dietary factors

Several dietary factors have been considered to be related to bladder cancer; however, the links remain controversial. Currently, there is limited evidence of a causal relationship between bladder cancer and dietary factors. A meta-analysis of 38 articles reporting data on diet and bladder cancer supported the hypothesis that vegetable and fruit intake reduces the risk of bladder cancer (18). For bladder cancer, there appears to be no association between dietary transfatty acid (TFA) intake and an increased risk, as observed for prostate cancer (19).
2.2.5 **Bladder schistosomiasis**

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean (20). Although there is a well-established relationship between squamous cell carcinoma of the bladder and schistosomiasis, the trends are changing for bladder cancer in endemic zones such as Egypt. Data from the National Cancer Institute (NCI) in Cairo, the largest tertiary cancer hospital in Egypt, showed that patients diagnosed in 2005 had a six-fold higher chance of developing urothelial carcinoma in comparison with patients diagnosed in 1980 (21). This shift from squamous cell carcinoma to urothelial carcinoma is attributed to a decline in the detection of bilharzia eggs in urine samples, probably due to better control of the disease in rural populations (22,23).

2.2.6 **Chronic urinary tract infection**

Muscle-invasive bladder cancer, particularly invasive squamous cell carcinoma, has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between bladder cancer and UTIs has been observed in several case-control studies, which have reported a twofold increased risk of bladder cancer in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias (24). Furthermore, to date, no clear relationship between any bacterial or viral infection and bladder cancer has been established in prospective studies (25). However, an increased risk of bladder cancer has been described in patients with long-term indwelling catheters (26).

2.2.7 **Chemotherapy**

The use of cyclophosphamide, an alkylating agent used to treat lymphoproliferative diseases and other nonneoplastic diseases, has been correlated with subsequent development of MIBC, with a latency period of 6-13 years. Acrolein is a metabolite of cyclophosphamide and is responsible for the increase in the incidence of bladder cancer. This effect occurs independently of the association of haemorrhagic cystitis with the same treatment (27,28) and was counteracted with concomitant application of mercaptog-ethanesulfonate (MESNA) (29).

2.2.8 **Synchronous and metachronous upper urinary tract tumours**

In some cases, there is an association between upper tract urothelial carcinoma (UTUC) and bladder cancer. The incidence of UTUC after a diagnosis of NMIBC has been reported to be between 1.7% and 26%. Although synchronous UTUC and NMIBC are uncommon, 46% of UTUCs are invasive.

In a retrospective review of 1,529 patients with primary non-muscle-invasive bladder carcinoma who underwent initial examination of the upper urinary tract with excretory urography, those with a tumour in the bladder trigone were almost six times more likely to develop a synchronous tumour in the upper urinary tract (30). Examination of the upper urinary tract alone in patients with a tumour in the trigone or with multiple bladder tumours was capable of diagnosing 41% or 69% of UTUCs, respectively. In multiple and high-risk tumours, there is an increased risk of tumour recurrence in the upper urinary tract. Carcinoma in situ (CIS) in the bladder is an important risk factor for subsequent upper urinary tract recurrence (31). As well, it has been shown in various studies that tumour involvement of the distal ureter at RC is an independent risk factor for metachronous upper urinary tract (mUUT) recurrence (32,33), with an approximately 2.6-fold increase in the relative risk (33).

In addition, the overall incidence of bladder cancer developing after treatment for UTUC has been reported in the literature as 15-50%. Level 1 evidence from prospective randomised trials is not yet available. Intraluminal tumour seeding and pan-urothelial field change effects have both been proposed to explain intravesical recurrences. In most cases, bladder cancer arises in the first 2 years after UTUC management. However, the risk is lifelong, and repeat episodes are common. No variables can be used to predict future bladder cancer recurrence in UTUC patients reliably. A history of bladder cancer prior to UTUC management and upper tract tumour multifocality are the only commonly reported clinical risk factors in the current literature (34).

2.2.9 **Gender**

In a retrospective study of patients who had undergone radical cystectomy, it was found that women were more likely to be diagnosed with primary muscle-invasive disease than men (85% vs. 51%) (2). It has been suggested that women are more likely to be older than men when diagnosed, with a direct effect on their survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, as the differential diagnosis in women includes diseases that are more prevalent than bladder cancer (35).

Differences in the gender prevalence of bladder cancer may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, postmenopausal status was associated with an
increase in bladder cancer risk even after adjustment for smoking status. This result suggests that the
differences in oestrogen and androgen levels between men and women may be responsible for some of the
difference in the gender prevalence of bladder cancer (36-38). Recently, a study of Egyptian women found that
younger age at menopause (< 45 y) was a factor associated with an increasing risk of bladder cancer, while
multiple pregnancies and use of oral contraceptives were associated with decreased odds of having bladder
cancer. The strength of the associations was greater in the urothelial carcinoma group (39). A recent publication
mentions that female gender has a significant negative impact on cancer-specific survival in patients who are
younger and have lymphovascular invasion, possibly suggesting different clinical phenotypes (40).

2.2.10 Ethnic and socioeconomic status
There are limited data on this topic, but a study based on 13,234 cases diagnosed in the SEER database in
the period 1979-2003 showed that the survival time from diagnosis was significantly lower among cancer
cases in patients with low socioeconomic status (SES) compared with those with higher SES. Hazard ratios
for all causes and cancer-specific mortality among blacks in comparison with whites for eight of the most
common types of cancer combined lost statistical significance after adjustment for SES factors and treatments.
However, blacks still had unfavourable prognoses in comparison with whites even after adjustment for SES and
treatment for tumours such as breast, colorectal, and urinary bladder cancer (41).

2.3 Conclusions and recommendations for epidemiology and risk factors

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The incidence of muscle-invasive disease has not changed for 5 years.</td>
<td></td>
</tr>
<tr>
<td>Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.</td>
<td>2a</td>
</tr>
<tr>
<td>The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy, or a combination of EBRT and brachytherapy, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.</td>
<td>3</td>
</tr>
<tr>
<td>The estimated male-to-female ratio for bladder cancer is 3.8 : 1.0. Women are more likely to be diagnosed with primary muscle-invasive disease than men.</td>
<td>3</td>
</tr>
<tr>
<td>Currently, treatment decisions cannot be based on molecular markers.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The principal preventable risk factor for muscle-invasive bladder cancer is active and passive smoking.</td>
<td>B</td>
</tr>
<tr>
<td>Notwithstanding stricter regulations, workers should be informed about the potential carcinogenic effects of a number of recognised substances, duration of exposure, and latency periods. Protective measures should be recommended.</td>
<td>A</td>
</tr>
</tbody>
</table>

2.4 References


3. CLASSIFICATION

3.1 Tumour, node, metastasis classification

The tumour, node, metastasis (TNM) classification of malignant tumours is the method most widely used to classify the extent of cancer spread. Recently, a seventh edition was published, effective as of 2010 (1 (Table 3). There are no significant modifications in it for bladder cancer in comparison with the previous edition (2002).

Table 3: TNM classification of urinary bladder cancer (2009)

<table>
<thead>
<tr>
<th>T - Primary Tumour</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: “flat tumour”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour invades superficial muscle (inner half)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour invades deep muscle (outer half)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades perivesical tissue:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>microscopically</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>macroscopically (extravesical mass)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades prostate stroma, seminal vesicles, uterus, or vagina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades pelvic wall or abdominal wall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional Lymph Nodes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph-node metastasis</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in common iliac lymph node(s)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant Metastasis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

3.2 Histological grading of non-muscle-invasive bladder tumours

A new classification of noninvasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) in 1998. It was published by the WHO in 2004 (2,3) (see table below). Its major contribution is a detailed histological description of the various grades using specific cytological and architectural criteria. A web site (http://www.pathology.jhu.edu/bladder) illustrating examples of various grades has been developed to improve accuracy in using the system.

World Health Organization (WHO) grading for urothelial papilloma in 1973 and 2004 (2,3)

<table>
<thead>
<tr>
<th>1973 WHO grading</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1:</td>
<td>well differentiated</td>
<td></td>
</tr>
<tr>
<td>Grade 2:</td>
<td>moderately differentiated</td>
<td></td>
</tr>
<tr>
<td>Grade 3:</td>
<td>poorly differentiated</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2004 WHO grading</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade papillary urothelial carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade papillary urothelial carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2.1 WHO grading

The 2004 WHO grading differentiates between papilloma, papillary urothelial neoplasms of low malignant potential (PUNLMP), and low-grade and high-grade urothelial carcinomas.
Papilloma is composed of a delicate fibrovascular core covered by normal urothelium. PUNLMP is defined as a papillary fibrovascular growth covered with proliferated urothelium, exceeding the normal thickness. Although PUNLMPs have a negligible risk of progression, they are not completely benign and have a tendency to recur (3b). The low-grade papillary urothelial carcinoma group includes the majority of former grade 1 (WHO 1973) cases and some former grade 2 cases (if there is variation in the architectural and cytological features at high magnification).

Use of the 2004 WHO classification is recommended, as this should result in a uniform diagnosis of tumours better classified according to their risk potential. However, until the 2004 WHO classification has been validated by further clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications (4). Most clinical trials published so far on bladder tumours have been performed using the 1973 WHO classification, so this is used in the 2013 edition of the guidelines.

3.3 Pathology
3.3.1 Handling of specimens by urologists
In transurethral resection (TUR) specimens, the superficial and deep areas of the tumour must be sent to the pathology laboratory separately. If random biopsies of the flat mucosa have been carried out, each biopsy of the flat mucosa must also be sent separately.

In radical cystectomy, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin. In some circumstances, this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed en bloc with the specimen should be checked, preferably by the urological surgeon (5).

3.3.2 Handling of specimens by pathologists
Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists (6,7). It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area must be included.

It is mandatory to study the urethra, ureter, and prostate in men and the radial margins (8). In urethra-sparing cystectomy, the level of urethral dissection, the completeness of the prostate specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra (in women) should be documented. All lymph node specimens should be provided in their totality, in clearly labeled containers. In case of doubt, or if there is adipose differentiation of the lymph node, the entire specimen is to be included.

Lymph nodes should be counted and measured on slides, and capsular bursting and the percentage of lymph-node invasion should be reported, as well as vascular emboli. If there is metastatic spread into the perivesical fat without real lymph node structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Fresh frozen sections can be helpful in determining the treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator lymph nodes, but similar studies are warranted to confirm these results (9). As yet, fresh frozen sections have mainly been used in the setting of clinical studies.

3.3.3 Pathology of muscle-invasive bladder cancer
In muscle-invasive bladder cancer, there are usually no cases of PUNLMP or low-grade carcinoma. All cases are high-grade urothelial carcinomas. For this reason, no further prognostic information can be provided by grading the lesions (10). However, some morphological subtypes can be helpful in assessing the prognosis and treatment options. The following differentiation is currently used:

1. Urothelial carcinoma (more than 90% of all cases).
2. Urothelial carcinomas with squamous and/or glandular partial differentiation (11,12).
3. Micropapillary urothelial carcinoma.
4. Nested carcinoma (13).
5. Urothelial carcinomas with trophoblastic differentiation.
7. Spindle cell carcinomas.

For staging, TNM 2002/2010 (6th or 7th edition) is recommended (both editions are identical for bladder cancer). Blood vessel invasion and lymph node infiltration have an independent prognostic significance (15). It
appears that the pN category is closely related to the number of lymph nodes studied by the pathologist (16). For this reason, some authors have reported that more than nine lymph nodes have to be investigated in order to reflect pN0 appropriately (17).

3.3.4 **pT2 substaging in node-negative disease after cystectomy**

In 1997, the American Joint Committee on Cancer (AJCC) updated the TNM staging system and introduced substaging for the T2 tumour stage (18). The latest version was published in 2009, but without any changes from the previous 2002 version (1). This substratification was intended to provide better risk assessment for follow-up strategies and to improve counselling of patients for adjuvant treatment options (19). However, in patients with node-negative, pT2a-T2b bladder cancer, subsequent studies have challenged the prognostic importance of substratifying pT2 tumours into those involving the inner half of the detrusor muscle (T2a) or its outer half (T2b) and have suggested that the two substages should be consolidated into one (20-22). The limitations of these studies were that the extent of lymphadenectomy and the numbers of retrieved lymph nodes were not exactly reported, which may have biased the final survival analysis (22). In addition, patients with non-urothelial cell carcinoma and those who underwent neoadjuvant chemotherapy were not excluded from the analyses (20,21).

A recent multicentre series including 565 patients with pT2 urothelial carcinoma of the bladder therefore attempted to overcome these limitations and reported significant differences in survival between the two substages in node-negative pT2 disease (23). These findings have also been confirmed in a single-centre Egyptian cohort including 1,737 patients with pT2 bladder cancer, 54% of whom had squamous cell carcinomas (24). Furthermore, significant differences in the recurrence-free and cancer-specific survival have also been confirmed in a single-centre series of patients with pT2 urothelial carcinoma of the bladder who were treated with an extended pelvic lymphadenectomy approach (25). pT2 substaging has also recently been incorporated into prognostic models designed to predict upstaging and recurrence after radical cystectomy. A multicentre study has suggested using a weighted prognostic model for patients with node-negative pT2 bladder cancer. Among various independent risk factors (presence of high-grade disease or lymphovascular invasion), pT2 substaging was the strongest one for recurrence-free survival (26). This finding was also confirmed in a large single-centre series including 948 patients with cT2N0M0 bladder carcinoma, in which pT2 substaging was also found to be predictive of the risk of recurrence (27,28). In conclusion, the present data support the current approach using substratification of node-negative pT2 bladder cancer and can be used to tailor the need for adjuvant treatment.

New prognostic markers are under investigation (29). Currently, there is insufficient evidence to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, as it does not yield sufficient data on which to base treatment in an individual patient.

3.3.5 **Recommendations for assessing tumour specimens**

<table>
<thead>
<tr>
<th>Mandatory evaluations</th>
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<tbody>
<tr>
<td>Histological subtype</td>
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<tr>
<td>Depth of invasion</td>
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<tr>
<td>Resection margins, including CIS</td>
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<td>Extensive lymph-node representation</td>
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<tr>
<th>Optional evaluation</th>
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<tbody>
<tr>
<td>Bladder wall blood vessel invasion</td>
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<td>CIS, carcinoma in situ</td>
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</table>

3.4 **Conclusions and recommendations for classification in MIBC**

<table>
<thead>
<tr>
<th>Conclusions and recommendations</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>The AJCC substratification into node-negative pT2 bladder cancer is of prognostic value after radical cystectomy in patients but who have not undergone neoadjuvant chemotherapy.</td>
<td>3</td>
<td>B</td>
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<tr>
<td>Substaging into pT2a and b is not tenable in TURB specimens.</td>
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<tr>
<td>The pathological depth of muscle invasion should be reported by the pathologist in patients with node-negative pT2 bladder cancer after cystectomy.</td>
<td>3</td>
<td>B</td>
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</table>
3.5 References


4. DIAGNOSIS AND STAGING

4.1 Primary diagnosis

4.1.1 Symptoms

Painless haematuria is the most common presenting complaint. Others include urgency, dysuria, increased frequency and, in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

4.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TUR to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall (1,2). However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging) some caution is suggested with the interpretation of bimanual examination (3).
4.1.3 **Bladder imaging**

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and or resection for histopathological diagnosis and staging.

4.1.4 **Urinary cytology and urinary markers**

Examination of a voided urine or bladder-washings for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3) and is useful indicator in cases of high-grade malignancy or CIS.

Positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% (4,5) (LE: 2b). However, negative cytology does not exclude tumour. Cytology should be performed on fresh urine with adequate fixation. Early morning urine is not suitable as cytolysis may often be present. There is no known urinary marker specific for the diagnosis of invasive bladder cancer (6).

4.1.5 **Cystoscopy**

Ultimately, the diagnosis of bladder cancer is made by cystoscopy and histological evaluation of resected tissue. In general, cystoscopy is initially performed in the office using flexible instruments. If a bladder tumour has been visualised unequivocally in earlier imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), a diagnostic cystoscopy may be omitted and the patient can proceed directly to TUR for a histological diagnosis.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended.

The use of photodynamic diagnosis could be considered, especially if a T1 high-grade tumour is present, to find associated CIS. The additional presence of CIS may lead to a modified treatment plan (see also Section 5.1). Photodynamic diagnosis is highly sensitive for the detection of CIS; with experience, the rate of false-positives may be similar to the technique of regular white light cystoscopy (7).

4.1.6 **Transurethral resection (TUR) of invasive bladder tumours**

The goal of TUR is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection biopsies.

The strategy of resection depends on the size of the lesion. Small tumours (less than 1 cm) can be resected en bloc, where the specimen contains the complete tumour plus a part of the underlying bladder wall including bladder muscle. Larger tumours have to be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and the edges of the resection area. At least the deepest part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him to make a correct diagnosis. Avoid cauterisation as much as possible during resection to prevent tissue destruction. In cases in which photodynamic diagnosis is used, fluorescing areas should be biopsied in order to detect primary or associated CIS lesions. Fluorescence endoscopy should not be used in the first 6 weeks after any instillation therapy due to a higher rate of false-positive results.

4.1.7 **Random bladder and prostatic urethral biopsy**

Bladder tumours are often multifocal and can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas, indistinguishable from inflammation, or may not be visible at all.

The biopsies from normal-looking mucosa in patients with invasive bladder tumours, so-called random biopsies (R-biopsies) show a low yield (8). Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitiser, which was experimentally 5-aminolevulinic acid (5-ALA), and more recently hexaminolaevulinate (HAL), following approval by the European Medicines Agency. It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumours, particularly CIS (9-12) (LE: 2a). However, false-positive results may be induced by inflammation, recent TUR or intravesical instillation therapy. A recent multicentre, prospective, international trial showed that, in experienced hands, the rate of false-positives is not higher than seen in regular, white-light cystoscopy (7). Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers.

The involvement of the prostatic urethra and ducts in male patients with bladder tumours is reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the
presence of bladder CIS and in multiple tumours (13,14) (LE: 3). Identification of involvement of the prostatic urethra can be determined either at the time of primary TUR or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative predictive value and is more accurate (15-17).

4.1.8 Second resection
There is a significant risk of leaving residual tumour in the bladder after the initial TUR (18,19) (LE: 1). Residual disease is observed in 33-53% of patients (19-25). The tumour may be understaged by the initial resection. There is a 4-25% probability that tumours initially staged as non-muscle invasive are muscle-invasive (20,21). Correct staging is extremely important since it will directly affect the type of treatment. A second TUR should always be performed if the initial resection has been incomplete, e.g. when multiple and/or large tumours are present, or if the pathologist reports that the specimen contains no muscle tissue. A second TUR should be performed when a high-grade, non-muscle-invasive tumour or a T1 tumour is detected at the initial TUR. There is no consensus about the strategy and timing of a second TUR. Most authors recommend resection at 2-6 weeks after the initial TUR. The procedure should include a resection of the primary tumour site.

4.1.9 Concomitant prostate cancer
Ruling out prostate cancer is important since 25-46% of patients undergoing cystectomy for bladder cancer (26,27) have prostate cancer confirmed by histopathology analysis of the resected specimen.

4.1.10 Specific recommendations for primary assessment of presumably invasive bladder tumours
(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder cancer [28])

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.</td>
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<tr>
<td>Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder carcinoma in situ is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.</td>
<td>C</td>
</tr>
<tr>
<td>In women undergoing a subsequent orthotopic neobladder, procedure information is required (including a histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.</td>
<td>C</td>
</tr>
<tr>
<td>The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle tissue are present in the specimen.</td>
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</table>

4.2 Imaging for staging MIBC
The treatment and prognosis for MIBC is determined by tumour stage and grade (29). In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist with treatment selection. Tumour staging must be accurate to ensure the correct choice of treatment is made. Imaging parameters required for staging MIBC are:
- the extent of local tumour invasion;
- tumour spread to lymph nodes;
- tumour spread to the upper urinary tract and other distant organs (liver, lungs, bones, peritoneum, pleura, adrenal glands and others).

4.2.1 Local staging of MIBC
Both CT and MRI may be used for assessment of local invasion, but they are unable to diagnose accurately microscopic invasion of perivesical fat (T3a) (30). The principal aim of CT and MRI is therefore to detect T3b disease or higher.

4.2.1.1 MRI for local staging of invasive bladder cancer
Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT (31). Dynamic contrast-enhanced MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because
enhancement of the tumour occurs earlier than the normal bladder wall due to neovascularisation (32-34).

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in a fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Alternatively, contrast-enhanced CT could be performed using iodinated contrast media (35) (LE: 4).

4.2.1.2 CT imaging for local staging of MIBC
The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages Ta to T3a, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% (36) and increases with more advanced disease (37).

4.2.2 Imaging of lymph nodes in MIBC
The assessment of metastases to lymph nodes based simply on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of lymph node metastases is low, ranging from 48-87%. Specificity is also low as nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of lymph node metastases in a variety of primary pelvic tumours (38-43). Pelvic nodes, measured on CT or MRI, greater than 8 mm and abdominal nodes greater than 10 mm in a maximum short-axis diameter, should be regarded as pathologically enlarged. (44,45).

Currently, there is no evidence supporting the routine use of positron emission tomography (PET), computed tomography (PET/CT) in the nodal staging of bladder cancer, although the method has been evaluated with varying results in small prospective trials (46-49).

4.2.3 Upper urinary tract urothelial carcinoma (UTUC)
Excretory-phase computed tomography urography is the imaging technique with the highest diagnostic accuracy for UTUC and has replaced conventional intravenous urography and ultrasonography as the first-line imaging test for investigating high-risk patients (50). The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99 depending on the technique used (51-58). Attention to technique is therefore very important for optimum results.

For UTUC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results and to provide information regarding the grade of the tumour to aid in the choice of treatment. (52,53,59-61). This is usually performed ureteroscopically.

4.2.4 Distant metastases other than lymph nodes
Prior to any treatment aimed at cure, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect metastases to lung and liver. Metastases to bones or brain at the presentation of invasive bladder cancer are rare. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases (62,63). Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy (64,65) (LE: 2b).

4.2.5 Future developments
Evidence is accruing in the literature suggesting that FDG-PET/CT might have potential clinical use for staging metastatic bladder cancer (66,67) but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made.

Recently, the first study was published showing the feasibility of diffusion-weighted imaging (DWI) over T2W and DCE for assessing the therapeutic response to induction chemotherapy against MIBC (68). The high specificity of DWI indicates that DWI is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.
**Conclusions and recommendations for staging in MIBC**

**Conclusions**

<table>
<thead>
<tr>
<th>Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.</th>
</tr>
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<tbody>
<tr>
<td>There is insufficient data on the use of DW MRI and FDG-PET/CT in MIBC currently to allow a recommendation to be made.</td>
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</table>

**Recommendations**

<table>
<thead>
<tr>
<th>In patients with confirmed muscle-invasive bladder cancer, CT of the chest, abdomen and pelvis is the optimal form of staging, including excretory-phase CT urography for complete examination of the upper urinary tracts.</th>
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<tbody>
<tr>
<td>Excretory-phase CT urography is preferred to MR urography for diagnosing UTUCs in terms of greater diagnostic accuracy, less cost, and greater patient acceptability. MR urography is used when CT urography is contra-indicated for reasons related to contrast administration or radiation dose.</td>
</tr>
<tr>
<td>Ureteroscopic-guided biopsy is recommended for histopathological confirmation of diagnosis in the pre-operative assessment of UTUC.</td>
</tr>
<tr>
<td>CT or MRI is recommended for staging locally advanced or metastatic disease in patients in whom radical treatment is being considered.</td>
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<tr>
<td>CT and MRI are generally equivalent in diagnosing local and distant abdominal metastases but CT is preferred to diagnose pulmonary metastases.</td>
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</table>

**References**


5. TREATMENT FAILURE OF NON-MUSCLE INVASIVE BLADDER CANCER

5.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rate of NMIBC is strongly associated with tumour grade and invasion into the lamina propria. The progression to T2 tumours varies from 6% to 25% in Ta and from 27% to 48% in T1 tumours of all grades. Inter- and intra-observer varying abilities in grading and staging and the completeness of TUR are key variables that confound the results of present long-term studies of TUR, with or without intravesical therapy.

The understaging error in TaT1 tumours of 35-62% presented in large cystectomy series is due to the presence of recurrent tumours of largely unknown pre-cystectomy therapy and the lack of a second TUR (1-3) (LE: 3). The latter identifies 24-49% of T2 tumours that have been diagnosed initially as non-muscle-invasive tumours (4,5) (LE: 3). However, in spite of these disadvantages, recent meta-analyses have demonstrated that Bacillus Calmette-Guérin (BCG) therapy prevents the risk of tumour recurrence (6,7). Two other meta-analyses showed that BCG therapy decreases the risk of tumour progression (8,9).

So far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy (8-10) (LE: 1).

The disease progression rate is low in patients with small tumours (< 3 cm) and without associated CIS. Twenty per cent of patients progress within 5 years, with approximately 90% of patients keeping their intact bladder during follow-up of up to 10 years (11) (LE: 2). However, in a recently published, prospective, multicentre trial, the progression rate was significantly lower than previously reported, even when the presence of concomitant CIS was considered. This was probably due to the combination of a second resection, prior to inclusion in the trial and maintenance treatment as part of the protocol (12) (LE: 1b).

Progression to MIBC significantly decreases cancer-specific survival (CSS). In a review of 19 trials and 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment in case of intravesical therapy failure (13,14).
According to the EAU NMIBC Guidelines, it is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression (14). These are:

- multiple and/or large (> 3 cm) T1, high-grade (G3) tumours;
- T1, high-grade (G3) tumours with concurrent CIS;
- recurrent T1, high-grade (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- micropapillary variant of urothelial carcinoma.

Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the 10-year recurrence-free survival is approximately 80% and similar to TUR and BCG maintenance therapy (1,3,15,16) (LE: 3). In the case of recurrent TaT1, mostly associated with CIS, the understaging at the time of cystectomy is 34%, but the 10-year survival is not significantly different for patients with pT1 and pT2 tumours (17) (LE: 3). This is in contrast to an earlier report, which indicates a significantly worse outcome for patients with previous TUR(s) (18) (LE: 3).

Undoubtedly, patients with muscle-invasive recurrence are best treated with radical cystectomy. However, the outcome in terms of the presence of lymph node metastases and cancer-free survival may be inferior to patients with the same tumour stage, but who receive radical cystectomy at first presentation (19) (LE: 3).

There is uncertainty about the treatment of patients who develop tumour recurrence in spite of BCG therapy because of different BCG therapy schedules and the absence of a uniform definition of BCG failure. It has been indicated that the recurrence (persistence) of tumour at 9 months in spite of BCG therapy is associated with a 30% chance of invasive tumours and death due to metastatic disease (20) (LE: 3). Solsosa et al. demonstrated that 80% of patients who had persistent disease at 3 months progressed to muscle-invasive disease (21) (LE: 3). In addition, adequate tissue sampling from the prostatic urethra is an essential factor in considering the outcome of conservative treatment, since urethral tumours are associated with a significant decrease in tumour-free survival (22) (LE: 3). However, with careful selection and surveillance, a durable complete response can also be achieved in patients diagnosed with superficial bladder transitional cell carcinoma involving the prostatic urethra (23). Based on these findings, cystectomy should be performed in appropriate patients at least at 9 months, because additional BCG therapy yields a response rate of only 27-51% and of unknown duration (24,25) (GR: C). Salvage chemotherapy is associated with a limited response and should not be offered (26,27) (LE: 3).

Patients with disease recurring within 2 years of initial TUR plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease (19) (LE: 3; GR: C).

### 5.2 Carcinoma in situ

Primary CIS confined to the bladder is treated with intravesical BCG, yielding a complete response rate of 83-93% (28,29) (LE: 2). Carcinoma in situ associated with TaT1 is treated according to the overt tumour.

Approximately 50% of patients develop recurrent disease with muscle invasion or extravesical tumour (28,30) (LE: 2). Between 11% and 21% die of the disease within 5-7 years after an initial complete response (28,31) (LE: 2). Non-responders or incomplete responders have a significant risk of tumour progression of 33-67% (21,32) (LE: 2).

The current guidelines on non-muscle-invasive bladder cancer define BCG failure as:

- a. Whenever muscle-invasive tumour is detected during follow-up.
- b. If high-grade, non-muscle-invasive tumour is present at both 3 and 6 months.
- c. High-grade recurrence after BCG (more recurrences, Ta → T1 or upgrading, appearance of CIS).

In patients with tumour present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases, both in patients with papillary tumours and CIS but with increasing risk of progression.

There are now several bladder preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy (33). However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time (34-36).
5.3 Recommendations for treatment failure of non-muscle-invasive bladder cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>In all T1 tumours at high risk of progression (i.e. high grade, multifocality, carcinoma in situ, and tumour size, as outlined in the EAU guidelines for Non-muscle-invasive bladder cancer [14]), immediate radical treatment is an option.</td>
<td>C</td>
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<tr>
<td>In all T1 patients failing intravesical therapy, radical treatment should be offered.</td>
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5.4 References


6. NEOADJUVANT CHEMOTHERAPY

6.1 Introduction
The standard treatment for patients with muscle-invasive bladder cancer is radical cystectomy. However, this ‘gold standard’ only provides 5-year survival in about 50% of patients (1-5). In order to improve these unsatisfactory results, the use of peri-operative chemotherapy has been explored since the 1980s. There are many advantages of administering chemotherapy before planned definitive surgery (or radiation therapy) to patients with operable urothelial carcinoma of the urinary bladder, muscle-invasive, clinically negative nodes (cN0), including:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of in-vivo chemosensitivity.
- Tolerability of chemotherapy is expected to be better before cystectomy rather than after.
- Hypothetically patients with micrometastatic disease might respond to neoadjuvant therapy and reveal a favourable pathological status, determined mainly by negative lymph node status and negative surgical margins.

6.2 The role of imaging to assess treatment response
For patients who respond to neoadjuvant chemotherapy, known as responders, and especially those who show a complete response (pT0 N0), neoadjuvant chemotherapy has a major impact on overall survival (OS) (6). The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks of neoadjuvant chemotherapy. The best option is early pre-operative identification of responders utilizing tumour molecular profiling in TUR-specimens, but there is still a lack of reliable methods for clinical use (7). Alternatively, some investigators are exploring imaging methods for the early identification of responders at the time of treatment cycles.

A small pilot study, using PET imaging to monitor response to chemotherapy, suggested that alterations in tumour metabolism occur long before visible changes appear on CT or MRI (8). In a recent retrospective evaluation of 27 patients undergoing total or partial cystectomy after neoadjuvant chemotherapy (n = 8), neoadjuvant chemoradiation (n = 10), or no neoadjuvant therapy (n = 9), tumour stage assessed by MRI was only consistent with post-cystectomy pathology findings in 59.3 % of the patients (9).

Another study evaluated conventional vs. fast dynamic contrast-enhanced MRI before and after 2, 4 and 6 cycles of MVAC (10). Only 9 of 22 patients subsequently underwent cystectomy. After two MVAC cycles, the
accuracy, sensitivity, and specificity of conventional MRI in distinguishing responders from non-responders were 73%, 79%, and 63%, respectively. With the dynamic technique, these figures were 95%, 93%, and 100%, respectively. The differences were not significant. The authors concluded that after two cycles, dynamic MRI helped detect 13 of 14 responders and eight of eight non-responders.

Finally, the application of results from the imaging of treatment responses in the adjuvant (metastatic) setting to the neoadjuvant setting should be done with caution. Finding robust and reproducible methods of imaging, early in the selection process for neoadjuvant chemotherapy, remains challenging.

In the adjuvant setting, present metastatic marker lesions are evaluated that allow testing of different and new imaging response criteria (11), while in the neoadjuvant setting the only marker lesion is the primary tumour itself. Tumour size measurement prior to and during neoadjuvant chemotherapy should be done to identify responders and non-responders.

Attempts have been made in small published series to identify responders while monitoring patients undergoing neoadjuvant chemotherapy, suggesting that the response after two cycles of neoadjuvant chemotherapy is related to outcome, but firm conclusions cannot yet be made (8,9).

The meaning of stable disease after two cycles of neoadjuvant chemotherapy is unknown. To identify progression during neoadjuvant chemotherapy imaging is being used, notwithstanding the lack of published data to support its efficacy.

### 6.2.1 Conclusions and recommendation

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Overtreatment of non-responders and those in the non-target population (i.e. patients without micrometastatic disease) is a major drawback in using neoadjuvant chemotherapy.</td>
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<tr>
<td>Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on overall survival.</td>
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</table>

**Recommendations**

In case of progression under neoadjuvant chemotherapy, this treatment should be discontinued.

### 6.3 Disadvantages of neoadjuvant chemotherapy

The disadvantages of neoadjuvant chemotherapy are:

- Clinical staging using CT or MR imaging may often result in over- and understaging and has a staging accuracy of only 70% (12,13). Overtreatment is the possible negative consequence.

- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (14,15).

The side effects of neoadjuvant chemotherapy affecting the outcome of surgical morbidity need to be considered. In one randomised trial (16), the same distribution of post-operative complications grade 3-4 was seen in both trial arms (16). In the combined Nordic trials NCS1 + NCS2, (n = 620), neoadjuvant chemotherapy did not have any major adverse effect on the percentage of performable cystectomies. In the intention-to-treat analysis, the cystectomy-frequency was 86% in the experimental arm and 87% in the control arm, while 71% of patients received all three chemotherapy cycles (17).

Several randomised phase III trials investigated the question of whether or not neoadjuvant chemotherapy improved survival, with conflicting results (18-34).

Differences in trial design were mainly the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles planned. From the statistical point of view, the studies differed in size, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment allowed (cystectomy and/or radiotherapy). Patients had to be fit for cisplatin. Because of the lack of clarity, even though a considerable number of randomised trials had been performed, three meta-analyses were undertaken to answer the very important question of whether or not neoadjuvant chemotherapy prolongs survival (35-37).

- The first meta-analysis, published in 2003 (35), included 10 randomised trials (except for results of the INT 0080-study [26]) and showed a 13% reduction in the risk of death, equivalent to 5% absolute benefit at 5 years (increased overall survival [OS] from 45% to 50%).
The second meta-analysis, published in 2004 (36), included 11 of 16 randomised trials with OS data of 2605 patients. A statistically significant decrease in the risk of death (10%) was seen, corresponding to an absolute improvement in OS of 5% (from 50% to 55%).

In the most recent meta-analysis, published in 2005 (38), with updated independent patient data of 11 randomised trials (3005 patients), a statistically significant survival benefit in favour of neoadjuvant chemotherapy was also seen. The results of this analysis confirmed the previously published data and showed 5% absolute improvement in survival at 5 years. The Nordic combined trial showed an absolute benefit of 8% in survival at 5 years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat (17). Of note, only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful benefit (35,37); the regimens tested were MVA(E)C, CMV, CM, cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and CarboMV. To date, it is unknown if more modern chemotherapy regimens are as effective.

The updated analysis of the largest randomised phase III trial (24) with a median follow-up of 8 years confirmed the former results and provided some additional interesting findings:

- A 16% risk reduction of death.
- An improvement in 10-year survival from 30% to 36% with neoadjuvant CMV.
- No benefit for locoregional control and locoregional disease-free survival, with the addition of neoadjuvant CMV independent of the definitive treatment.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastatic nodal deposits are detected more often in post-cystectomy specimens of these extensive tumours (38). Further data support the use of neoadjuvant chemotherapy in the subgroup of T2b-T3b tumours (former classification T3), which has been shown to provide a modest but substantial improvement in long-term survival and significant downstaging.

### 6.4 Conclusions and recommendations for neoadjuvant chemotherapy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival.</td>
<td>1a</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations.</td>
<td></td>
</tr>
<tr>
<td>In current routine clinical practice, it is difficult to select patients who will respond to neoadjuvant chemotherapy due to the lack of a widely applicable test. In the future, genetic markers, in a ‘personalised medicine’ setting, will make it easier to select patients for treatment and to differentiate responders from non-responders.</td>
<td></td>
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<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatinum-based combination therapy.</td>
<td>A</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy is not recommended in patients with PS ≥ 2 and/or impaired renal function.</td>
<td>B</td>
</tr>
</tbody>
</table>

### 6.5 References


7. RADICAL SURGERY AND URINARY DIVERSION

7.1 Removal of the tumour-bearing bladder

7.1.1 Background

Radical cystectomy is the standard treatment for localised MIBC in most countries of the Western world (1,2). Recent interest in patients’ quality of life (QoL) has increased the trend toward bladder preservation treatment modalities, like radio- and/or chemotherapy (see Chapters 9 and 10). Performance status and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better performance status. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a recent multivariate analysis (3). The analysis found an association between comorbid disease and adverse pathological and survival outcome following radical cystectomy (3). Performance status and comorbidity have a different impact on treatment outcome and must be evaluated independently (4).

Controversy remains about age, radical cystectomy and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients older than 80 years (3). The largest, retrospective, single-institution study on cystectomy to date found that patients above 80 years had increased post-operative morbidity but not an increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion (5). It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 7.1.4) (6).

7.1.2 Timing and delay of cystectomy

A retrospective series of 153 patients, with a clear indication for radical surgery of locally advanced bladder cancer, found that patients treated more than 90 days after the primary diagnosis showed a significant increase in extravesical disease (81 vs 52%) (7).

The delay in cystectomy not only affects the outcome of treatment, but also the type of urinary diversion. In organ-confined urothelial cancer of the bladder, the average time from primary diagnosis to cystectomy was 12.2 months in patients who received a neobladder and 19.1 months in those who received an ileal conduit. This was even more noticeable with organ-confined invasive cancer; the average time to surgery was 3.1 months with a neobladder and 15.1 months with an ileal conduit (8). Similar results have been observed in a series of 247 patients: recurrence-free survival and OS were significantly better in patients treated before 90 days compared to others treated after 90 days (9).

7.1.3 Indications

Traditionally, radical cystectomy was recommended for patients with MIBC T2-T4a, N0-Nx, M0 (1). Other indications include high-risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (see Chapter 5), as well as extensive papillary disease that cannot be controlled with TUR and intravesical therapy alone.

Salvage cystectomy is indicated for non-responders to conservative therapy, recurrences after bladder-sparing treatments, non-urothelial carcinomas (these tumours respond poorly to chemo- and radiotherapy), and as a purely palliative intervention, including in fistula formation, pain or recurrent macrohaematuria (see Section 8.1 Palliative cystectomy).

7.1.4 MIBC and comorbidity

Complications related to radical cystectomy may be directly related to pre-existing patient comorbidities as well as the surgical procedure, the bowel anastomosis, or the urinary diversion. A significant body of literature...
has evaluated the usefulness of age as a prognostic factor for radical cystectomy (10-12). Advanced age has been identified as a risk factor for complications due to radical cystectomy, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior radiotherapy (13), while an increased body mass index is associated with a higher rate of wound dehiscence and hernia (14).

7.1.4.1 Evaluation of comorbidity
Rochon et al. showed that an evaluation of comorbidity provides a better indicator of life expectancy in MIBC than does the patient’s age (15). The evaluation helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC (16).

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman et al., who demonstrated an association between comorbidity and adverse pathological and survival outcome following radical cystectomy (17). Similar results were found for the impact of comorbidities on cancer-specific and other-cause mortalities in a population-based competing risk analysis of more than 11,260 patients from the SEER registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased cancer-specific survival (18). Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes (19).

Unfortunately, most series evaluating radical cystectomy do not include indices of comorbidity in the patient evaluation.

7.1.4.2 Comorbidity scales
A range of comorbidity scales have been developed (20), six of which have been validated (LE: 3):

- CIRS (Cumulative Illness Rating Scale) (21);
- Kaplan-Feinstein index (22);
- Charlson Comorbidity Index (CCI) (23);
- ICD (Index of Coexistent Disease) (24);
- ACE-27 (25);
- Total Illness Burden Index (TIBI) (26).

The Charlson Comorbidity Index ranges from 0 to 30 according to the importance of comorbidities described in four levels and is calculated by the healthcare practitioner from the patient’s medical record. The score was widely studied in patients with bladder cancer and found to be an independent prognostic factor for perioperative mortality (27,28), overall mortality (29), and cancer-specific mortality (30-33). Only the age-adjusted version of the Charlson comorbidity index was correlated with both cancer-specific mortality and other cause-mortality (34).

The ICD evaluates 14 possible comorbidities and is also calculated from the patient’s medical record.

The CIRS provides a quantification of the severity of organic disease in 14 systems and is calculated from the medical record. Nurses and doctors were shown to provide comparable calculations of CIRS (35). Although CIRS has been validated in elderly subjects (36,37), it has not been validated in bladder cancer treatment.

The Kaplan Feinstein index evaluated 12 comorbidities using a score from 0 to 3, with 0 indicating no problem, 1 indicating a light and non-chronic decompensated comorbidity, 2 indicating a significant decompensation, and 3 indicating severe decompensation. The final score of 0-3 is the highest rating given to a disease. The final score may be 3 if two or more pathologies have been given a score of 2. The healthcare practitioner calculates the Kaplan Feinstein index data from the medical record.

The TIBI evaluates the 16 diseases across 110 items. The TIBI questionnaire is completed by the patient himself. The TIBI was initially validated in a cohort of patients with type 2 diabetes. The TIBI was then correlated to the QoL, age, number of days spent in bed during the previous three months, and reduced mobility in a cohort of 1,638 men with a prostate cancer (38). None of the four last scales mentioned above (ICD, CIRS, Kaplan Feinstein index, TIBI) were not validated in the setting of bladder cancer treatments.

Performances of the Charlson Comorbidity Index and ACE-27 are approximately equivalent (LE: 3). The age-adjusted Charlson Comorbidity Index (Table 4) is the most widely used comorbidity index in cancer for estimating long-term survival and must be easily calculated using a specific calculator (39).
Table 4: Calculation of Charlson Comorbidity Index

<table>
<thead>
<tr>
<th>Number of points</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 point</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50-60 years</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular insufficiency</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td></td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td></td>
<td>Ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Mild liver disease</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td>2 points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61-70 years</td>
</tr>
<tr>
<td></td>
<td>Hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe kidney disease</td>
</tr>
<tr>
<td></td>
<td>Diabetes with organ damage</td>
</tr>
<tr>
<td></td>
<td>Tumours of all origins</td>
</tr>
<tr>
<td>3 points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>71-80 years</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe liver disease</td>
</tr>
<tr>
<td>4 points</td>
<td>81-90 years</td>
</tr>
<tr>
<td>5 points</td>
<td>&gt; 90 years</td>
</tr>
<tr>
<td>6 points</td>
<td>Metastatic solid tumours</td>
</tr>
<tr>
<td></td>
<td>AIDS</td>
</tr>
</tbody>
</table>

Interpretation
1. Calculate Charlson Score or Index = i
   a. Add comorbidity score to age score
   b. Total denoted as ‘i’ in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score.

2. Calculate Charlson Probability (10-year mortality)
   a. Calculate $Y = 10 \times 0.9$
   b. Calculate $Z = 0.983^Y$ (where Z is the 10-year survival)

The assessment of the health of the oncology patient must be supplemented by measuring the activity level of the patient. Extermann et al. showed that there was no correlation between morbidity and competitive activity level of the patient (4). ECOG-PS scores and Karnofsky index have been validated to measure the activity level of the patient (LE: 3) (40). Performance status was correlated to patient overall survival after radical cystectomy (32,41) and palliative chemotherapies (42-44).

The ASA score has been validated to assess, prior to surgery, the risk of post-operative complications. In the bladder cancer setting, ASA scores equal to or greater than 3 were associated with major complications (45,46), particularly those related to the type of urinary diversion (Table 5) (47).

Table 5: ASA score (48).

<table>
<thead>
<tr>
<th>ASA</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No organic pathology or patients in whom the pathological process is localised and does not cause any systemic disturbance or abnormality.</td>
</tr>
<tr>
<td>2.</td>
<td>A moderate but definite systemic disturbance caused either by the condition that is to be treated or surgical intervention, or which is caused by other existing pathological processes, forms this group.</td>
</tr>
<tr>
<td>3.</td>
<td>Severe systemic disturbance from any cause or causes. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgment.</td>
</tr>
<tr>
<td>4.</td>
<td>Extreme systemic disorders which have already become an imminent threat to life, regardless of the type of treatment. Because of their duration or nature, there has already been damage to the organism that is irreversible.</td>
</tr>
<tr>
<td>5.</td>
<td>Moribund patients not expected to survive 24 hours, with or without surgery.</td>
</tr>
</tbody>
</table>
According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of the elderly, to catalogue the resources and strengths of the elderly, to assess needs services to the individual and to develop a coordinated plan of care. The SGA is thus a medico-psycho-social index.

The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The protocol is the most complete Comprehensive Geriatric Assessment (CGA) (49). The CGA is suited to the care of cancer patients (50). In bladder cancer, the CGA was used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced bladder carcinoma (51).

The Senior Adult Oncology Program proposed by Balducci et al. presents a less comprehensive evaluation than a SGA evaluation (52). Even though these protocols identified previously unrecognised geriatric medical and social problems, their usefulness is not clearly demonstrated yet. (53). Similarly, the CGA, when performed in patients in general medicine, does not alter the risk of hospitalisation or death within 2 years of the evaluation (54). To provide benefit to patients, the CGA should be associated with the management problems it identifies (55).

### 7.1.4.3 Conclusions and recommendations for comorbidity scales

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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</thead>
<tbody>
<tr>
<td>Chronological age is of limited relevance.</td>
<td>3</td>
</tr>
<tr>
<td>A comorbidity score developed in particular for assessment of patients diagnosed with bladder cancer would be most helpful.</td>
<td>3</td>
</tr>
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<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>The decision regarding bladder sparing or radical cystectomy in the elderly/geriatric patient with invasive bladder cancer should be based on tumour stage and comorbidity best quantified by a validated score, such as the Charlson Comorbidity Index.</td>
<td>B</td>
</tr>
<tr>
<td>The ASA score does not address comorbidities and should not be used in this setting.</td>
<td>B</td>
</tr>
</tbody>
</table>

### 7.1.5 References


Radical cystectomy - technique and extent

Radical cystectomy also includes the dissection of regional lymph nodes. There is substantial data on the extent of lymphadenectomy. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

In the only autopsy investigation performed so far, it was shown that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal lymph nodes. There was also a significant correlation between nodal metastases and concomitant distant metastases (p < 0.0001). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation (1).

Several localisation studies of lymphadenectomy (2–7) have demonstrated both retrospectively and prospectively that metastatic lymph nodes in bladder cancer patients are not found outside the pelvis if the pelvic lymph nodes are free of tumour.

An attempt has been made to categorise the extent of lymphadenectomy. A standard lymphadenectomy in bladder cancer patients involves the removal of all nodal tissue cranially up to, and including, the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes (8). An extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation and common iliac vessels medially to the crossing ureters. The lateral boarders are the genitofemoral nerves, caudally the circumflex iliac vein, the ligamentum lacunare and the lymph node of Cloquet, as well as the area described in the standard lymphadenectomy (9–11). A superextended lymphadenectomy extends cephalad to the level of the inferior mesenteric artery (12).

In order to assess how and if cancer outcomes are influenced by the different extents of lymphadenectomy for patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken for comparative studies. The systematic review methodology is outlined in detail elsewhere (13). In brief, a systematic review of the literature was conducted in accordance with the PRISMA guidelines (14). Two independent reviewers
performed abstract and full text screening, data abstraction and risk of bias assessment. The results were tabulated in baseline characteristics and summary of findings tables. A narrative synthesis of the evidence was performed. Out of 1,696 abstracts retrieved and assessed, 18 studies fulfilled the review criteria and were included (15-31,31b). Of the nine studies comparing extended lymphadenectomy with standard or limited lymphadenectomy, six studies reported a survival benefit in favour of extended lymphadenectomy. Two studies compared the results of a high-volume centre performing extended lymphadenectomy vs. another high-volume centre performing a superextended lymph node dissection in patients undergoing radical cystectomy. Both studies reported no difference in regard to overall survival and cancer recurrence.

Two other reviews reported similar findings. Karl et al. (33) concluded that a more limited field of lymph node dissection (LND) in the pelvis was associated with suboptimal staging as well as poorer outcomes compared with a standard or extended lymphadenectomy, both in patients with node-positive and node-negative disease. Svatek and colleagues (34) concluded that extended lymph node dissection (LND) with complete skeletonisation of all pelvic structures up to the mid-upper third of the common iliac vessels was superior to limited LND. However, all of these identified studies suffer from significant methodological limitations and are prone to biases, thereby compromising the quality and reliability of the evidence. Further data from ongoing randomised trials on the therapeutic impact of extent of lymphadenectomy are awaited.

It has been suggested that progression-free survival as well as OS might be correlated with the amount of lymph nodes removed during surgery, although there are no reliable data on the minimum number of lymph nodes which must be removed. Nevertheless, the probability of survival increases with the number of dissected lymph nodes (35). Removal of more than 10-15 lymph nodes has been postulated as sufficient for the evaluation of the lymph node status as well as being beneficial for OS in retrospective studies (7,36,37). The number of lymph nodes removed does, however, not appear to correlate well with the anatomic template of lymphadenectomy. Suggested explanations include variability between patients, difficulties in accurate anatomical assignment of removed lymph nodes, inter-surgeon variability, and differences in method of lymph node submission and processing (38-41).

Laparoscopic/robotic-assisted laparoscopic cystectomy
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy (RALC) have been shown to be feasible both in male and female patients (42,43). Both cystectomy and lymphadenectomy have been done in small series, according to the same principles used in cystectomy and anterior exenteration for several decades now (44). However, these techniques are still experimental because of the limited number of cases reported, an absence of long-term oncological and functional outcome data, and a possible selection bias (45,46).

Laparoscopic intracorporeal construction of urinary diversion (with or without robotic assistance) has been tested in small series only (45,47,48). It is a challenging and lengthy procedure with the current technical equipment available and must therefore be regarded as experimental. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of urinary diversion, is an option for surgical treatment (LE: 3).

Laparoscopic and robot-assisted radical cystectomy data suffer from selection bias including younger patients, lower stage, and minimal comorbidities compared to most contemporary open series (49-51). This selection bias makes interpretation of peri-operative outcomes difficult.

Urinary diversion after radical cystectomy
From an anatomical standpoint, three alternatives are presently used after cystectomy:
• Abdominal diversion, such as an uretherocutaneousostomy, ileal or colonic conduit, and various forms of a continent pouch.
• Urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution).
• Rectosigmoid diversions, such as uretero (ileo-) rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon, and the appendix (52). Several studies have compared certain aspects of health-related QoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socioeconomic status, time interval to primary surgery, etc.

Preparations for surgery
For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the
urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered (53). Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary (54). Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation and gastrointestinal stimulation with metoclopramide and chewing gum (55).

Patients undergoing continent urinary diversion have to be motivated both to learn about their diversion and to be manually skilful in manipulating their diversion. Contraindications to more complex forms of urinary diversion include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- impaired liver or renal function;
- transitional cell carcinoma of the urethral margin or other surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative radiation therapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence (56-58).

7.2.1.1 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports the complications of radical cystectomy, while ignoring the fact that most complications are diversion-related (59). Age alone is not a criterion for offering continent diversion (60,61). Medical comorbidities, cardiac and pulmonary function and cognitive function are all important factors that should be considered, along with the patient's social support and patient preference.

7.2.2 Ureterocutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered as a safe procedure. It is therefore preferred in older, or otherwise compromised, patients, who need a supravesical diversion (62,63). However, others have demonstrated that, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible (64).

Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transuretero-ureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas (62).

In a recent retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to an ileal or colon conduit (65). Despite the limited comparative data available, however, it has to be taken into consideration that older data and clinical experience suggest stricturing on skin level and ascending UTI are more frequent complications in comparison to an ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders (66).

7.2.3 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, uretero-ileal leakage and stenosis (66). The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the upper urinary tract in up to 30% (67-69). An increase in complications was seen with increased follow-up in the Berne series of 131 patients followed for a minimum of 5 years (median follow-up 98 months) (67): the rate of complications increased from 45% at 5 years to 94% in those surviving longer than 15 years. In the latter group, 50% of patients developed upper urinary tract changes and 38% developed urolithiasis.

7.2.4 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileoceleal and sigma pouches have also been described (70-72). Different antireflux techniques can be used (73). Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% (74). A stomal stenosis in 23.5% of patients with an appendix stoma and 15% with an efferent intussuscepted ileal nipple was observed in a study, reviewing retrospectively the results of more than 800 patients. Stone formation in the pouch occurred in 10% of patients (74-76). In a small series of previously irradiated female patients, incontinence and stomal stenosis was 18% (8/44 patients) (77).
7.2.5  **Ureterocolonic diversion**

The oldest and most common form was primarily a refluxive and later an antirefluxive connection of ureters into the intact rectosigmoidum (uretero [recto] sigmoidostomy) (78,79). Most indications for this procedure have become obsolete due to a high incidence of upper urinary tract infections and the long-term risk of developing colon cancer (80,81). Bowel frequency and urge incontinence were additional side-effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between ureters and rectum or sigmoid in order to augment capacity and to avoid direct contact between the urothelium and colonic mucosa as well as faeces and urine (82).

7.2.6  **Orthotopic neobladder**

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy (58,83,84). In elderly patients (> 80 years), however, it is very rarely performed, even in high-volume expert centres (85,86).

The terminal ileum is the gastrointestinal segment most often used for bladder substitution and there is less experience with ascending colon, including caecum, and the sigmoid (83). The emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported (87,88). Long-term complications include diurnal (8-10%) and nocturnal incontinence (20-30%), uroenteric stenosis (3-18%), urinary retention (4-12%) both in males and female patients, metabolic disorders and vitamin B12 deficiency in series with 1054 and more than 1300 patients (58,89). In a recent study, which compared cancer control and the patterns of disease recurrence in neobladder and conduit patients, no cancer-specific survival difference could be identified between the two groups when adjusting for pathological stage (90). Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) (58,91). These results indicate that the choice of a neobladder both in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether a neobladder is better for QoL compared to a non-continent urinary diversion (92-94).

Various forms of upper tract reflux protection, including a simple isoperistaltic tunnel, an ileal intussusception, a tapered ileal prolongation implanted subserosally, and a direct (sub)mucosal or subserosal ureteral implantation, have been described (76,88). According to the reported long-term results, the upper urinary tract is protected sufficiently by either method.

In conclusion, standard radical cystectomy in male patients with bladder neoplasms includes removal of the entire bladder, prostate, seminal vesicles, distal ureters (length of the segment undefined), and corresponding lymph nodes (extent undefined) (LE: 2b). Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions will prefer ileal orthotopic neobladders and ileal conduits based on clinical experience (95,96). In selected patients, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to radical cystectomy and urinary diversions are listed in section 7.6.2.

7.3  **Morbidity and mortality**

In a recent comprehensive long-term study (n = 1054), peri-operative mortality was reported in 3% of cases, and early complications, defined as any complication within 3 months of surgery, in 28% (84,89). Late morbidity is usually due to the type of urinary diversion (see above). Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and not less than that associated with muscle-invasive tumours (97). In general, a lower morbidity and mortality has been observed by surgeons and by hospitals with a higher case load and therefore more experience (98).

7.4  **Survival**

Research findings have demonstrated good survival outcomes:

- According to a multi-institutional database of 888 consecutive patients undergoing cystectomy and lymphadenectomy for bladder cancer, the outcome at 5 years was 58% for a mean recurrence-free survival and 66% for bladder cancer-specific survival (99).
- The recurrence-free and OS in a large single centre study of 1054 male and female patients was 68% and 66% at 5 years and 80% and 43%, at 10 years, respectively (100).
- In node-positive patients, another study reported that 10-year disease-specific and OS rates were 27.7% and 20.9%, respectively (148). In this cohort, 10-year disease-specific and OS rates were 72.9% vs. 49.1% for organ-confined disease (defined as ≤ pT3a), and 33.3% vs. 22.8% for non-organ-confined disease (101).
- In another study, 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for
pT2, 52% in pT3, and 36% in pT4 tumours (102). Tumour stage and nodal involvement are the only independent predictors of survival (103).

### 7.5 Conclusions for radical cystectomy and urinary diversion

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
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<tbody>
<tr>
<td>For MIBC radical cystectomy is the curative treatment of choice.</td>
<td>3</td>
</tr>
<tr>
<td>A higher case load reduces morbidity and mortality of cystectomy.</td>
<td>3</td>
</tr>
<tr>
<td>Radical cystectomy includes removal of regional lymph nodes.</td>
<td>3</td>
</tr>
<tr>
<td>There are data to support that an extended LND (vs. a standard or limited LND) improves survival after radical cystectomy.</td>
<td>3</td>
</tr>
<tr>
<td>Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.</td>
<td>3</td>
</tr>
<tr>
<td>The type of urinary diversion does not affect oncological outcome.</td>
<td>3</td>
</tr>
<tr>
<td>Laparoscopic and robotic-assisted laparoscopic cystectomy is feasible but still investigational.</td>
<td>3</td>
</tr>
<tr>
<td>In patients older than 80 years with MIBC, cystectomy is an option.</td>
<td>3</td>
</tr>
<tr>
<td>Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.</td>
<td>2</td>
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<tr>
<td>Surgical complications of cystectomy and urinary diversion should be reported in a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.</td>
<td>2</td>
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</table>

### 7.6 Recommendations for radical cystectomy and urinary diversion

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Radical cystectomy is recommended in T2-T4a, N0 M0, and high-risk non-muscle-invasive bladder cancer (as outlined above).</td>
<td>A*</td>
</tr>
<tr>
<td>Do not delay cystectomy more than 3 months since it increases the risk of progression and cancer-specific death.</td>
<td>B</td>
</tr>
<tr>
<td>Pre-operative radiotherapy is not recommended in subsequent cystectomy with urinary diversion.</td>
<td>A</td>
</tr>
<tr>
<td>Lymph node dissection should be an integral part of cystectomy. An extended LND is recommended.</td>
<td>B</td>
</tr>
<tr>
<td>The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly.</td>
<td>B</td>
</tr>
<tr>
<td>Laparoscopic and robot-assisted laparoscopic cystectomy are both management options. However, current data have not sufficiently proven the advantages or disadvantages for both oncological and functional outcomes of laparoscopic and robotic-assisted laparoscopic cystectomy.</td>
<td>C</td>
</tr>
<tr>
<td>Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.</td>
<td>B</td>
</tr>
<tr>
<td>Pre-operative bowel preparation is not mandatory. ‘Fast track’ measurements may reduce the time of bowel recovery.</td>
<td>C</td>
</tr>
<tr>
<td>An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection.</td>
<td>B</td>
</tr>
</tbody>
</table>

LND = lymph node dissection.

*Upgraded following EAU Working Panel consensus.
7.7 References


78. Simon J. Ectopia Vesicae (Absence of the anterior walls of the Bladder and the pubic abdominal parietes) Operation for directing the orifices of the ureteres into the rectum, temporary success. JAMA 1911;56:398.


8. NON-RESECTABLE TUMOURS

8.1 Palliative cystectomy for muscle-invasive bladder carcinoma

For patients with inoperable locally advanced tumours (T4b, invading the pelvic or abdominal wall), radical cystectomy is not usually a therapeutic option (1). Treatment of these patients remains a clinical challenge. These patients are candidates for palliative treatments, such as palliative radiotherapy.

Inoperable locally advanced tumours may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. There are several treatment options for patients with these symptoms. In advanced bladder cancer complicated by bleeding, cystectomy with urinary diversion is the most invasive treatment. It carries the greatest morbidity and should be considered only if there are no other options (1).

In patients with locally advanced pelvic cancer and urinary bladder involvement, palliative radical cystectomy with urinary diversion using intestinal segments is usually performed for the relief of symptoms such as pain, recurrent bleeding, urgency and fistula formation (2). Zebic, et al. (2005) (3) retrospectively analysed patients aged ≥ 75 years, who had received radical cystectomies with either curative or palliative intent. The indications for palliative cystectomy were advanced pelvic malignancy with severe irritating voiding symptoms, severe pain and recurrent macrohaematuria requiring blood transfusions (3). Zebic, et al. (2005) concluded that elderly people have a greater risk of peri-operative morbidity and mortality, especially those with very advanced pelvic malignancies, who have undergone palliative cystectomy (3).

Advanced MIBC can be associated with ureteral obstruction. In invasive tumours, the mechanism of ureteral obstruction is probably caused by a combination of mechanical blockade by the tumour and invasion of ureteral orifices by tumour cells interfering with ureteral peristalsis. Bilateral ureteral obstruction, or unilateral obstruction to a solitary functioning kidney, can result in uraemia. Treatment of such patients is still a dilemma. El-Tabey et al. retrospectively reviewed the records of patients who presented with bladder cancer and obstructive uraemia (4). Patients with inoperable locally advanced bladder tumours (23 patients, 37.7%) were treated with permanent nephrostomy tubes to relieve obstruction; radical cystectomy was not an option. Ten patients underwent surgery (26.3%); palliative cystectomy without lymphadenectomy was carried out for advanced nodal involvement in four patients and for locally advanced disease infiltrating the pelvic wall in six patients. In all 10 patients, local pelvic recurrence was reported within the first year of follow-up (4).

In another study, post-operative outcome was reported for primary radical cystectomy in 20 T4 bladder cancer patients (of which seven cases were T4b). The authors concluded that primary cystectomy for T4 bladder cancer was technically feasible and had a very tolerable therapy-related morbidity and mortality (5).
8.2 Conclusions and recommendations for non-resectable tumours

Conclusions
Primary radical cystectomy in T4b bladder cancer is not a curative option.
If there are symptoms, radical cystectomy may be a therapeutic/palliative option.
Intestinal or non-intestinal forms of urinary diversion can be used with or without palliative cystectomy.

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and cannot be offered as curative treatment.</td>
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<td>B</td>
</tr>
<tr>
<td>In patients with symptoms palliative cystectomy may be offered.</td>
<td></td>
<td></td>
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<tr>
<td>Prior to any further interventions, surgery-related morbidity and quality-of-life should be fully discussed with the patient.</td>
<td>3</td>
<td>B</td>
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8.3 Supportive care
Severe, localised problems can occur in patients with invasive, non-operable bladder cancer and those in whom cystectomy has not been performed because of metastatic disease. These problems include pain, bleeding, voiding problems and obstruction of the upper urinary tract (UUT).

Obstruction of the UUT
Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction, but patients find the tubes are inconvenient and prefer ureteral stenting. However, stenting can be difficult to achieve and stents must be regularly replaced. There is also the risk of stent obstruction or displacement. Another possible solution is the possibility of a urinary diversion with, or without, a palliative cystectomy.

Bleeding and pain
In the case of bleeding, first screen the patient for coagulation disorders or review the patient’s use of anticoagulant drugs. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective (12), and can usually be done without any form of anaesthesia. The instillation of formalin (2.5-4% during 30 minutes) is a more aggressive and more painful procedure, requiring general or regional anaesthesia. Formalin instillation also has a higher risk of side effects, e.g. bladder fibrosis, but is more likely to control the bleeding (13). Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy for control of bleeding, which is also used to control pain. In an older report, haematuria and pain control were 59% and 73%, respectively (14). Irritative bladder and bowel complaints due to irradiation are possible but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% (15). Radical surgery is a last resort and includes cystectomy and diversion.

8.4 References


9. NEOADJUVANT / ADJUVANT RADIOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

Contrary to literature addressing radiotherapy prior to surgical intervention for muscle-invasive bladder cancer, data discussing findings for adjuvant radiotherapy after radical cystectomy are extremely scarce and outdated and relate mostly to non-urothelial cancer only (1). Possibly also due to late gastro-intestinal complications, post-operative radiotherapy has never been widely used. With the availability of equipment allowing for more precise targeting resulting in less damage to surrounding tissue, there may be reason to revisit this option in the future (2,3).

9.1 Pre-operative radiotherapy

9.1.1 Retrospective studies

Several retrospective studies have looked at the effect of pre-operative radiotherapy in patients with bladder cancer.

- The largest retrospective series (n = 526) showed that pre-operative radiotherapy at a dose of 50 Gy resulted in downstaging in 73% of cT3 patients versus 29% of patients who were not given pre-operative radiotherapy (4,5). Local control improved from 72% to 91% in pT3b patients (n = 91), but not in pT2 or pT3a patients, while overall survival improved from 40% to 52%.

- The results of a non-randomised study comparing 40 Gy vs. 5-20 Gy vs. no radiotherapy showed that only 40 Gy pre-operative radiotherapy reduced the risk of local recurrence from 27% to 11% and improved survival from 21% to 63% (6).

- Overall, nearly all retrospective studies of pre-operative radiotherapy at doses of 40-50 Gy, followed after 4-6 weeks by cystectomy, showed (4-12):
- downstaging of the tumour stage (40-65% of patients);
- lower risk of local recurrence (10-42%);
- improved survival (11-12%).

- Some studies showed that an improvement in local control was highest for T3b tumours (5-7).
- Other studies showed that achievement of a pathological complete remission (pCR) was a prognostic factor for survival (6-8).
- One retrospective study (8) found no significant increase in toxicity due to pre-operative radiotherapy (10% vs. 3%).

9.1.2 Randomised studies
There have been six published randomised studies investigating pre-operative radiotherapy.

- The largest randomised trial (n = 234 evaluable patients) administered pre-operative radiotherapy at a dose of 45 Gy in fractions of 1.8-2.2 Gy in muscle-invasive tumours. The results showed a significant increase in pCR (9% to 34%) in favour of pre-operative radiotherapy and no significant increase in 5-year survival of 33% to 45% (13). In patients not given adjuvant chemotherapy, survival was significantly better in patients given pre-operative radiotherapy (25-52%). Pathological complete remission was a prognostic factor for better survival. A major limitation was the exclusion from the analysis of almost 50% of patients because they did not receive the planned treatment.
- The Southwest Oncology Group (SWOG) trial (n = 124), which used a pre-operative dose of 5 x 4 Gy, did not show a survival advantage (14).
- An Egyptian study in patients with bladder cancer caused by bilharzia (predominantly squamous cell carcinoma, n = 92) showed a significant survival advantage for > T3 tumours, but a marginal and nonsignificant difference for the whole group (15).
- A small, randomised study of 44 patients (16) showed a significant increase in pCR (18-55%) and a small increase in 5-year survival (61-72%, not significant), but the results were limited by a small patient population and differing radiotherapy schedules (32-54 Gy).
- In another small, three-armed study (n = 72), patients were randomised between surgery, surgery with pre-operative radiotherapy (45 Gy in 4-5 weeks) and radiotherapy alone (50-60 Gy in 4-6 weeks) (17). Pre-operative radiotherapy resulted in 24% of patients achieving pCR. There were no significant differences in survival or toxicity between the three arms.
- There was no reported increase in toxicity due to pre-operative radiotherapy in any of the above-mentioned studies.
- The effect on the local recurrence rate was not specifically documented in any of the studies.
- Three of the randomised studies looked at downstaging and found an increase in pCR following pre-operative radiotherapy from 9% to 34% (10), 0% to 24% (14) and from 18% to 55% (16).
- Local recurrences were not reported (13,17), nor were they similar in any of the randomised studies (16).
- All five randomised studies looked at survival. The largest study found a significant survival advantage from 25% to 52% in those patients who did not receive adjuvant chemotherapy (13). The Egyptian study found a survival advantage only for T3 patients or higher (15). No study found a significant survival advantage for the whole group.
- A meta-analysis of the randomised trials on the value of pre-operative radiotherapy showed an odds ratio for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06). However, the meta-analysis was potentially biased by the many patients in the largest trial, who did not receive the planned treatment. When the results of the largest trial were excluded, the odds ratio became 0.95 (95% CI: 0.57-1.55), indicating that improved survival with pre-operative radiotherapy had not been proven (18,19).
- The sixth RCT was not included in the meta-analysis (18) since its findings deviated from all the others. Furthermore, the follow-up period was only two years (20).

9.1.3 Effect of pre-treating patients with neoadjuvant radiotherapy before cystectomy
A recent study compared the long-term outcome of pre-treating patients before cystectomy with neoadjuvant radiotherapy (n = 90) vs. not pre-treating with radiotherapy (n = 97). The clinical stage of tumours was T1-3. Downstaging to T0 after cystectomy occurred in 7% (7/97) without radiotherapy vs. 57% (51/90) with radiotherapy. In cT3 tumours, these results were 0% (0/16) vs. 59% (19/34), respectively. Downstaging resulted in a longer PFS. In cT3 tumours, there was also a significant longer disease-specific survival. However, the results are limited by the small patient numbers and the retrospective nature of the study.

Another recent retrospective study on neoadjuvant radiotherapy also found a survival advantage, though the results were also limited (21).
9.2 Conclusions and recommendations for pre-operative radiotherapy

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>No data exist to support that pre-operative radiotherapy for operable muscle-invasive bladder cancer increases survival.</td>
<td>2</td>
</tr>
<tr>
<td>Pre-operative radiotherapy for operable muscle-invasive bladder cancer, using a dose of 45-50 Gy in fractions of 1.8-2 Gy results in downstaging after 4-6 weeks.</td>
<td>2</td>
</tr>
<tr>
<td>Pre-operative radiotherapy with a dose of 45-50 Gy in fractions of 1.8-2 Gy does not significantly increase toxicity after surgery.</td>
<td>3</td>
</tr>
<tr>
<td>There are suggestions in older literature that pre-operative radiotherapy decreases local recurrence of muscle-invasive bladder cancer.</td>
<td>3</td>
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<table>
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<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Pre-operative radiotherapy is not recommended to improve survival.</td>
<td>B</td>
</tr>
<tr>
<td>Pre-operative radiotherapy for operable muscle-invasive bladder cancer results in tumour downstaging after 4-6 weeks.</td>
<td>C</td>
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</table>

9.3 References


10. BLADDER-SPARING TREATMENTS FOR LOCALISED DISEASE

10.1 Transurethral resection of bladder tumour (TURB)
When patients with an initially invasive bladder cancer, presenting with pT0 or pT1 status at second resection, are selected for transurethral resection of bladder tumour (TURB) alone, about half of them will have to undergo radical cystectomy for recurrent muscle-invasive cancer, with a disease-specific death rate ranging up to 47% within this group (1,2).

A disease-free status at re-staging TUR appears to be crucial in making the decision not to perform radical cystectomy (3,4). A prospective study by Solsona et al. (3) included 133 patients with a radical TUR and negative biopsies, and recently reported 15 year follow-up (5). Patients had regular cystoscopy and biopsies, and were treated additionally according to their findings. In all, only 6.7% were understaged during the initial TURB, 30% had recurrent NMIBC and went on to intravesical therapy, and 30% (n=40) progressed, of which 27 died of bladder cancer. This results in a cancer-specific survival (CSS) of 81.9%, 79.5% and 76.7%, and a progression-free survival (PFS) with intact bladder of 75.5%, 64.9%, 57.8%, after 5, 10 and 15 years respectively.

TUR alone is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual tumour (6). TUR alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery (7).
10.1.1 Conclusion and recommendation for TURB

<table>
<thead>
<tr>
<th>Conclusion and recommendation</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Transurethral resection of bladder tumour (TURB) alone is not a curative treatment option in most patients.</td>
<td>2a</td>
<td>B</td>
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</table>

10.1.2 References


10.2 External beam radiotherapy (EBRT)

The target field usually comprises the bladder only, with a safety margin of 1.5-2 cm to allow for unavoidable organ movements (1-4). Any beneficial effect with larger pelvic fields has not been demonstrated. The target dose for curative radiotherapy for bladder cancer is 60-66 Gy, with a subsequent boost using external radiotherapy or interstitial brachytherapy. The daily dose is usually 1.8-2 Gy, and the course of radiotherapy should not extend beyond 6-7 weeks to minimise the repopulation of cancer cells. The use of modern standard radiotherapy techniques results in major, related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients (5-9). As well as the response to radiotherapy, important prognostic factors for outcome include:

- tumour size;
- hydronephrosis;
- completeness of the initial TURB.

Overall, 5-year survival rates in patients with MIBC range between 30% and 60%, depending on whether they have a complete response (CR) following radiotherapy. Cancer-specific survival rates are between 20% and 50% (10-14).

Prognostic factors for success were investigated in an Italian single institution series of 459 irradiated patients, including approximately 30% of unfit T1 patients, with 4.4 years average follow-up. Significant factors were found in a multivariate survival analysis to be:

- age;
- T category (for all end points);
- tumour dose (only for failure-free survival) (15).

Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an overall survival benefit compared to radiotherapy (16).

External radiotherapy can be an alternative treatment in patients unfit for radical surgery, as demonstrated in a group of 92 elderly or disabled patients with T2-4 N0-1 M0 bladder cancer and a median age of 79 years. The
total dose given was 55 Gy in 4 weeks. The cystoscopic complete remission rate at 3 months was 78%, 3-year local control rate 56%, and 3-year overall survival 36%. Pre-treatment bladder capacity was demonstrated in 81% of patients (17).

Similar long-term results were reported by Chung et al (18). Three hundred and forty patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10 year DSS and OS were 35% and 19% respectively. Complete response was 64%, 79%, and 52% after EBRT alone, concurrent chemotherapy (n=36), and neoadjuvant chemotherapy (n=57) respectively, although in this last group most patients had T3 and T4 tumours. Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival. For example, in the T2 group, 5 year OS was 44% and DSS was 58%. A relapse within 2 to 3 years was a bad prognostic sign. The authors concluded that EBRT monotherapy was an option only in highly selected patients.

10.2.1 Conclusions and recommendation for external beam radiotherapy

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.</td>
<td>3</td>
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<tr>
<td>Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.</td>
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<th>Recommendation</th>
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<tr>
<td>Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches since they are more effective than radiotherapy alone.</td>
<td>B</td>
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</tbody>
</table>

10.2.2 References


10.3 Chemotherapy
Chemotherapy alone rarely produces durable CRs. In general, a clinical complete response rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% (1-2). Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival (3), though it may be confounded by patient selection.

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours (4-7). Neoadjuvant chemotherapy with 2-3 cycles of methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) or cisplatin, methotrexate plus vinblastine (CMV) has led to a downstaging of the primary tumour in different prospective series (4-6). Pathological complete responses of bladder primary tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/cisplatin (GC) in phase II and phase III trials (4-6,8-16). Contemporary series with GC followed by radical cystectomy reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery (17). As for bladder preservation, response is evaluated by cystoscopy and CT-imaging only, followed by close surveillance. This approach is prone to an imminent staging error, which can put the patient at risk for local recurrence and/or consecutive metastatic disease.

For very selected patients, a bladder-conserving strategy with TUR of the bladder and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder (18). However, this approach cannot be recommended for routine use.

10.3.1 Conclusion and recommendation for chemotherapy for muscle-invasive bladder tumours

<table>
<thead>
<tr>
<th>Conclusion</th>
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<tr>
<td>With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported.</td>
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<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Chemotherapy alone is not recommended as primary therapy for localised bladder cancer.</td>
<td>A</td>
</tr>
</tbody>
</table>
10.3.2 References


10.4 Multimodality bladder-preserving treatment

Recent organ-preservation strategies combine TURB, chemotherapy and radiation (1,2). The rationale for performing TURB and radiation is to achieve local tumour control. Application of systemic chemotherapy, most commonly as methotrexate, cisplatin and vinblastine (MCV), aims at the eradication of micrometastasis. Many protocols use cisplatin and/or 5-FU and, recently, gemcitabine with radiation, because of their established role as radiosensitisers. Cisplatin-based chemotherapy in combination with radiotherapy, following TURB, results in a complete response rate of 60-80%.

In a recent, small, phase 1-2 study the value of gemcitabine in multimodality treatment was emphasised, with a 5 year OS of 70.1% and DSS of 78.9% (3).

Another recent study with a mean follow-up of 42 months compared TURB + radiochemotherapy (n=331) with TURB + radiotherapy (n=142) (4). The overall CR was high (70.4%). However, the radiochemotherapy group had a clear survival advantage (median survival 70 months) compared to the radiotherapy group (median survival 28.5 months). Long-term results were dependent on stage, lymphatic invasion (LVI), residual tumour status and initial response at restaging TUR.

The importance of the radicality of the initial TUR was also confirmed in a recent Japanese study with 82 patients treated with TURB and chemoradiotherapy (5). Initial pCR rate was relatively low (39%) in the absence of a radical initial TURB. Still, clinical CR (84%) and survival data were high (5 year OS 77.7%, 5 year PFS 64.5%), although this included salvage treatment. Primary cT2 patients showed a significant improvement in survival compared to cT3-4 and recurrent cases.

Several other smaller recent series confirm the potential of multimodality protocols (6-9). Five year OS rates around 70% are reported. However, protocols differ for each study, as does patient selection. Recurring patients usually do badly, and so do patients with tumours progressing from NMIBC to MIBC. Low stage and complete TUR remain important prognostic variables.

It is recommended that early cystectomy is performed in individuals who do not achieve a complete response following combination therapy. About 40-45% of these patients may survive with an intact bladder at 4-5 years (2).

A comparable long-term survival rate of 50-60% at 5 year follow-up is reported by both multimodality bladder-preserving trials and cystectomy series. However, these therapeutic approaches have never been directly compared and patients in multimodality series are highly selected (2,10-12). A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a complete response to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence. About half of patients can be expected to survive with their native bladder intact. A T0 status at repeat TUR after the initial transurethral resection of the primary tumour, followed by chemotherapy in combination with radiotherapy, was identified as a prognostically important variable. However, even the latter patients are at a life-long risk of developing intravesical tumour recurrences and need meticulous surveillance and multiple invasive procedures. It has been postulated that a delay in radical cystectomy due to an initial bladder-preserving approach increases the risk of lymph node metastases to a lymph node positive rate of 26% when cystectomy becomes necessary due to treatment failure.
10.4.1 Conclusions and recommendations for multimodality treatment in muscle-invasive bladder cancer

Conclusions

| LE | In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy. |
| 3 |
| 2b | Delay in surgical therapy can compromise survival rates. |

Recommendations

| GR | Transurethral resection of bladder tumour alone cannot be offered as a standard curative treatment option in most patients. |
| B |
| B | Radiotherapy alone is less effective than surgery and is only recommended as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach. |
| B | Chemotherapy alone is not recommended as primary therapy for muscle-invasive bladder cancer. |
| A | Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches since they are more effective than radiotherapy alone. |
| B | Multimodality treatment could be offered as an alternative in selected, well-informed, well selected and compliant patients, especially for whom cystectomy is not an option. |

10.4.2 References


11. ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy for patients after radical cystectomy with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate (1,2). The benefits of chemotherapy in the adjuvant setting include:

- Chemotherapy is administered after accurate pathological staging.
- Overtreatment in patients at low risk for micrometastases is avoided.
- No delay in definitive surgical treatment, especially in patients not sensitive to chemotherapy.

The drawbacks of adjuvant chemotherapy are:

- Assessment of in vivo chemosensitivity of the tumour is not possible.
- Delay or intolerability of chemotherapy, due to post-operative morbidity.

There is not enough evidence in favour of the routine use of adjuvant chemotherapy (2,8). To date, there have been only five published randomised trials of adjuvant chemotherapy (3-7) and one meta-analysis (8), with updated individual patient data from six trials and a total of only 491 patients for survival analysis. Furthermore, all these trials were suboptimal with serious deficiencies, including low sample size (underpowered), substandard chemotherapy, early stopping of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases (2). The data are not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

From the evidence so far available, it is unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior or if the two approaches are equivalent with respect to the endpoint overall survival. In recent trial updates, cisplatin-based combination chemotherapy was able to produce long-term disease-free survival, even in metastatic disease, albeit mainly in patients with lymph node metastases only, and with a good performance status (9-11).

Patients with extravesical and/or node positive disease following cystectomy should be enrolled in clinical trials whenever possible. In non-protocol-eligible patients, adjuvant cisplatin-based chemotherapy is an option provided the patient is well informed about the scarce data available.

Published trials of randomised adjuvant chemotherapy have used three to four cycles of CMV (cisplatin, methotrexate, vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycine), MVA(E)C (methotrexate, vinblastine, adriamycine or epirubicine, and cisplatin) and CM (cisplatin, methotrexate) (12). There is no evidence that more modern or carboplatin-containing chemotherapy combinations are as effective. Patients ineligible for cisplatin should not receive adjuvant chemotherapy.

11.1 Conclusion and recommendation for adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy is under debate. Neither randomised trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy.</td>
<td>1a</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy is advised within clinical trials, but not as a routine therapeutic option.</td>
<td>A</td>
</tr>
</tbody>
</table>
11.2 References


12. METASTATIC DISEASE

Approximately 30% of patients with urothelial cancer present with muscle-invasive disease, and about half relapse after radical cystectomy, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for ~30% of relapses, whereas distant metastases are more common. About 10-15% of patients are already metastatic at diagnosis (1). Before the development of effective chemotherapy, patients with metastatic urothelial cancer rarely had a median survival that exceeded 3-6 months (2).

12.1 Prognostic factors and treatment decisions

Outcome of chemotherapy depends on patient-related factors and pre-treatment disease. Prognostic factors for response and survival have been established. In a multivariate analysis, Karnofsky performance status (PS) of ≤ 80% and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC (methotrexate, vinblastine, Adriamycin and cisplatin). These so-called Bajorin prognostic factors (3) have also been validated for newer combination chemotherapy regimens (4,5) and carboplatin combinations (6). These prognostic factors are crucial for assessing phase II study results and stratifying phase
Ill trials (7,8). Additional data on the prognostic value of elevated alkaline phosphatase and the number of disease sites (more or less than three) have been generated prospectively (9). A retrospective analysis showed that, in elderly patients, Eastern Cooperative Oncology Group (ECOG) PS 2-3 and haemoglobin < 10 mg/dL were independent predictors of poor survival (9). Age itself has no impact on response or toxic events (10).

For patients refractory to or progressing shortly after platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that developed in patients treated with vinflunine and validated in an independent data set: Hb < 10 g/dL; presence of liver metastases; and ECOG PS ≥ 1 (11).

12.1.1 Comorbidity in metastatic disease
Comorbidity is defined as “the presence of one or more diseases in addition to an index disease” (see Chapter 7). Patients with a history of cancer have an average of three co-morbid conditions and comorbidity is the rule rather than the exception. Incidence and prevalence of comorbidity increase with age. Comorbidity is an important predictor of clinical outcome (12). However, patients with comorbidity are mostly excluded from clinical trials (13).

In several studies, comorbidity was predictive of 1-5-year mortality rates, which was only partly true for age and sex.

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Comorbidity</th>
<th>Predictive capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson13</td>
<td>218</td>
<td>+</td>
<td>5-year mortality</td>
</tr>
<tr>
<td>Inouye14</td>
<td>318</td>
<td>+</td>
<td>2-year mortality</td>
</tr>
<tr>
<td>Lee15</td>
<td>8009</td>
<td>+</td>
<td>4-year mortality</td>
</tr>
<tr>
<td>Walter16</td>
<td>1427</td>
<td>+</td>
<td>1-year mortality</td>
</tr>
</tbody>
</table>

Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. Physiological impairment varies substantially between individuals. There are several definitions by which patients can be selected as potentially fit or unfit for chemotherapy, but age is not among them.

12.1.2 Not eligible for cisplatin (unfit)
The European Organisation for Research and Treatment of Cancer (EORTC) conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy (14). Their definitions are:
- fit: GFR > 60 mL/min and PS 0-1
- unfit: GFR < 60 mL/min and/or PS 2

A further survey of patients with metastatic urothelial cancer classified patients unfit for cisplatin-based chemotherapy who had: PS > 1; GFR > 60 mL/min; grade ≥ 2 audiometric loss and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure (15).

More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy (16-19).

Renal function assessment is of utmost importance in the urothelial cancer population. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tends to underestimate clearance in patients aged > 65 years compared to measured CrCl (16,21).

12.2 Single-agent chemotherapy
Response rates to single-agent, first-line chemotherapy have varied. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several large phase II trials (32-39).

Responses with single agents are usually short-lived and complete responses are rare. Of note, no long-term disease-free survival has been reported with single-agent chemotherapy. The median survival in such patients is only 6-9 months. Patients with WHO PS 3-4, with or without additional negative prognostic factors, are not expected to benefit from combination chemotherapy. The most appropriate approach for this patient group is best supportive care (BSC) or, at most, single-agent chemotherapy.

12.3 Standard first-line chemotherapy for fit patients
Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s. MVAC has been proven superior to cisplatin monotherapy and CISCA (cisplatin, cyclophosphamide and Adriamycin)
(8,30) and, more recently, to cisplatin/docetaxel (31). MVAC and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months, respectively compared to cisplatin monotherapy and CISCA (32-34). Neither of the two combinations is superior to the other, but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the anticipated equivalence of the two regimens (9). The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC (34) has resulted in it becoming a new standard regimen (35). MVAC is better tolerated when combined with granulocyte colony stimulating factor (G-CSF) (31,35).

High-dose intensity MVAC (HD-MVAC) with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and 2-year survival rate. However, there is no significant difference in median survival between the two regimens (36,37).

All disease sites have been shown to respond to cisplatin-based combination chemotherapy, but responses have been reported most often in lymph nodes. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal lymph nodes vs. 29% and 33% at extranodal sites (36). The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at 5 years compared to only 6.8% of patients with visceral metastases (9).

Further intensification of treatment using the new PCG triple regimen (paclitaxel, cisplatin and gemcitabine) did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to gemcitabine/cisplatin (38). However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%; P=0.0031), the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; HR=0.85, P=0.075) became significant in the eligible population and in the post-hoc analysis of patients who had primary bladder tumour. PCG is one new option for first-line treatment of UC.

Adding paclitaxel to GC did not induce major additional side effects. G4 neutropenia was more common (35.8% vs. 20% for GC), as was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). GC alone caused more G4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%).

12.4 Carboplatin-containing chemotherapy in fit patients
Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard.

Several randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms (49-52).

12.5 Non-platinum combination chemotherapy
Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in patients who are fit enough (29,43-49).

12.6 Chemotherapy in patients unfit for cisplatin
Up to 50% of patients are ineligible for cisplatin-containing chemotherapy, either because of poor PS and/or impaired renal function, or because of comorbidity that prevents high-volume hydration (50,51). The first randomised phase II/III trial in this setting was conducted by EORTC and compared methotrexate/carboplatin/vinblastine (M-CAV) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo vs. 23% with M-CAV, while the ORR was 42% for GemCarbo and 30% for M-CAV. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit (52). The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group (52). Recent phase III data have confirmed these results (53).

12.7 Second-line treatment
Second-line chemotherapy data are highly variable and prognostic factors have been established only recently (see 12.1, [11]).

A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least
6-12 months after first-line cisplatin-based combination chemotherapy.

Second-line response rates of paclitaxel (weekly), docetaxel, oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials (64-72). Although gemcitabine has also shown excellent response rates in second-line use (22,26-29,63,64), most patients already receive this drug as part of their front-line treatment.

Paclitaxel/gemcitabine have shown response rates of 38-60%, depending on patient selection. No adequate randomised phase III trial has been conducted to assess the true value of this second-line combination (2,44,48).

Vinflunine, a novel third-generation vinca alkaloid, has shown objective response rates of 18% and disease control in 67% of patients (65). A recent randomised phase III trial has compared vinflunine plus best supportive care against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease (66). The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment; any other treatment should take place in the context of clinical trials.

12.8 Low-volume disease and post-chemotherapy surgery
With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with lymph node but not other metastases, good PS, and adequate renal function, including a high degree of CRs, with up to 20% of patients achieving long-term disease-free survival (9,37,67,68). Stage migration may play a role in this positive prognostic development. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term disease-free survival in selected patients (69-71).

12.9 Treatment of bone metastases
The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30-40% (72). Skeletal complications due to MBD have a detrimental effect on pain and quality of life and are also associated with increased mortality (73). Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with bladder cancer, SREs caused by bone metastases were delayed (74). Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor-κB ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with urothelial carcinoma (75). Denosumab has recently been approved by the European Medicines Agency (EMA) for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment (73).

Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for jaw osteonecrosis and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions (86). For denosumab, no dose adjustments are required for variations in renal function.

12.10 Conclusions and recommendations for metastatic disease

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.</td>
<td>1b</td>
</tr>
<tr>
<td>In a second-line setting, prognostic factors are: liver metastasis, PS and haemoglobin (&lt; 10 g/dL)</td>
<td>2</td>
</tr>
<tr>
<td>Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.</td>
<td>1b</td>
</tr>
<tr>
<td>Single-agent chemotherapy provides low response rates of usually short duration.</td>
<td>2a</td>
</tr>
<tr>
<td>Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.</td>
<td>2a</td>
</tr>
</tbody>
</table>
Non-platinum combination chemotherapy produced substantial responses in first- and second-line settings, but has not been tested against standard chemotherapy in patients who are fit or unfit for treatment.

There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.

Vinflunine reached the highest level of evidence ever reported for second-line use.

Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival.

Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay SREs in MBD.

---

**Recommendations**

**First-line treatment for fit patients:**

Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.

Carboplatin and non-platinum combination chemotherapy is not recommended.

**First-line treatment in patients ineligible (unfit) for cisplatin:**

Use carboplatin combination chemotherapy or single agents.

For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0-1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.

**Second-line treatment:**

In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.

Zoledronic acid or denosumab is recommended for treatment of bone metastases.

---

*B Grade A recommendation is weakened by a problem of statistical significance.*

BSC = best supportive care; GC = gemcitabine plus cisplatin; GCSF = granulocyte colony stimulating factor; GFR = glomular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status; ZA = zoledronic acid

---

**12.11 Biomarkers**

Modest disease control rates, with sporadic marked responses, in some patients with urothelial bladder cancer have led to the investigation of biomarkers for assessment of post-operative prognosis and the potential value of peri-operative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression (87), serum vascular endothelial growth factor (88), urinary and tissue basic fibroblast growth factor (89), urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 (90), and more recently, thrombospondin-1 (91), circulating tumour cells (92,93), and multidrug resistance gene expression (94). Although a few biomarkers have shown potential, none has sufficient evidence to support its routine clinical use (LE: 3).

---

**Recommendation on the use of biomarkers**

Currently, no biomarkers can be recommended in daily clinical practice because they have no impact on predicting outcome, treatment decisions or monitoring therapy in muscle-invasive bladder cancer.

*Upgraded following panel consensus.*
Figure 2: Flowchart for the management of metastatic urothelial cancer

Patient characteristics:

<table>
<thead>
<tr>
<th>PS 0-1/2/ &gt;2</th>
<th>GFR ≥&lt; 60mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
</tbody>
</table>

CISPLATIN?

YES

PS 0-1 and GFR ≥ 60mL/min
STANDARD GC MVAC HD MVAC

NO

PS 2 or GFR < 60mL/min
comb. chemo: Carbo- based

Second-line treatment

PS 0-1

1. Progression > 6-12 months after first-line chemotherapy, adequate renal function⁹,¹⁰
   a. re-exposition to first line treatment (cisplatin based)
   b. clinical study

2. Progression > 6-12 months after first-line chemotherapy, PS 0-1, impaired renal function¹¹
   a. Vinflunine
   b. clinical study

3. Progression < 6-12 months after first-line chemotherapy, PS 0-1¹¹
   a. Vinflunine
   b. clinical study
   a. best supportive care
   b. clinical study

NO

PS ≥ 2

PS ≥ 2 and GFR < 60mL/min
NO comb. chemo⁸ studies, monotherapy, BSC

BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status

12.12 References


http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=1543


http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=10&abstractID=798

http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=16&abstractID=2413


http://www.asco.org/ASCOv2/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=16&abstractID=677


13. QUALITY OF LIFE

13.1 Introduction
The evaluation of health-related quality of life (HRQoL) considers physical, psychological, emotional and social functioning.

Several questionnaires have been validated for assessing HRQoL in patients with bladder cancer, including FACT (Functional Assessment of Cancer Therapy)-G (1), EORTC QLQ-C30 (2), EORTC QLQ-BLM (muscle-invasive bladder cancer module) (3), and SF (Short Form)-36 (4,5) and recently the BCI questionnaire specifically designed and validated for bladder cancer patients (6).

A psychometric test, such as the FACT-BL, should be used for recording bladder cancer morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients’ individual preferences in life (7).

Unfortunately, most retrospective studies do not evaluate the association between HRQoL and bladder cancer-specific issues after cystectomy, such as day-time and night-time incontinence or potency. Furthermore, important co-variables, such as a patient’s age, mental status, coping ability and gender, have rarely been considered (8,9). It remains difficult to predict the impact of post-therapeutic symptoms because of individual differences in symptom tolerance.

13.2 Choice of urinary diversion
There is controversy about which type of urinary diversion is best for a patient’s HRQoL (10). Some studies have not demonstrated any difference in HRQoL (9,11,12). Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit (13). Another study reported that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation (14).
Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes (3,15-18). Two studies have shown a statistically significant difference in HRQoL in favour of neobladders (18,19). Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for overall survival (20). Patients with a continent bladder-substitute generally scored more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function (14,15,21).

### 13.3 Non-curative or metastatic bladder cancer

In non-curative or metastatic bladder cancer, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life (22). There is limited literature describing HRQoL in bladder cancer patients receiving palliative care (23), but there are reports of bladder-related symptoms relieved by palliative surgery (24), radiotherapy (25), and/or chemotherapy (26).

Alternative definitive treatments of MIBC, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial (26-31).

### 13.4 Conclusions and recommendations for HRQoL

**Conclusions LE**

- No randomised, prospective HRQoL study has evaluated the different forms of definitive treatment for MIBC.

- In most patient groups studied, the overall HRQoL after cystectomy remains good, irrespective of the type of urinary diversion used. The suggestion that continent diversions are associated with a higher HRQoL, has not been sufficiently substantiated.

**Recommendations GR**

- The use of validated questionnaires is recommended to assess HRQoL in patients with MIBC.
- Unless a patient’s comorbidities, tumour variables and coping abilities present clear contraindications, a continent urinary diversion should be offered.
- Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.
- Patients should be encouraged to take active part in the decision-making process. Clear and exhaustive information on all potential benefits and side-effects should be provided, allowing them to make informed decisions.

HRQoL = health-related quality of life; MIBC = muscle-invasive bladder cancer

### 13.5 References


14. FOLLOW-UP

An appropriate schedule for disease monitoring should be based on:
- natural timing of recurrence;
- probability of disease recurrence;
- functional deterioration at particular sites;
- possibilities of treatment of a recurrence (1).

Nomograms on cancer-specific survival following radical cystectomy have been developed and externally validated. However, their wider use cannot be recommended prior to further data (2-4).

Contemporary cystectomy series have demonstrated 5-15% probability of pelvic recurrence. Most recurrences manifest during the first 24 months, often within 6-18 months after surgery. However, late recurrences have occurred up to 5 years after cystectomy. Again, pTN and pN were predictive of the development of pelvic recurrence.

Patients have a poor prognosis after pelvic recurrence. Even with treatment, the median survival ranges from 4-8 months following diagnosis. Definitive therapy can sometimes provide prolonged survival, but in most cases provides significant palliation of symptoms. Treatment is with systemic chemotherapy, local surgery or radiotherapy.

14.1 Site of recurrence

14.1.1 Distant recurrences

Distant recurrences are seen in up to 50% of patients treated with cystectomy. Most recurrences occur in the first 24 months, although progression has been observed after more than 10 years (5). Again, pTN and pN were risk factors (6).
The most likely sites for distant recurrences are the lungs, liver and bones (7). Upper urinary tract recurrence is rarely seen (1.8-6.0%). However, when it develops, it usually does so within 28-49 months after cystectomy (8). Surveillance regimens often fail to detect tumours before symptoms develop. Radical nephro-ureterectomy can provide prolonged survival (9).

**14.1.2 Urothelial extravesical recurrences (see comment below)**

The incidence of secondary urethral tumours after radical cystectomy is 1.5-6.0% in males, with a mean recurrence-free interval of 13.5-39 months and a median survival of 28-38 months, of which > 50% died because of systemic disease.

Secondary urethral tumours are particularly likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and a history of previously recurrent NMIBC (8).

In women, the main risk factor is disease at the bladder neck (10). Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4%) (11-14) is significantly less than after non-orthotopic diversion (6.4-11.1%) (11,13).

There is little data and agreement about urethral follow-up, with some authors recommending routine surveillance with urethral wash cytology and urine cytology (14), and others doubting the need for routine urethral surveillance (12,15-17). Urethral washes and urine cytology do not appear to have any effect on survival (15,18,19). However, there is a significant survival advantage in males with urethral recurrence diagnosed asymptptomatically versus symptomatically, so follow-up of the male urethra is indicated in those patients at risk of urethral recurrence (8).

Treatment is influenced by the local stage and grade of a urethral occurrence:
- In CIS of the urethra, BCG instillations have shown success rates of 83% (14).
- In invasive disease, urethrectomy should be performed if the urethra is the only site of disease.
- In distant disease, systemic chemotherapy is indicated (7).

**14.1.3 Conclusions and recommendations for specific recurrence sites**

<table>
<thead>
<tr>
<th>Site of recurrence</th>
<th>Conclusion</th>
<th>LE</th>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic recurrence</td>
<td>Poor prognosis</td>
<td></td>
<td>Treatment should be individualized depending on the local extent of tumour</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination</td>
<td>C</td>
</tr>
<tr>
<td>Upper urinary tract</td>
<td></td>
<td></td>
<td>See EAU guidelines on Upper Urinary Tract Carcinomas (20)</td>
<td></td>
</tr>
</tbody>
</table>

UUTTs occur in 1.8-6% of cases in contemporary series and represent the most common sites of late recurrence (3 years of disease-free survival following radical cystectomy). The median OS is 10-55 months, and 60-67% of patients will die of metastatic disease (8).

A recent meta-analysis found that 38% of UUT recurrence was diagnosed by follow-up investigation, whereas in the remaining 62% diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and with UUT imaging it was 29.6% (22).

The meta-analysis made the following useful conclusions:
- Patients with superficial cancer have a probability of a UUT-TCC lesion twice as high as those with invasive disease.
- Multifocality increases the risk of recurrence by 3-fold and recurrence from 2 to 4-fold.
- Positive ureteral or urethral margins increase the risk by 7-fold.
Table 6 Follow-up of invasive TCC with or without cystectomy

<table>
<thead>
<tr>
<th>Radiological procedure</th>
<th>Rating scale¹</th>
<th>Comments</th>
<th>Relative radiation level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray chest</td>
<td>9</td>
<td>Minimum</td>
<td></td>
</tr>
<tr>
<td>CT urography</td>
<td>8</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>X-ray abdomen loopogram</td>
<td>8</td>
<td>In patients with an ideal loop post-cystectomy</td>
<td>Medium</td>
</tr>
<tr>
<td>X-ray intravenous urography</td>
<td>5</td>
<td>Utilisation of intravenous urography has continued to decline with the increasingly widespread use of CT urography</td>
<td>Medium</td>
</tr>
<tr>
<td>MR imaging abdomen and pelvis without and with contrast</td>
<td>5</td>
<td>See ESUR guidelines on contrast media version 7.0 (21)</td>
<td>None</td>
</tr>
<tr>
<td>CT abdomen and pelvis with contrast</td>
<td>5</td>
<td>Appropriate if CT urography is not available. Visceral/nodal status evaluated during CT urography</td>
<td>High</td>
</tr>
<tr>
<td>CT chest with contrast</td>
<td>3</td>
<td>Performed if chest X-ray is equivocal</td>
<td>Medium</td>
</tr>
<tr>
<td>US pelvis (bladder)</td>
<td>3</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>FDG-PET whole body indicated for suspected or nodal metastasis</td>
<td>2</td>
<td>Indicated for suspected nodal or distant metastasis</td>
<td>High</td>
</tr>
<tr>
<td>After 5 years of follow-up, oncological surveillance can be stopped and surveillance continued with functional surveillance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ 1 is least appropriate; 9 is most appropriate.  
* Adapted from: American College of Radiology. Follow-up Imaging of Bladder Carcinoma. Date of origin: 1996; Last review date: 2000.

14.1.4 Follow-up of functional outcomes and complications

Urinary-diversion related complications are detected in 45% of patients during the first 5 years of follow-up. This rate increases with time being more than 54% after 15 years of follow-up. Long-term follow-up of functional outcomes are desirable (8) (LE:3). Follow-up may stop after 15 years.

14.2 References


### 15. Abbreviations Used in the Text

This list is not comprehensive for the most common abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>5-ALA</td>
<td>5-aminolevulinic acid</td>
</tr>
<tr>
<td>ASA (score)</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BC</td>
<td>bladder cancer</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>BSC</td>
<td>best supportive care</td>
</tr>
<tr>
<td>BT</td>
<td>brachytherapy</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson Comorbidity Index</td>
</tr>
<tr>
<td>CGA</td>
<td>Comprehensive Geriatric Assessment</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CISCA</td>
<td>cisplatin, cyclophosphamide and adriamycin</td>
</tr>
<tr>
<td>CIRS</td>
<td>Cumulative Illness Rating Scale</td>
</tr>
<tr>
<td>CIS</td>
<td>carcinoma in situ</td>
</tr>
<tr>
<td>CM</td>
<td>cisplatin, methotrexate</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CrCl</td>
<td>calculation of creatinine clearance</td>
</tr>
<tr>
<td>CSS</td>
<td>cancer-specific survival</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DCE</td>
<td>dynamic contract enhanced</td>
</tr>
<tr>
<td>DSS</td>
<td>disease-specific survival</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted imaging</td>
</tr>
<tr>
<td>DW MRI</td>
<td>diffusion-weighted magnetic resonance imaging</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>EBRT</td>
<td>external-beam radiotherapy</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>ESUR</td>
<td>European Society of Urogenital Radiology</td>
</tr>
<tr>
<td>FACT</td>
<td>Functional Assessment of Cancer Therapy</td>
</tr>
<tr>
<td>FDG-PET/CT</td>
<td>fluorodeoxyglucose-positron emission computed tomography</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>GC</td>
<td>gemcitabine, cisplatin</td>
</tr>
<tr>
<td>GFR</td>
<td>glomular filtration rate</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
</tr>
<tr>
<td>HAL</td>
<td>hexaminolaevulinate</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>ICD</td>
<td>Index of Coexistent Disease</td>
</tr>
<tr>
<td>IMRT</td>
<td>intensity-modulated radiotherapy</td>
</tr>
<tr>
<td>ISUP</td>
<td>International Society of Urological Pathology</td>
</tr>
<tr>
<td>ITT</td>
<td>intention-to-treat</td>
</tr>
<tr>
<td>IVU</td>
<td>intravenous urography</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>LND</td>
<td>lymph node dissection</td>
</tr>
<tr>
<td>M-CAVI</td>
<td>methotrexate, carboplatin, vinblastine</td>
</tr>
<tr>
<td>MCV</td>
<td>methotrexate, cisplatin and vinblastine</td>
</tr>
<tr>
<td>MBD</td>
<td>metastatic bone disease</td>
</tr>
<tr>
<td>MD CT</td>
<td>multidetector computed tomography</td>
</tr>
<tr>
<td>MDCTU</td>
<td>multidetector computed tomography urography</td>
</tr>
<tr>
<td>MESNA</td>
<td>mercapto-ethanesulfonate</td>
</tr>
<tr>
<td>MIBC</td>
<td>muscle-invasive bladder cancer</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>mUUT</td>
<td>metachronous upper urinary tract</td>
</tr>
<tr>
<td>MVAC</td>
<td>methotrexate, vinblastine, adriamycin and cisplatin</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NMIBC</td>
<td>non-muscle-invasive bladder cancer</td>
</tr>
<tr>
<td>NSF</td>
<td>nephrogenic systemic fibrosis</td>
</tr>
</tbody>
</table>
Conflict of interest

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Primary Urethral Carcinoma

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# PRIMARY URETHRAL CARCINOMAS - MARCH 2013

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1. INTRODUCTION

The European Association of Urology (EAU) Guidelines Group on Muscle-invasive and Metastatic Bladder Cancer has prepared these guidelines to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma (UC). When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary UC, in contrast to secondary UC, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary UC is reported after radical cystectomy for bladder cancer (1) (see Chapter 14 of the EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer [2]).

2. METHODOLOGY

A systematic literature search was performed to identify studies reporting urethral malignancies. Medline was searched using the controlled vocabulary of the Medical Subject Headings (MeSH) database, along with a free-text protocol, using one or several combinations of the following terms: adenocarcinoma, adjuvant treatment, anterior, chemotherapy, distal urethral carcinoma, lower, neoadjuvant, partial, penectomy, penile-preserving surgery, posterior, primary, proximal urethral carcinoma, radiotherapy, recurrence, risk factors, squamous cell carcinoma, survival, transitional cell carcinoma, urethra, urethrectomy, urethral cancer, urinary tract, and urothelial carcinoma. No randomised controlled trials (RCTs) were identified and articles were selected based on study design, treatment modality and long-term outcomes. Older studies (> 10 years) were considered if they contained historically relevant data or in the absence of newer data.

3. LEVEL OF EVIDENCE AND GRADE OF RECOMMENDATION

References in the text have been assessed according to their level of scientific evidence (LE), and guideline recommendations have been graded according to the listings in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). Grading aims to provide transparency between the underlying evidence and the recommendation given (3). Due to the fact that primary UC belongs to the family of rare cancers, most studies are retrospective, and recommendations given in these guidelines are mainly based on level 3 evidence.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (3).

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation when there are methodological limitations or disparity in published results.

Alternatively, the absence of a high level of evidence does not preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed - perhaps for ethical or other reasons - and in this case, unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as
“upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very
important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a
grade is assigned (4-6).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/
national preferences in a systematic fashion. However, whenever these data are available, the Expert Panel will
include the information.

Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency that addressed specific recommendations, including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (3).

Publication history
This 2013 guidelines document on Primary Urethral Carcinoma is the first publication on this topic by the EAU.
This document was subjected to blinded peer review prior to publication.

Potential conflict of interest statement
The expert panel have submitted potential conflict of interest statements that can be viewed on the EAU
website: http://www.uroweb.org/guidelines/online-guidelines/.

4. **Epidemiology**

Primary UC is considered a rare cancer, accounting for < 1% of all malignancies (7) (ICD-O3 topography code: C68.0 [8]).

The RARECARE project, which has been set up to describe the epidemiology of rare urogenital cancers in 64 European population-based cancer registries (covering 32% of the population of the 27 Member States of the European Union (EU), has reported recently on 1,059 new cases of epithelial urethral tumours detected between 1995 and 2002 (9). In early 2008, the prevalence of UC in the 27 EU countries was 4,292 cases with an estimated annual incidence of 655 new cases. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; a male to female ratio of 2.9) (9). There were differences between European regions; potentially caused by registration or classification (9). Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the ≥ 75 years age group (7.6/1,000,000). The age-standardised rate was 4.3/million in men and 1.5/
/ million in women, and was almost negligible in those aged < 55 years (0.2/million) (10).

5. **Etiology and Risk Factors**

For male primary UC, various predisposing factors have been reported, including urethral strictures (11,12),
chronic irritation after intermittent catheterisation/urethroplasty (13-15), external beam irradiation therapy (16),
radioactive seed implantation (17), and chronic urethral inflammation/urethritis following sexually transmitted
diseases (i.e. condylomata associated with human papilloma virus 16) (18,19). In female UC, urethral diverticula
(20-22) and recurrent urinary tract infections (23) have been associated with primary carcinoma. Clear cell
adenocarcinoma may also have a congenital origin (24).
6. **HISTOPATHOLOGY**

Both the RARECARE project and SEER database have reported that urothelial carcinoma of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by squamous cell carcinoma (SCC; 16-22%) and adenocarcinoma (AC; 10-16%) (9,10). A recent SEER analysis of 2,065 men with primary urethral cancer (mean age: 73 years) found that urothelial carcinoma (78%) was most common, and SCC (12%) and AC (5%) were significantly less frequent (25). In women, a recent report of the National Cancer Registry of the Netherlands on primary urethral cancer reported that urothelial carcinoma occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histological entities in 6% (26). Several other rare histological types of urethral malignancies have been also described in these studies.

7. **CLASSIFICATION**

7.1 **TNM staging system**

In men and women, UC is classified according to the 7th edition of the TNM classification (8) (Table 3). It should be noted that there is a separate TNM staging system for prostatic UC (8). Of note, for cancers occurring in urethral diverticulum stage T2 is not applicable as urethral diverticula are lacking periurethral muscle (27).

<table>
<thead>
<tr>
<th>T - Primary tumour (men and women)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades any of the following structures: corpus spongiosum, prostate, peri-urethral muscle</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades other adjacent organs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary tumour in prostatic urethra</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>Tis pu</td>
<td>Carcinoma in situ in the prostatic urethra</td>
</tr>
<tr>
<td>Tis pd</td>
<td>Carcinoma in situ in the prostatic ducts</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades other adjacent organs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single lymph node &gt; 2 cm in greatest dimension or in multiple nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
7.2 Tumour grade
The former WHO grading system of 1973 which differentiated urothelial carcinomas into three different grades (G1-G3) has been replaced by the grading system of 2004 that differentiates urothelial UC into PUNLMP, low grade and high grade. Non-urothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately differentiated (G2), and poorly differentiated tumours (G3). Table 4 lists the different grading systems according to the WHO 1973 and 2004 systems (28).

Table 4: Histopathological grading of urothelial and non-urothelial primary UC (28)

<table>
<thead>
<tr>
<th>PUNLMP</th>
<th>Papillary urothelial neoplasm of low malignant potential</th>
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<td>G3</td>
<td>Poorly differentiated</td>
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Recommendation LE GR
Pathological staging and grading of primary UC should follow the 2009 TNM classification and WHO 2004 grading system. 3 B

8. SURVIVAL

8.1 Long-term survival after primary urethral carcinoma
According to the RARECARE project, the mean 1- and 5-year overall survival in patients with UC in Europe is 71% and 54%, respectively (9). With longer follow-up, a SEER analysis of 1,615 cases reported median 5- and 10-year overall survival rates of 46% and 29%, respectively. Cancer-specific survival at 5 and 10 years was 68% and 60%, respectively (10).

8.2 Predictors of survival in primary urethral carcinoma
In Europe, mean 5-year overall survival does not substantially differ between the sexes (9). Predictors of decreased survival in patients with primary UC are:
• Advanced age and race (≥ 65 years) (9,29)
• Stage, grade, nodal involvement and metastasis (25)
• Tumour size and proximal tumour location (25)
• Extent of surgical treatment and treatment modality (25, 29)
• Underlying histology (9,26,29)

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low (n = 91) (26). In the large SEER database (n = 2,046), therapy is not well specified in relation to survival (25). Finally, in contrast to the RARECARE project (9), the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients (29).

Conclusion LE
Risk factors for survival in primary UC are: age, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, and type and modality of treatment. 3
9. DIAGNOSIS AND STAGING

9.1 History
When becoming clinically apparent, most patients (45-57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) (26,30). At initial presentation visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include an extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocystaneous fistula (10%), abscess formation (5%) or dyspareunia (30).

9.2 Clinical examination
In men, physical examination should comprise palpation of the extern genitalia for suspicious indurations or masses and digital rectal examination (31). In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies.

Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes, describing location, size and mobility (32).

9.3 Urinary cytology
The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55 and 59% (33). Detection rate depends on the underlying histological entity. In male patients, the sensitivity for urothelial carcinoma and SCC was reported to be 80% and 50%, respectively, whereas in female patients sensitivity was found to be 77% for SCC and 50% for urothelial carcinoma.

9.4 Diagnostic urethrocystoscopy and biopsy
Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology (31). To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist. Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours (2). A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis. In patients with suspected urothelial carcinoma of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at 5 and 7 o’clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate (34).

9.5 Radiological imaging
Radiological imaging of urethral cancer aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is superior to computed tomography (CT) in terms of staging accuracy. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (≥ cT1N0M0 (35-39). If imaging of the remainder of the urothelium is required, then CT urography with an excretory phase (40).

9.6 Regional lymph nodes
In contrast to penile cancer, in which clinically enlarged lymph nodes at initial diagnosis are not uncommon due to inflammatory conditions (41), enlarged lymph nodes in urethral cancer often represent metastatic disease (42). In men, lymphatics from the anterior urethra drain into the superficial and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drains into the superficial and deep inguinal nodes (43,44).

Nodal control in urethral cancer can be achieved either by regional lymph node dissection (31), radiotherapy (45) or chemotherapy (42). Currently, there is no clear evidence to support prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral cancer. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease (31).
Conclusion

Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathological lymph node metastasis.

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<th>Recommendations</th>
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<tr>
<td>Diagnosis includes urethrocystoscopy with biopsy and urinary cytology.</td>
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<tr>
<td>CT of the thorax and abdomen should be used to assess distant metastases.</td>
<td>3</td>
<td>B</td>
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<tr>
<td>Pelvic MRI is the preferred method to assess local extent of urethral tumour.</td>
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10. TREATMENT OF LOCALISED PRIMARY URETHRAL CARCINOMA

10.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior urethral cancer has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin (31). Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours (46). Therefore, optimising treatment of distal urethral cancer has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with <5-mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease (47). This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have been reported in other retrospective series (30,48).

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<tr>
<td>In localised anterior urethral tumours, penile-preserving surgery is an alternative to primary urethrectomy, if negative surgical margins can be achieved.</td>
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10.2 Treatment of localised urethral carcinoma in females

10.2.1 Urethrectomy and urethra-sparing surgery

In women with localised urethral cancer, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernous muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and proximal diversion through appendico-vesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women (31).

Many recent series have reported outcomes in women with mainly anterior urethral cancer undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract (49,50). In long-term series with median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22-60%, and distal sleeve resection of >2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery (49,50). Ablative surgical techniques, that is, transurethral resection (TUR) or laser, used for small distal urethral cancer, have also resulted in a considerable local failure rate of 16%, with a cancer-specific survival rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral cancer to prevent local and systemic progression (49).

10.2.2 Radiotherapy

In women, radiotherapy was investigated in several older long term series with a medium follow-up of 91-105 months (45,47). With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year cancer-specific survival was 49% (45). Most local failures (95%) occurred within the first 2 years after primary treatment (47). The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam vs. interstitial brachytherapy) was not (45). In one study, the addition of brachytherapy to external beam radiotherapy reduced the risk of local recurrence by a factor of 4.2 (51). Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and haemorrhagic cystitis, with 30% of the reported complications graded as severe (45).
Recommendations

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<tr>
<td>In women with anterior urethral tumours, urethra-sparing surgery is an alternative to primary urethrectomy if negative surgical margins can be achieved intraoperatively.</td>
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<td>B</td>
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<tr>
<td>In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours.</td>
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11. MULTIMODAL TREATMENT IN ADVANCED URETHRAL CARCINOMA

11.1 Preoperative cisplatinum-based chemotherapy

Recent retrospective studies have reported that modern cisplatin-based polychemotherapeutic regimens are effective in advanced primary urethral cancer, providing prolonged survival even in lymph-node-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy for achieving long-term survival in patients with locally advanced urethral cancer. The largest retrospective series reported outcomes in 44 patients with advanced primary urethral cancer. Patients were subjected to specific cisplatinum-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72%. The median overall survival of the entire cohort was 32 months. Of note, patients who underwent surgery after chemotherapy had significantly improved overall survival compared with those who were managed with chemotherapy alone (42).

11.2 Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy prior to surgery in locally advanced SCC has been reported in several case series (52-57). The largest and most recent series reported outcomes in 18 patients with primary locally advanced urethral cancer. A complete response to primary chemoradiotherapy was observed in 83% of the patients. The 5-year overall and disease-specific survival was 60% and 83%, respectively. Patients undergoing salvage surgery after chemoradiotherapy experienced a higher 5-year disease-free survival than those without salvage surgery (72% vs. 54%) (57).

Conclusions

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<tr>
<td>In locally advanced UC, cisplatinum-based chemotherapy with curative intent prior to surgery improves survival compared to surgery alone.</td>
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<tr>
<td>In locally advanced SCC of the urethra, combination of curative radiotherapy with radiosensitising chemotherapy with curative intent prior to surgery improves survival compared to surgery alone.</td>
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Recommendations

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<tbody>
<tr>
<td>Patients with locally advanced UC should be discussed within a multidisciplinary team of urologists, radio-oncologists and oncologists.</td>
<td>4</td>
<td>A</td>
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<tr>
<td>Chemotherapeutic regimens with curative intent should be cisplatinum based.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>In locally advanced SCC of the urethra, chemoradiotherapy with curative intent prior to surgery is an option.</td>
<td>4</td>
<td>C</td>
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</table>
12. TREATMENT OF UROTHELIAL CARCINOMA OF THE PROSTATE

Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC (58,59). Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) (60). Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement (61). In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75% (58,62). Some former series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement (63,64). In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a lymph node mapping study found that 12 patients had positive lymph nodes, with an increased proportion located above the iliac bifurcation (65).

**Recommendations**

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<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Patients with non-invasive UC or carcinoma in situ of the prostatic urethra and prostatic ducts can be treated with a urethra-sparing approach with TUR and BCG.</td>
<td>3</td>
<td>C</td>
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<tr>
<td>In patients with non-invasive UC or carcinoma in situ, prior TUR of the prostate should be performed to improve response to BCG.</td>
<td>3</td>
<td>C</td>
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<tr>
<td>Cystoprostatectomy with extended pelvic lymphadenectomy should be reserved for patients not responding to BCG or as primary treatment option in patients with extensive ductal or stromal involvement.</td>
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13. FOLLOW-UP

**COMMENTARY:** Given the low incidence of primary urethral cancer, defined follow-up has not been investigated systematically so far. Therefore, it seems reasonable to tailor surveillance regimens according to the patients’ individual risk factors (Chapter 8.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocytoscopy and cross-sectional imaging despite the lack of specific data.

14. REFERENCES


http://www.ncbi.nlm.nih.gov/pubmed/16426729


15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

<table>
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<td>AC</td>
<td>Adenocarcinoma</td>
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<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille-Calmette-Guérin</td>
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<tr>
<td>BT</td>
<td>Brachytherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MVAC</td>
<td>Methotrexate, Vinblastin, Doxorubicin, Cisplatin</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>Papillary urothelial neoplasm of low malignant potential</td>
</tr>
<tr>
<td>RC</td>
<td>Radical cystectomy</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
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<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology and End Results</td>
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<tr>
<td>TNM</td>
<td>Tumour-Node-Metastasis</td>
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<tr>
<td>TUR</td>
<td>Transurethral Resection</td>
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<td>UC</td>
<td>Urothelial carcinoma</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Conflict of interest

All members of the Muscle-invasive and Metastatic Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. INTRODUCTION

1.1 Introduction
The European Association of Urology (EAU) Guidelines Group for Prostate Cancer have prepared this guidelines document to assist medical professionals assess the evidence-based management of prostate cancer. The multidisciplinary panel of experts include urologists, radiation oncologists, a medical oncologist, and a pathologist specialized in prostate cancer.

1.2 Data identification and evidence sources
The recommendations provided in the current guidelines are based on a systemic literature search performed by the panel members (1). MedLine, Embase, and Web of Science databases were searched to identify original articles, review articles and editorials addressing “epidemiology”, “risk factors”, “diagnosis”, “staging” and “treatment” of prostate cancer. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a “free-text” protocol, combining “prostate cancer” with the terms “diagnosis”, “screening”, “staging”, “active surveillance”, “radical prostatectomy”, “external beam radiation”, “brachytherapy”, “androgen deprivation”, “chemotherapy”, “relapse”, “salvage treatment”, and “follow-up” to ensure sensitivity of the searches.

All articles published between January 2010 (previous update) and November 2011 were considered for review. The expert panel reviewed these records to select the articles with the highest evidence, according to a rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). Additionally, publications from the major urological (EAU, AUA) and oncological meetings (ASCO, ESMO, ASTRO) have been considered. Where possible, abstracts will be replaced by the full scientific publications when these become available. Also no major recommendations can be based on evidence from abstract only.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, also taking individual circumstances and patient preferences into account.

1.3 Level of evidence and grade of recommendation
The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

*Modified from Sackett, et al. (1).

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as ‘upgraded based on panel consensus’. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (2-4).
The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.

**Table 2: Grade of recommendation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

Modified from Sackett, et al. (1).

### 1.4 Publication history

The Prostate Cancer Guidelines were first published in 2001, with partial updates achieved in 2003 and 2007, followed by a full text update in 2009. Also in 2011 and 2012 a considerable number of sections of the PCa guidelines were revised. This 2013 publication includes a number of updated chapters as detailed below.

Standard procedure for EAU publications includes an annual assessment of newly published literature in this field, guiding future updates.

An ultra-short reference document is being published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

**Summary of updated and new information**

- **Chapter 8 “Treatment: deferred treatment (watchful waiting)”**
  In section 8.2.1 (Watchful waiting), the findings of the PIVOT trial have been included.

- **Chapter 9 “Treatment Radical Prostatectomy”**
  The literature has been updated and additional recommendations for lymph node dissection have been included in section 9.7 (Summary of radical prostatectomy and eLND in high-risk localized disease).

- **Chapter 10 “Treatment: definitive radiotherapy”**
  The literature has been updated, as well as the findings in section 10.10 (Guidelines for definitive radiotherapy). The text has been completely restructured, in particular in sections 10.3.2 (Neoadjuvant or adjuvant hormone therapy plus radiotherapy), 10.3.2.3 (high-risk group), 10.3.4 (The benefits of lymph-node irradiation in the prostate), 10.3.4.2 (Very high-risk PCa) and 10.7.1 (Immediate [adjuvant] postoperative external irradiation after radical prostatectomy).

- **Chapter 12 “Hormonal therapy; rationale and available drugs”**
  The literature has been updated. The chapter has been completely restructured and a section of the text was moved into a separate chapter (Chapter 15 “Metastatic prostate cancer – Hormonal therapy”), to facilitate consultation.

- **Chapter 13 “Metastatic Prostate Cancer – Hormonal therapy”**
  The literature has been updated and the text was restructured. In particular information has been added, in sections 13.1 (Prognostic factors), and 13.4 (Indications for hormonal therapy). Also section 13.4 (indications for hormonal therapy) was revised.

- **Chapter 15 “Quality of life of patients with localised prostate cancer”**
  The literature has been updated.

- **Chapter 18 “Treatment of biochemical failure after treatment with curative intent”**
  The literature has been updated and the text has been restructured.

- **Chapter 19 “Treatment of biochemical failure after curative intent”**
  The literature has been updated. Additional information on imaging modalities has been added, most notably in the summary at the end of section 19.4.1 (Diagnostic procedures for PSA relapse following radical prostatectomy). New data has been included in sections 19.4.2 (Diagnostic studies for PSA relapse following radiation therapy), 19.5.1 (Radiotherapy for PSA-only recurrence after radical prostatectomy) and on new techniques in section 19.6.1 (Salvage radical prostatectomy).

- **Chapter 20 “Castration-resistant prostate cancer (CRPC)”**
  The literature has been updated resulting in minor changes to the recommendations. The text has been completely restructured and a new algorithm for PSA progression following initial hormonal therapy was added in section 20.5 (Secondary hormonal therapy). New information was included in
sections 20.8 (Novel hormonal drugs targeting the endocrine pathways), 20.9 (Non-hormonal therapy), as well as in section 20.11, resulting in expanding the recommendations for salvage treatment after Docetaxel. The summary of treatment recommendations (section 20.13) was subjected to a minor revision.

New topics included in this 2012 print
- Quality of life of patients with localised prostate cancer
- Chapter 16, A section has been added on salvage high-intensity focused ultrasound (HIFU)
- Chapter 17, Section 17.10.4 RANK ligand inhibitors

1.5 Potential conflict of interest statement
The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.6 References

2. BACKGROUND
Cancer of the prostate (PCa) is now recognised as one of the most important medical problems facing the male population. In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer (1). Furthermore, PCa is currently the second most common cause of cancer death in men (2). In addition, since 1985, there has been a slight increase in most countries in the number of deaths from PCa, even in countries or regions where PCa is not common (3).

Prostate cancer affects elderly men more often than young men. It is therefore a bigger health concern in developed countries with their greater proportion of elderly men. Thus, about 15% of male cancers are PCa in developed countries compared to 4% of male cancers in developing countries (4). It is worth mentioning that there are large regional differences in incidence rates of PCa. For example, in Sweden, where there is a long life expectancy and mortality from smoking-related diseases is relatively modest, PCa is the most common malignancy in males, accounting for 37% of all new cases of cancer in 2004 (5).

2.1 References
### 3. CLASSIFICATION

The 2009 TNM (Tumour Node Metastasis) classification for PCa is shown in Table 3 (1).

**Table 3: Tumour Node Metastasis (TNM) classification of PCa**

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
<th>T0</th>
<th>T1a</th>
<th>T1b</th>
<th>T1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour cannot be assessed</td>
<td>No evidence of primary tumour</td>
<td>Clinically inapparent tumour not palpable or visible by imaging</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one half of one lobe or less</td>
<td>T2b</td>
<td>Tumour involves more than half of one lobe, but not both lobes</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement</td>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
<th>N0</th>
<th>N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regional lymph node metastasis</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis</td>
<td>Distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s)</td>
<td></td>
</tr>
</tbody>
</table>

---

1. Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.
3. Metastasis no larger than 0.2 cm can be designated pN1 mi.
4. When more than one site of metastasis is present, the most advanced category should be used.
### Prognostic grouping

<table>
<thead>
<tr>
<th>Group</th>
<th>T category</th>
<th>N category</th>
<th>PSA category</th>
<th>Gleason category</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1a-c</td>
<td>N0</td>
<td>M0 PSA &lt; 10</td>
<td>&lt;= 6</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0 PSA &lt; 10</td>
<td>&lt;= 6</td>
</tr>
<tr>
<td>IIA</td>
<td>T1a-c</td>
<td>N0</td>
<td>M0 PSA &lt; 20</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>T1a-c</td>
<td>N0</td>
<td>M0 PSA &gt; 10 &lt; 20</td>
<td>&lt;= 6</td>
</tr>
<tr>
<td></td>
<td>T2a, b</td>
<td>N0</td>
<td>M0 PSA &lt; 20</td>
<td>&lt;= 7</td>
</tr>
<tr>
<td>IIb</td>
<td>T2c</td>
<td>N0</td>
<td>M0 Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M0 PSA &gt; 20</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M0 Any PSA</td>
<td>Gleason &gt; 8</td>
</tr>
<tr>
<td>III</td>
<td>T3a, b</td>
<td>N0</td>
<td>M0 Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N0</td>
<td>M0 Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0 Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1 Any PSA</td>
<td>Any Gleason</td>
</tr>
</tbody>
</table>

**Note:** When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA or Gleason is available. When neither is available, and prognostic grouping is not possible, use stage grouping.

### 3.1 Gleason score

The ISUP 2005 Gleason score is the current standard for grading adenocarcinoma of the prostate on core biopsy and operative specimens (2). The Gleason score is the sum of the two most common patterns (grades 1-5) of tumour growth found. The Gleason score ranges between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. In needle biopsies, the worst grade should always be incorporated in the Gleason score, even if comprising < 5% of the cancer (2).

### 3.2 References


### 4. RISK FACTORS

The factors that determine the risk of developing clinical PCa are not well known, although a few have been identified. There are three well-established risk factors for PCa:

- increasing age;
- ethnic origin;
- heredity.

If one first-line relative has PCa, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases by 5-11-fold (1,2). A small subpopulation of individuals with PCa (about 9%) has true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before age 55 (2). Patients with hereditary PCa usually have an onset 6-7 years prior to spontaneous cases, but do not differ in other ways (2).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (3). This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the USA and Northern Europe and low in Southeast Asia (4). However, if Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men (4) (LE: 2).

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa...
to clinical PCa. Factors such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation (5,6) and occupational exposure have all been discussed as being aetiologically important (6). Prostate cancer may be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to some specific features: high prevalence, long latency, endocrine dependency, availability of serum markers (PSA), and histological precursor lesions (atypical small acinar proliferation [ASAP] or prostatic intraepithelial neoplasia [PIN]) (5). Dietary/nutritional factors that may influence disease development include total energy intake (as reflected by body mass index), dietary fat, cooked meat, micronutrients and vitamins (carotenoids, retinoids, vitamins C, D, and E), fruit and vegetable intake, minerals (calcium, selenium), and phyto-estrogens (isoflavonoids, flavonoids, lignans), or statins and/or cholesterol intake. Since most studies reported to date are case-control analyses, there remain more questions than evidence-based data available to answer them. Several ongoing large randomised trials are trying to clarify the role of such risk factors and the potential for successful prostate cancer prevention (7).

Several studies posed that metabolic syndrome may be involved in the pathogenesis and progression of prostate diseases such as benign prostatic hyperplasia (BPH) and PCa (8,9). Even though the underlying causes are still unclear, investigators established an association between an increase of insulin resistance and hyperinsulinemia, responsible for insulin-like growth factor 1 (IGF-1) production in the liver. IGF-1 is a potent mitogenic factor and apoptosis inhibitor that has been linked to PCa risk (10).

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on this risk. The key question is whether there is enough evidence to recommend lifestyle changes (lowered intake of animal fat and increased intake of fruit, cereals, and vegetables) in order to decrease the risk (11). There is some evidence to support such a recommendation and this information can be given to male relatives of PCa patients who ask about the impact of diet (LE: 2-3).

4.1 References


5. SCREENING AND EARLY DETECTION

Population or mass screening is defined as the examination of asymptomatic men (at risk). It usually takes place as part of a trial or study and is initiated by the screener. In contrast, early detection or opportunistic screening comprises individual case findings, which are initiated by the person being screened (patient) and/or his physician. The primary endpoint of both types of screening has two aspects:

1. Reduction in mortality from PCa. The goal is not to detect more carcinomas, nor is survival the endpoint because survival is strongly influenced by lead-time from diagnosis.
2. The quality of life is important as expressed by quality-of-life adjusted gain in life years (QUALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world (1). Decreased mortality rates due to PCa have occurred in the USA, Austria, UK, and France, while in Sweden the 5-year survival rate has increased from 1960 to 1988, probably due to increased diagnostic activity and greater detection of non-lethal tumours (2). However, this trend has not been confirmed in a similar study from the Netherlands (3). The reduced mortality seen recently in the USA is often attributed to the widely adopted aggressive screening policy, but there is still no absolute proof that prostate-specific antigen (PSA) screening reduces mortality due to PCa (4) (LE: 2).

A non-randomised screening project in Tyrol (Austria) may support the hypothesis that screening can be effective in reducing mortality from PCa. An early detection programme and free treatment have been used to explain the 33% decrease in the PCa mortality rate seen in Tyrol compared to the rest of Austria (5) (LE: 2b). In addition, a Canadian study has claimed lower mortality rates in men randomised to active PCa screening (6), though these results have been challenged (7). Positive findings attributed to screening have also been contradicted by a comparative study between the US city of Seattle area (highly screened population) and the US state of Connecticut (seldom screened population) (8). The study found no difference in the reduction in the rate of PCa mortality (LE: 2b), even allowing for the very great diversity in PSA testing and treatment.

In 2009, the long awaited results of two prospective, randomised trials were published. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomly assigned 76,693 men at 10 US centres to receive either annual screening with PSA and DRE, or standard care as the control. After 7 years’ follow-up, the incidence of PCa per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group (rate ratio, 1.22) (9). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio, 1.13). The data at 10 years were 67% complete and consistent with these overall findings. The PLCO project team concluded that PCa-related mortality was very low and not significantly different between the two study groups (LE: 1b).

The European Randomized Study of Screening for Prostate Cancer (ERSPC) included a total of 162,243 men from seven countries aged between 55 and 69 years. The men were randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years, the cumulative incidence of PCa was 8.2% in the screened group and 4.8% in the control group (10). The rate ratio for death from PCa was 0.80 in the screened group compared with the control group. The absolute risk difference was 0.71 deaths per 1,000 men. This means that 1,410 men would need to be screened and 48 additional cases of PCa would need to be treated to prevent one death from PCa. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from PCa by 20%, but was associated with a high risk of over-diagnosis (LE: 1b).

Both trials have received considerable attention and comments. In the PLCO trial, the rate of compliance in the screening arm was 85% for PSA testing and 86% for DRE. However, the rate of contamination in the control arm was as high as 40% in the first year and increased to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40-52% versus 86% in the ERSPC. Thus, the PLCO trial will probably never be able to answer whether or not screening can influence PCa mortality.

In an update of the Gothenburg section of the ERSPC trial, which includes 20,000 men, the authors reported a reduction in PCa mortality of 50% after a median follow-up of 14 years. However, this finding was accompanied by a substantial risk of over-diagnosis (11).

In the complete ERSCP trial, the real benefit will only be evident after 10-15 years of follow-up, especially once the 41% reduction of metastasis in the screening arm has had an impact. A longer follow-up may reduce the number needed to screen and to treat (12).

Based on the results of these two large, randomised trials, most if not all of the major urological societies conclude that at present widespread mass screening for PCa is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man (see also Chapter 6, Diagnosis). Two key questions remain open:

- At what age should early detection start?
- What is the screening interval for PSA and DRE?
A baseline PSA determination at age 40 years has been suggested, upon which the subsequent screening interval may then be based (13) (GR: B). A screening interval of 8 years might be enough in men with initial PSA levels < 1 ng/mL (14). Further, PSA testing in men older than 75 years is not recommended because its early detection would not have any clinical impact (15).

5.1 References

6. **DIAGNOSIS**

The main diagnostic tools to obtain evidence of PCa include DRE, serum concentration of PSA, and transrectal ultrasonography (TRUS). Its definite diagnosis depends on the histopathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens.

6.1 **Digital rectal examination (DRE)**

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level (1) (LE: 2a). A suspect DRE in patients with a PSA level of up to 2 ng/mL has a positive predictive value of 5-30% (2) (LE: 2a). A suspect DRE is a strong indication for prostate biopsy as it is predictive for more aggressive (Gleason score ≥ 7) prostate cancer (3,4).

6.2 **Prostate-specific antigen (PSA)**

The measurement of PSA level has revolutionised the diagnosis of PCa (5). PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. For practical purposes, it is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS (6).

There are many different commercial test kits for measuring PSA, but no commonly agreed international standard exists (7). The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa. The finding that many men may harbour PCa, despite low levels of serum PSA, has been underscored by recent results from a US prevention study (8) (LE: 2a). Table 4 gives the rate of PCa in relation to serum PSA for 2,950 men in the placebo-arm and with PSA values ≤ 4 ng/mL.

**Table 4: Risk of PCa in relation to low PSA values**

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>Risk of PCa</th>
<th>Risk of Gleason ≥ 7 PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>6.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>0.6-1</td>
<td>10.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>1.1-2</td>
<td>17.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>2.1-3</td>
<td>23.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>3.1-4</td>
<td>26.9%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

The findings in Table 4 clearly demonstrate the occurrence of aggressive PCa even at very low PSA levels, precluding an optimal PSA threshold value for detecting non-palpable, but clinically significant, PCa (LE: 3). Use of nomograms may help reducing the number of unnecessary prostate biopsies (9).

Several modifications of serum PSA value have been described, which may improve the specificity of PSA in the early detection of PCa. They include: PSA density, PSA density of the transition zone, age-specific reference ranges, and PSA molecular forms. However, these derivatives and PSA isoforms (cPSA [complex PSA], proPSA [precursor isoforms of PSA], BPSA [benign PSA], iPSA [intact PSA]) have limited usefulness in the routine clinical setting and have therefore not been considered for inclusion in these guidelines.

6.2.1 **Free/total PSA ratio (f/t PSA)**

The free/total PSA ratio (f/t PSA) is the concept most extensively investigated and most widely used in clinical practice to discriminate BPH from PCa. The ratio is used to stratify the risk of PCa for men who have total PSA levels between 4 and 10 ng/mL and a negative DRE. In a prospective multicentre trial, PCa was found on biopsy in 56% of men with f/t PSA < 0.10, but in only 8% of men with f/t PSA > 0.25 (10) (LE: 2a). Nevertheless, the concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA, e.g. instability of free PSA, variable assay characteristics and very large prostate size (11). For example, free PSA is unstable at both 4°C and at room temperature. In addition, assay characteristics may vary, and concomitant BPH in large prostates may result in a dilution effect (11). Furthermore, f/t PSA is of no clinical use in total serum PSA values > 10 ng/mL or during follow-up of patients with known PCa.

*Acknowledgment: Section 6.4 is partly based on the Guidelines of the AUO Study Group Urologic Oncology of the Austrian Society of Urologists and Andrologists (W. Höltl, W. Loidl, M. Rauchenwald, M. Müller, M. Klimpfinger, A. Schratter-Sehn, C. Brössner).*
6.2.2 **PSA velocity (PSAV), PSA doubling time (PSADT)**

There are two methods of measuring PSA over time:

- **PSAV**, which is defined as an absolute annual increase in serum PSA (ng/mL/year) (12) (LE: 1b);
- **PSADT**, which measures the exponential increase of serum PSA over time, reflecting a relative change (13).

These two concepts may have a prognostic role in patients with treated PCa (14), but they have limited use in the diagnosis of PCa because of background noise (total volume of prostate, BPH), the variations in interval between PSA determinations, and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have shown that these measurements do not provide additional information compared to PSA alone (15-18).

6.2.3 **PCA3 marker**

An increasingly studied new biomarker is PCA3, detectable in urine sediments obtained after three strokes of prostatic massage during digital rectal examination. The costly Progensa urine test for PCA3 is now commercially available. The amount of the prostate-specific non-coding mRNA marker, PCA3 normalised against PSA mRNA (urine sediment) gives a PCA3 score. The PCA3 score is superior to PSA total, and percent free PSA in detection of PCa in men with elevated PSA as it shows slight but significant increases in the AUC for positive biopsies (19-22). The PCA3 score may be used together with PSA and other clinical risk factors in a nomogram or other risk stratification tools to make a decision with regard to first or repeat biopsy (23). The PCA3 score increases with prostate cancer volume, but there is conflicting data about whether the PCA3 score independently predicts the Gleason score and its use as a monitoring tool in active surveillance has not been confirmed (23). The main current indication of the PCA3 urine test may be to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome, but its cost-effectiveness remains to be shown.

6.3 **Transrectal ultrasonography (TRUS)**

The classic picture of a hypoechoic area in the peripheral zone of the prostate will not always be seen. Gray-scale TRUS does not detect areas of PCa with adequate reliability (24). It is therefore not useful to replace systematic with targeted biopsies of suspect areas. However, additional biopsies of suspect areas may be useful.

6.4 **Prostate biopsy**

6.4.1 **Baseline biopsy**

The need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious DRE. The patient's biological age, potential co-morbidities (ASA Index and Charlson Comorbidity Index), and the therapeutic consequences should also be considered (25). Risk stratification is becoming an important tool to reduce unnecessary prostate biopsies (25).

The first elevated PSA level should not prompt an immediate biopsy. The PSA level should be verified after a few weeks by the same assay under standardised conditions (i.e. no ejaculation and no manipulations, such as catheterisation, cystoscopy or TUR, and no urinary tract infections) in the same diagnostic laboratory, using the same methods (26,27) (LE: 2a).

It is now considered the standard of care to perform prostate biopsies guided by ultrasound. Although a transrectal approach is used for most prostate biopsies, some urologists prefer to use a perineal approach. The cancer detection rates of perineal prostate biopsies are comparable to those obtained for transrectal biopsies (28,29) (LE: 1b).

The ultrasound-guided perineal approach is a useful alternative in special situations, e.g. after rectal amputation.

6.4.2 **Repeat biopsy**

The indications for a repeat biopsy are:

- rising and/or persistently elevated PSA;
- suspicious DRE (30);
- atypical small acinar proliferation (ASAP);
- extensive (multiple biopsy sites) prostatic intraepithelial neoplasia (PIN) (31).

High-grade PIN as an isolated finding is no longer considered an indication for repeat biopsy (32) (LE: 2a). A repeat biopsy should therefore be prompted by other clinical features, such as DRE findings and PSA level. If PIN is extensive (i.e. in multiple biopsy sites), this could be a reason for early repeat biopsy, because the risk of subsequent PCa is slightly increased. If clinical suspicion for PCa persists in spite of negative prostate biopsies, magnetic resonance imaging (MRI) may be used to investigate the possibility of an anterior located...
PCa, followed by TRUS or MRI-guided biopsies of the suspicious area (33).

6.4.3 **Saturation biopsy**
The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is between 30% and 43% and depends on the number of cores sampled during earlier biopsies (34) (LE: 2a). In special situations, saturation biopsy may be performed with the transperineal technique. This will detect an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback (35) (LE: 2b).

6.4.4 **Sampling sites and number of cores**
On baseline biopsies, the sample sites should be as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS. These should be chosen on an individual basis.

Sextant biopsy is no longer considered adequate. At a glandular volume of 30-40 mL, at least eight cores should be sampled. The British Prostate Testing for Cancer and Treatment Study has recommended 10 core biopsies (36) (LE: 2a). More than 12 cores are not significantly more conclusive (37) (LE: 1a).

6.4.5 **Diagnostic transurethral resection of the prostate (TURP)**
The use of diagnostic TURP instead of repeat biopsies is a poor tool for cancer detection (38) (LE: 2a).

6.4.6 **Seminal vesicle biopsy**
Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA levels > 15-20 ng/mL, the odds of tumour involvement are 20-25% (39) (LE: 2a), but a biopsy is only useful if the outcome will have a decisive impact on treatment, i.e. if the biopsy result rules out radical removal for tumour involvement or radiotherapy with intent to cure.

6.4.7 **Transition zone biopsy**
Transition zone (TZ) sampling during baseline biopsies provides a very low detection rate and TZ sampling should therefore be confined to repeat biopsies (40) (LE: 1b).

6.4.8 **Antibiotics prior to biopsy**
Oral or intravenous antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin superior to ofloxacin (41) (LE: 1b), but in the last few years increased resistance to quinolones has been reported (42) associated with a rise in severe infectious complications after biopsy (43).

6.4.9 **Local anaesthesia prior to biopsy**
Ultrasound-guided peri-prostatic block is state-of-the-art (44) (LE: 1b). It does not make any difference whether the depot is apical or basal. Intrarectal instillation of a local anaesthetic is clearly inferior to peri-prostatic infiltration (45) (LE: 1b).

6.4.10 **Fine-needle aspiration biopsy**
Fine-needle aspiration biopsy is no longer state-of-the-art.

6.4.11 **Complications**
Complications include macrohaematuria and haematospermia (Table 5) (46). Severe post-procedural infections were initially reported in < 1% of cases, but this rate has increased in the last few years as a consequence of the evolution of antibiotic resistance strains with more post-biopsy hospitalisations for infectious complications while the rate of non-infectious complications has remained stable (43).

Low-dose aspirin is no longer an absolute contraindication (47) (LE: 1b).

| Table 5: Percentage given per biopsy session, irrespective of the number of cores* |
|----------------------------------------|-------------------------------|
| Complication                          | % of biopsies                 |
| Haematospermia                        | 37.4                          |
| Haematuria > 1 day                    | 14.5                          |
| Rectal bleeding < 2 days              | 2.2                           |
| Prostatitis                           | 1.0                           |
| Fever > 38.5°C (101.3°F)              | 0.8                           |
Epididymitis 0.7
Rectal bleeding > 2 days ± requiring surgical intervention 0.7
Urinary retention 0.2
Other complications requiring hospitalisation 0.3

* Adapted from NCCN Guidelines Prostate Cancer Early Detection. V.s.2012 (46).

6.5 Pathology of prostate needle biopsies

6.5.1 Grossing and processing
Prostate core biopsies taken from different sites are usually sent to the pathology laboratory in separate vials and should be processed in separate cassettes. Before processing, number of cores per vial and length of each core should be recorded. There is a significant correlation between the length of prostate biopsy tissue on the histological slide and the detection rate of PCa (48). To achieve optimal flattening and alignment of individual cores, one should embed a maximum of three cores per cassette and use sponges or paper to keep the cores stretched and flat (49,50). To optimise the detection of small lesions, blocks should be cut at three levels (40). It is helpful routinely to mount intervening tissue sections in case additional immunostaining is needed.

6.5.2 Microscopy and reporting
Diagnosis of prostate cancer is based on histological examination. Ancillary staining techniques (e.g. basal cell staining) and additional (deeper) sections should be considered if a suspect lesion is identified (51-53). Diagnostic uncertainty in biopsies may often be resolved by intradepartmental consultation or a second opinion from an external institution (51). Table 6 lists recommended concise terminology to report prostate biopsies (50).

Table 6: Recommended diagnostic terms to report prostate biopsy findings*

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign/negative for malignancy. If appropriate, include a description (e.g. atrophy)</td>
<td></td>
</tr>
<tr>
<td>Active inflammation, negative for malignancy</td>
<td></td>
</tr>
<tr>
<td>Atypical adenomatous hyperplasia/adenosis, no evidence of malignancy</td>
<td></td>
</tr>
<tr>
<td>Granulomatous inflammation, negative for malignancy</td>
<td></td>
</tr>
<tr>
<td>High-grade PIN, negative for adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>High-grade PIN with atypical glands suspicious for adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation suspicious for cancer</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
</tbody>
</table>

*From Van der Kwast, 2003 (49).

PIN = prostatic intra-epithelial neoplasia.

For each biopsy site, the proportion of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported (54). A recent study has demonstrated the improved concordance of pattern and change of prognostic groups for the modified Gleason grading (55). According to current international convention, the (modified) Gleason score of cancers detected in prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component plus the highest grade, irrespective of its extent (no 5% rule). When the carcinoma largely consists of grade 4/5 carcinoma, identification of a small portion (< 5% of the carcinoma) of Gleason grade 2 or 3 glands should be ignored. A diagnosis of Gleason score 4, or lower, should not be given on prostate biopsies (54). The presence of intraductal carcinoma and extraprostatic extension should be reported. In addition to a report of the carcinoma features for each biopsy site, an overall Gleason score based on findings in the individual biopsies is commonly provided.

The proportion (%) or length (mm) of tumour involvement per biopsy core correlates with tumour volume, extraprostatic extension, and prognosis after prostatectomy (56-58), and an extent of > 5 mm or > 50% of adenocarcinoma in a single core is used as a cut-off triggering immediate treatment versus active surveillance in patients with Gleason score 6 carcinoma. For these reasons a measure of the extent of cancer involvement (mm or %) should be provided for each core. Length of carcinoma and percentage of carcinoma involvement of the biopsy have equal prognostic impact (59).

The extent of a single, small focus of adenocarcinoma, which is located in only one of the biopsies, should be clearly stated (e.g. < 1 mm or < 1%), as this might be an indication for further diagnostic work-
up before selecting therapy as this finding is associated with an increased risk of vanishing cancer (60-62). A prostate biopsy that does not contain glandular prostate tissue should be reported as inadequate for diagnostics, except for staging biopsies.

6.6 Pathohistology of radical prostatectomy (RP) specimens

6.6.1 Processing of the RP specimen

The histopathological examination of RP specimens aims to provide information about the actual pathological stage, grade, and surgical margin status of the prostate cancer. The weight and dimensions of the specimen are recorded before embedding it for histological processing. It is generally recommended that RP specimens are totally embedded to enable the best assessment of location, multifocality, and heterogeneity of the cancer.

However, for cost-effectiveness, partial embedding using a standard method may also be considered, particularly for large prostates (> 60 g). The most acceptable method includes the complete embedding of the posterior (dorsal) part of the prostate in addition to a single mid-anterior left and right section. Compared to total embedding, this method of partial embedding permitted detection of 98% of prostate cancers with a Gleason score \( \geq 7 \) and accurate staging in 96% of cases (63).

Upon receipt in the histopathology laboratory, the entire RP specimen is inked in order to appreciate the surgical margin status. The specimen is fixed by immersion in buffered formalin for a few days, preferably prior to incision of the sample, as incision causes distortion of the tissue. Fixation can be enhanced by injecting formalin using 21-gauge syringes, which provides a more homogeneous fixation and sectioning after 24 hours (64). After fixation, the apex is removed and cut with (para)sagittal or radial sections; the shave method is not recommended (65). Separate removal and sagittal sectioning of the bladder neck is optional. The remainder of the RP specimen is generally cut in transverse sections at 3-4 mm steps, perpendicularly to the posterior surface. The resultant tissue slices can be embedded and processed either as whole-mounts or after quadrant sectioning. Whole-mount processing provides better topographic visualisation of the carcinoma and faster histopathological examination. However, it is a more time-consuming and more expensive technique that requires specialised equipment and personnel. Although whole-mount sectioning may be necessary for research, its advantages do not outweigh its disadvantages for routine sectioning.

6.6.1.1 Recommendations for processing a prostatectomy specimen

<table>
<thead>
<tr>
<th>Recommendations for processing a prostatectomy specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total embedding of a prostatectomy specimen is preferred, either by conventional (quadrant sectioning) or by whole-mount sectioning.</td>
</tr>
<tr>
<td>The entire surface of RP specimens should be inked before cutting to evaluate the surgical margin status.</td>
</tr>
<tr>
<td>The apex should be separately examined using the cone method with sagittal or radial sectioning.</td>
</tr>
</tbody>
</table>

6.6.2 RP specimen report

The pathology report provides essential information on the prognostic characteristics relevant for making clinical decisions (Table 7). As a result of the complex information provided on each RP specimen, the use of synoptic-(like) or checklist reporting is recommended (Table 8). Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (66).
Table 7: Information provided by the pathology report

| Typing (> 95% of PCa represents conventional (acinar) adenocarcinoma) |
|-------------------|------------------|
| Grading according to the Gleason score |
| (Sub)staging and surgical margin status of the tumour |
| If appropriate, location and extent of extraprostatic extension, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion, location and extent of positive surgical margins |
| Additional information may be provided on multifocality, diameter of the dominant tumour and zonal location (transition zone, peripheral zone, anterior horn) of the dominant tumour |

Table 8: Example checklist - reporting of prostatectomy specimens

<table>
<thead>
<tr>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of carcinoma, e.g. conventional acinar, ductal, etc.</td>
</tr>
<tr>
<td>Histological grade</td>
</tr>
<tr>
<td>Primary (predominant) grade</td>
</tr>
<tr>
<td>Secondary grade</td>
</tr>
<tr>
<td>Tertiary grade (if applicable)</td>
</tr>
<tr>
<td>Total/global Gleason score</td>
</tr>
<tr>
<td>Approximate percentage of Gleason grade 4 or 5 (optional)</td>
</tr>
<tr>
<td>Tumour quantitation (optional)</td>
</tr>
<tr>
<td>Percentage of prostatic gland involved</td>
</tr>
<tr>
<td>Tumour size of dominant nodule (if identified), greatest dimension in mm</td>
</tr>
<tr>
<td>Pathological staging (pTNM)</td>
</tr>
<tr>
<td>Presence of extraprostatic extension (indicate focal or extensive)</td>
</tr>
<tr>
<td>• If present, specify site(s)</td>
</tr>
<tr>
<td>• Presence of seminal vesicle invasion</td>
</tr>
<tr>
<td>If applicable, regional lymph nodes</td>
</tr>
<tr>
<td>• Location</td>
</tr>
<tr>
<td>• Number of lymph nodes retrieved</td>
</tr>
<tr>
<td>• Number of lymph nodes involved</td>
</tr>
<tr>
<td>Surgical margins</td>
</tr>
<tr>
<td>Presence of carcinoma at margin</td>
</tr>
<tr>
<td>• If present, specify sites and extra- or intraprostatic involvement</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>If identified, presence of angioinvasion</td>
</tr>
<tr>
<td>Location (site, zone) of dominant tumour (optional)</td>
</tr>
<tr>
<td>Perineural invasion (optional)</td>
</tr>
<tr>
<td>• If present, specify extra- or intraprostatic location</td>
</tr>
</tbody>
</table>

6.6.2.1 Gleason score
Grading of conventional prostatic adenocarcinoma using the (modified) Gleason score system (54) is the single strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is therefore one of the parameters incorporated in nomograms that predict the risk of recurrence after prostatectomy (67).

6.6.2.2 Interpreting the Gleason score
The Gleason score is the sum of the most dominant and second most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises ≤ 5% of the cancer volume, this grade is not incorporated in the Gleason score (5% rule). Both the primary and the secondary grade are reported in addition to the Gleason score (e.g. Gleason score 7 [4 + 3]). A global Gleason score is
given when there are multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. A tertiary Gleason grade 4 or 5, particularly if exceeding 5% of the prostate cancer volume, is an unfavourable prognostic indicator for biochemical recurrence. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported (68), in addition to the Gleason score.

6.6.2.3 Definition of extraprostatic extension

The TNM staging system of the International Union Against Cancer (UICC) is recommended for pathological staging of prostate carcinoma (65,69). Pathologic substaging of pT2 prostate cancer is optional, since it does not correlate with clinical T2 substage and it lacks prognostic significance (70).

Extraprostatic extension is the recommended term for the presence of tumour beyond the confines of the prostate. Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or bulging out beyond the contours of the prostate gland, e.g. at the neurovascular bundle or the anterior prostate. Bladder neck invasion is also considered to be an extraprostatic extension.

It is useful to report not only the location, but also the extent of extraprostatic extension because extension is related to the risk of recurrence. There are no well-established and internationally accepted definitions of the terms ‘focal’ and ‘non-focal’ or ‘extensive extraprostatic extension’. Some authors describe focal as ‘a few glands’ (71) or extension < 1 high-power field (72), whereas others measure the depth of extent in mm (73). Currently, it is considered clinically useful to report the extent of extraprostatic extension (e.g. less or more than 1 high-power field or 1 mm) (74).

At the apex of the prostate gland, tumour mixed with skeletal muscle does not constitute extraprostatic extension. In the bladder neck, microscopic invasion of small fibres of smooth muscle is not equated to (gross) bladder wall invasion, because it does not carry independent prognostic significance for PSA recurrence (75,76) and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as an extraprostatic extension (pT3a) with positive margin and not as pT4 disease. Stage pT4 can only be assigned when the tumour invades the muscle wall of the bladder as determined by the urologist (77).

6.6.3 Prostate cancer volume

The independent prognostic value of the volume of PCa in RP specimens has not been established (72,78-81). Nevertheless, a PCa volume cut-off of 0.5 mL continues to be an important parameter to distinguish insignificant from clinically relevant cancer (78). Continued improvement in radioimaging of the prostate gland has allowed more accurate measurement of cancer volume before surgery. Therefore, it may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate.

6.6.4 Surgical margin status

Surgical margin status is an independent risk factor for biochemical recurrence. Margin status is positive if tumour cells are in touch with the ink on the surface of the specimen. Margin status is negative if tumour cells are very close to the inked surface of the margin (79) or when they are at the surface of the tissue lacking any ink.

If the tissue has severe crush artifacts (usually at the apex), it may not be possible to assign a surgical margin status (82). Surgical margin status is independent of the pathological stage and a positive margin is not evidence of extraprostatic extension (83). There is insufficient evidence to prove a relationship between the extent of positive margin and the risk of recurrence (72). However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in millimetres, or number of blocks with positive margin involvement.

6.6.5 Other factors

According to the College of American Pathologists consensus statement (84), additional potential biomarkers have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting (category III), including perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, prostate-specific antigen derivatives, and other factors (e.g. oncogenes, tumour suppressor genes, or apoptosis genes).

6.7 References


7. CLINICAL STAGING

The primary extension assessment of prostate cancer (PCa) is usually made by DRE, PSA measurement, and bone scan, supplemented with computed tomography (CT) or MRI and chest X-ray in specific situations.

7.1 T-staging
The first level is the assessment of local tumour stage, where the distinction between intracapsular (T1-T2) and extraprostatic (T3-T4) disease has the most profound impact on treatment decisions. DRE often underestimates the tumour extension; a positive correlation between DRE and pathological tumour stage was found in fewer than 50% of cases (1). However, more extensive examinations for adequate T-staging are only recommended in selected cases when more precise staging directly affects the treatment decision, i.e. when curative treatment is an option.

Serum PSA levels increase with advancing stage. Nevertheless, when PSA level is measured in an individual patient, it appears to have a limited ability to predict the final pathological stage accurately. Due to the production of PSA by benign and malignant prostatic tissue, there is no direct relationship between serum PSA concentration and the clinical and pathological tumour stage (2). A combination of serum PSA level, Gleason score on prostate biopsy and clinical T-stage, however, has been proven to be more useful in predicting the final pathological stage than the individual parameters per se (3).

The ability of the molecular forms of PSA to predict T-stage is controversial and their routine measurement is not indicated (4,5). The most commonly used method for viewing the prostate is TRUS. However, only 60% of tumours are visible with TRUS, and the remainder are not recognised due to their isoechogenicity. In a large multi-institutional study, TRUS was no more accurate at predicting organ-confined disease than was DRE (6). These findings were supported by another large study, which showed that there was no meaningful superiority of TRUS over DRE (7). A combination of DRE and TRUS can detect T3a PCa more accurately than either method alone (8) (LE: 3).

Three-dimensional TRUS (3D-TRUS) claimed to have better staging accuracy than 2-D techniques (9). Several adjuncts to 3D greyscale TRUS have been investigated. A greater sensitivity for cancer detection has been achieved with the addition of power colour Doppler and contrast agents (10-12). Unfortunately, all TRUS techniques remain largely operator-dependent and are not able to differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine use in staging.

Seminal vesicle invasion is predictive of local relapse and distant failure. Seminal vesicle biopsies may be used to increase the accuracy of pre-operative staging (13). This is not recommended as a first-line examination, but should be reserved for patients with a substantial risk of seminal vesicle invasion in whom a positive seminal vesicle biopsy would modify treatment decisions. Patients with a clinical stage greater than T2a and a serum PSA level of more than 10 ng/mL could be candidates for seminal vesicle biopsies (14,15). Patients with any of the basal biopsies positive for cancer are more likely to have positive seminal vesicle biopsies (16).

Of the prostate needle biopsy parameters examined, the percentage of tissue with cancer was the strongest predictor for positive surgical margins, seminal vesicle invasion and non-organ-confined disease (17). An increased number of biopsies involved with tumour independently predicts extraprostatic extension, margin involvement and lymph node invasion (18).

In a multivariate analysis, the best risk predictors of extracapsular extension on one side were the overall average of positive biopsy cores being 15% or greater, and the average from three ipsilateral biopsies being 15% or greater. When used in combination, these two factors yielded a model with a positive predictive value of 37%, and a negative predictive value of 95%. The high negative predictive value of the side-specific model identifies patients who are good candidates for nerve-sparing surgery (19). Furthermore, it may be useful to correlate the biopsy Gleason score with the final pathological stage: about 70% of patients have localised disease when the biopsy Gleason score is ≤ 6 (20).

It has been shown that transperineal three-dimensional prostate mapping biopsy (3D-PMB) provides more accurate determination of the extent and location of tumour compared to ultrasound guided 10-12 core biopsy, with Gleason score upgrading in 27.2% and up-staging in 45.6% of cases (21). The technique improves the differentiation between clinically significant cancers and low risk disease. Unlike transrectal saturation biopsy, 3D-PMB has acceptable morbidity.

Both CT and MRI are now of a high technical standard, but neither modality is sufficiently reliable to make their use mandatory in the assessment of local tumour invasion (22,23). Endorectal MRI (e-MRI) may allow for more accurate local staging by complementing the existing clinical variables by improvements in spatial characterisation of the prostatic zonal anatomy and molecular changes (24). Image quality and localisation improves significantly with e-MRI compared with external coil MRI (25). When compared with DRE and TRUS
prostate biopsy findings, e-MRI contributes significant incremental value for local PCa staging (26), particularly in the pre-operative identification of extraprostatic extension (EPE) and seminal vesicle invasion (SVI) when interpreted by dedicated genitourinary radiologists (27,28).

Endorectal MRI could impact on the decision to preserve or resect the neurovascular bundle (NVB) at the time of radical surgery (27,29,30).

When assessed for the ability to predict organ-confined PCa, the contribution of e-MRI to staging nomograms was significant in all risk categories, but the greatest benefit was seen in the intermediate and high risk groups (31). The combination of dynamic contrast-enhanced MRI and T2-weighted MR imaging yields improved assessment of EPE and better results for PCa staging compared with either technique independently (32) (LE: 3).

MR spectroscopic imaging (MRSI) allows for the assessment of tumour metabolism by displaying the relative concentrations of citrate, choline, creatinine and polyamines. Differences in the concentrations of these chemical metabolites between normal and malignant prostate tissues allow for better tumour localisation within the peripheral zone, increasing the accuracy of EPE detection among less-experienced readers, and decreasing interobserver variability (33). Furthermore, correlations have been demonstrated between the metabolic signal pattern and a pathological Gleason score, suggesting the potential for a non-invasive assessment of PCa aggressiveness (34).

Despite the proposed accuracy and benefit of e-MRI and MRSI in PCa characterisation and localisation, e-MRI has several limitations that hamper its widespread application in PCa staging, e.g. difficulties in interpreting signal changes related to post-biopsy haemorrhage and inflammatory changes of the prostate, and the unquantifiable but significant inter- and intra-observer variability seen between both non-dedicated and dedicated radiologists that may lead to under- or overestimation of tumour presence and the local extent of disease (LE: 3). The overall accuracy of 11C-choline positron emission tomography (PET) in defining local tumour stage (pT2 and pT3a-4) has been reported to be around 70%. PET tends to understage PCa, and has a limited value for making treatment decisions in patients with clinically localised PCa, especially if a nerve-sparing procedure is being considered (35) (LE: 2b).

7.2 N-staging

N-staging should be performed only when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatments are planned. High PSA values, stages T2b-T3 disease, poor tumour differentiation and peri-neural tumour invasion have been associated with a higher risk of the presence of nodal metastases (3,36,37). The measurement of PSA level alone is unhelpful in predicting the presence of lymph node metastases for an individual patient.

The nomograms could be used to define a group of patients with a low risk of nodal metastasis, i.e. < 10% (38). In such cases, patients with a serum PSA level of less than 20 ng/mL, stage T2a or less, and a Gleason score of 6 may be spared N-staging procedures before potentially curative treatment (3).

The extent of the Gleason 4 pattern in sextant biopsies has also been used to define the risk of N1 disease. If any core had a predominant Gleason 4 pattern, or > three cores any Gleason 4 pattern, the risk of nodal metastases was found to be 20-45%. For the remaining patients, the risk was 2.5%, supporting the idea that nodal staging is unnecessary in selected patients (39).

In the current published literature, the results indicate that CT and MRI perform similarly in the detection of pelvic lymph node metastases, although CT seems to be slightly superior (40) (LE: 2a). In either case, the decision about whether nodal involvement is present rests solely on whether there is enlargement of the investigated lymph nodes. A threshold of 1 cm for the oval nodes, and 0.8 cm for the round nodes, has been recommended as the criteria for the diagnosis of lymph node metastases (41).

A fine-needle aspiration biopsy (FNAB) might provide a decisive answer in cases of positive imaging results. However, the lymph node can be difficult to reach because of the anatomical position. In addition, FNAB is not a highly sensitive staging procedure, and a false-negative rate of 40% has been reported (41).

High-resolution MRI with lymphotrophic ultra-small super-paramagnetic iron oxide particles (USPIO) was more recently suggested in the detection of small and otherwise occult lymph node metastases in patients with PCa (42,43).

In asymptomatic patients with newly diagnosed PCa and a serum PSA level of less than 20 ng/mL, the likelihood of positive findings on CT or MRI is approximately 1% (32). CT scanning may therefore be warranted in patients with a very high risk of harbouring lymph node metastases, as the specificity of a positive scan is high (93-96%). Radio-immunoscintigraphy and PET have been investigated in order to improve the diagnosis of metastatic disease to the lymph nodes. Both methods are still under investigation, and further evaluation is needed before they can be recommended for routine use in clinical practice, especially as negative results should be interpreted with caution (44).

The results obtained using 18F-choline PET/CT scans for initial N-staging were discouraging, especially in terms of inability to detect small metastases/micrometastases (< 5 mm) (45). Furthermore,
\(^{11}\text{C}\)-choline PET/CT has quite a low sensitivity for the detection of lymph node metastases, but performed better than clinical nomograms, with equal sensitivity and better specificity (46).

The gold standard for N-staging is operative lymphadenectomy, either by open or laparoscopic techniques. It is worth pointing out that recent studies with more extensive lymphadenectomy have shown that the obturator fossa is not always the primary site for metastatic deposits in the lymph nodes, and pelvic lymph node dissection that is limited to the obturator fossa will therefore miss about 50\% of lymph node metastases (47,48). When deciding on pelvic lymph node dissection, extended lymphadenectomy should be considered, despite its disadvantages: it requires surgical experience; it is time-consuming; and it often leads to more complications than the limited procedures. Furthermore, it may fail to identify lymph node metastases, however present, even outside the region of extended dissection (49).

The primary removal of the so-called sentinel lymph node (SLN), defined as the first lymph node that receives lymphatic drainage from PCa, has the main aim of reducing the eventual morbidity associated with an extended pelvic node dissection, while preserving maximal sensitivity for diagnosis of metastatic disease (50) (LE: 3) (see section 9.7 Treatment: radical prostatectomy, indication and extent of eLND).

7.3 M-staging

The axial skeleton is involved in 85\% of patients who die from PCa (51). The presence and extent of bone metastases accurately reflect the prognosis for an individual patient. Elevated skeletal alkaline phosphatase levels may indicate the presence of bony metastasis in 70\% of affected patients (52). Furthermore, the measurement of skeletal alkaline phosphatase and PSA at the same time increases clinical effectiveness to approximately 98\% (53). In a prospective study, multiple regression analysis showed the extent of bone disease to be the only variable influencing the serum levels of skeletal alkaline phosphatase and PSA. However, in contrast to serum PSA, skeletal alkaline phosphatase demonstrated a statistical correlation with the extent of bone disease (54).

Early detection of bone metastases will alert the clinician to the possible complications inherent in skeletal destruction. Bone scintigraphy remains the most sensitive method of assessing bone metastases, being superior to clinical evaluation, bone radiographs, serum alkaline phosphatase measurement and prostatic acid phosphatase (PAP) determination (55,56). Technetium diphosphonates are the optimum radiopharmaceuticals currently available because of their extremely high bone-to-soft tissue ratio (57).

Increased \(^{18}\text{F}\)-fluoride uptake in malignant bone lesions reflects the increase in regional blood flow and bone turnover that characterise these lesions.

Studies have shown that \(^{18}\text{F}\)-fluoride PET/CT is a highly sensitive and specific imaging modality for detection of bone metastases (58,59). However, no definitive results have been obtained and therefore no final recommendations can be made (60).

Besides bone, PCa may metastasise to any organ, but most commonly it affects distant lymph nodes, lung, liver, brain and skin. Clinical examination, chest X-ray, ultrasound, CT and MRI scans are appropriate methods of investigation, but only if symptoms suggest the possibility of soft-tissue metastasis.

The need for reliable serum markers to improve the pre-treatment staging of patients with PCa has long been recognised. At present, PSA is the marker of choice. A pre-treatment serum PSA level greater than 100 ng/mL has been found to be the single most important indicator of metastatic disease, with a positive predictive value of 100\% (61). Furthermore, it has helped to reduce the number of patients with newly diagnosed PCa who require a bone scan. Patients with a low serum PSA concentration have only rarely been found to harbour detectable skeletal metastases. The correlation between serum PSA and bone scintigraphy in patients with newly diagnosed untreated PCa has been further investigated (62). Results suggest that a staging bone scan may be superfluous if the serum PSA concentration is less than 20 ng/mL in asymptomatic patients with well or moderately differentiated (up to 7: 3+4) tumours. In contrast, in patients with poorly differentiated tumours and locally advanced disease, a staging bone scan should be obtained irrespective of the serum PSA value (63).
7.4 Guidelines for the diagnosis and staging of PCa

<table>
<thead>
<tr>
<th>Diagnosis of PCa - Conclusions</th>
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<tbody>
<tr>
<td>An abnormal DRE result or elevated serum PSA measurement could indicate PCa. The exact cut-off level of what is considered to be a normal PSA value has yet to be determined, but values of approximately &lt; 2-3 ng/mL are often used for younger men.</td>
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<tr>
<td>The diagnosis of PCa depends on histopathological (or cytological) confirmation.</td>
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<th>Staging of PCa - Conclusions</th>
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<tr>
<td>Despite its high specificity in the evaluation of EPE and SVI, TRUS has low sensitivity and a tendency to understage PCa. Even with the advent of colour power Doppler and contrast enhancement the accuracy of TRUS in local staging remains inadequate and largely operator-dependent. In comparison with DRE, TRUS and CT, MRI demonstrates higher accuracy for the assessment of uni- or bi-lobar disease (T2), EPE and SVI (T3), as well as the invasion of adjacent structures (T4).</td>
</tr>
<tr>
<td>Currently only sentinel lymph node dissection or extended PLND allow for histological detection of lymph node metastases with high sensitivity.</td>
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<thead>
<tr>
<th>Diagnosis of PCa - Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Biopsy and further staging investigations are only indicated if they affect the management of the patient.</td>
<td>C</td>
</tr>
<tr>
<td>Transrectal ultrasound (TRUS)-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 8 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volume prostates.</td>
<td>B</td>
</tr>
<tr>
<td>Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates.</td>
<td>C</td>
</tr>
<tr>
<td>One set of repeat biopsies is warranted in cases with persistent indication for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy).</td>
<td>B</td>
</tr>
<tr>
<td>Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.</td>
<td>C</td>
</tr>
<tr>
<td>Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies.</td>
<td>A</td>
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<tr>
<th>Staging of PCa - Recommendations</th>
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<tbody>
<tr>
<td>Local staging (T-staging) of PCa should be based on MRI. Further information is provided by the number and sites of positive prostate biopsies, the tumour grade, and the level of serum PSA.</td>
</tr>
<tr>
<td>For local staging TRUS should not be used since it has low sensitivity and a tendency to understage PCa.</td>
</tr>
<tr>
<td>Lymph node status (N-staging) need only be assessed when potentially curative treatment is planned. Patients with stage T2 or less, PSA &lt; 20 ng/mL and a Gleason score ≤ 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation.</td>
</tr>
<tr>
<td>In clinically localised PCa, staging must be done by pelvic lymph node dissection since it presents the only reliable staging method, given the significant limitations of pre-operative imaging in the detection of small metastases (&lt; 5 mm).</td>
</tr>
<tr>
<td>Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is &lt; 20 ng/mL in the presence of well or moderately differentiated tumours.</td>
</tr>
<tr>
<td>In equivocal cases, 11C-choline-, 18F-flouride-PET/CT or whole body MRI are an option.</td>
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</table>

CT = computed tomography; DCE-MRI = dynamic contrast-enhanced MRI; DRE = digital rectal examination; EPE = extraprostatic extension; MRI = magnetic resonance imaging; MRSI = magnetic resonance spectroscopic imaging; PCa = prostate cancer; PET = positron emission tomography; PLND = pelvic lymph-node dissection; PSA = prostate-specific antigen; SVI = seminal vesicle invasion; TRUS = transrectal ultrasound.
References


8. TREATMENT: DEFERRED TREATMENT (WATCHFUL WAITING/ACTIVE MONITORING)

8.1 Introduction
There is a great difference between the incidence of PCa and deaths from PCa. In 2007, in the USA, there were 240,890 new cases with only 33,720 deaths (1). Several autopsy studies of people dying from different causes have shown that while 60-70% of older men have histological PCa (2), a large proportion of these tumours will not progress. Prostate cancer is diagnosed in only 15-20% of men during their lifetime, with a 3% lifetime risk of death (3).

The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of prostate-specific antigen (PSA) screening and ‘multicore’ schemes of prostate biopsy. These data suggest that many men with localised PCa would not actually benefit from definitive treatment. With the aim of reducing the risk of overtreatment in this subgroup of patients, two conservative management strategies of ‘watchful waiting’ and ‘active surveillance’ have been proposed.
8.1.1 Definition
8.1.1.1 Watchful waiting (WW)
Watchful waiting is also known as ‘deferred treatment’ or ‘symptom-guided treatment’. This term was coined in the pre-PSA screening era (before 1990) and referred to the conservative management of PCa until the development of local or systemic progression. At this point, the patient would then be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction, and hormonal therapy or radiotherapy for the palliation of metastatic lesions.

8.1.1.2 Active surveillance (AS)
Active surveillance is also known as ‘active monitoring’. It is the new term for the conservative management of PCa. Introduced in the past decade, it includes an active decision not to treat the patient immediately. Instead, the patient is followed up under close surveillance and treated at pre-defined thresholds that classify progression (i.e. short PSA doubling time and deteriorating histopathological factors on repeat biopsy). The treatment options are intended to be curative.

8.2 Deferred treatment of localised PCa (stage T1-T2, Nx-N0, M0)
8.2.1 Watchful waiting
The rationale behind WW is the observation that PCa often progresses slowly, and is diagnosed in older men, in whom there is a high incidence of co-morbidity and related high competitive mortality (4). Watchful waiting can be considered as an option for treating patients with localised PCa and a limited life expectancy or for older patients with less aggressive cancers.

There have been several attempts to summarise the key papers dealing with deferred treatment in patients with presumed localised PCa (5-7). Most have presented the same results, as they analyse roughly the same series, but using somewhat different methodologies. The outcome studies in WW usually included patients, whose PSA readings were not always available and who had predominantly palpable lesions that would currently be defined as intermediate-risk tumours (8). The most recent study used data from the PSA era of the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute in the USA (9). These studies included patients with a follow-up of up to 25 years, for whom the endpoints are overall survival (OS) and disease-specific survival (DSS).

Several WW series show a very consistent DSS ratio at 10 years, ranging from 82-87% (5,10-14), and up to 80-95% if T1-T2 Gleason ≤ 7 (9). In three studies with data beyond 15 years, the DSS was 80%, 79% and 58%, respectively (11,13,14). Two of them reported a 20-year DSS of 57% and 32%, respectively (11,13).

Chodak et al. reported a pooled analysis of the original data from 828 patients treated by WW (5). The paper was based on patients from six non-randomised studies and described cancer-specific survival and metastasis-free survival after 5 and 10 years of follow-up (5) (LE: 2b).

Tumour grade is clearly significant, with very low survival rates for grade 3 tumours. Although the 10-year cancer-specific rate is equally good (87%) for grade 1 and 2 tumours, the latter have a significantly higher progression rate, with 42% of these patients developing metastases (Table 9).

Table 9: Outcome of deferred treatment in localised PCa in relation to tumour grade (6): percentage of patients (95% confidence interval) surviving at 5 and 10 years

<table>
<thead>
<tr>
<th>Grade</th>
<th>5 years (%)</th>
<th>10 years (%)</th>
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<tbody>
<tr>
<td>Disease-specific survival</td>
<td></td>
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<tr>
<td>Grade 1</td>
<td>98 (96-99)</td>
<td>87 (81-91)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>97 (93-98)</td>
<td>87 (80-92)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>67 (51-79)</td>
<td>34 (19-50)</td>
</tr>
<tr>
<td>Metastasis-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>93 (90-95)</td>
<td>81 (75-86)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>84 (79-89)</td>
<td>58 (49-66)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>51 (36-64)</td>
<td>26 (13-41)</td>
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</table>

The importance of tumour grade on survival after conservative management of PCa was also underlined in a large register study using the SEER database (9) (LE: 3). Patients with grade 1, 2 and 3 tumours had 10-year cancer-specific survival rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis.

The paper by Chodak et al. also specifically described the outcome for stage T1a patients (5), with cancer-specific 10-year survival rates of 96% and 94%, respectively, for grade 1 and 2 tumours. The metastasis-free survival rate was 92% for patients with grade 1 tumours, but 78% for those with grade 2...
tumours, indicating a higher risk of progression in individuals with moderately differentiated tumours. This difference in progression rate correlates with other studies on stage T1a disease (15,16).

The impact of grade on the risk of tumour progression and ultimately death from PCa was also described in a paper by Albertsen et al. in the pre-PSA era (17). The study re-evaluated all biopsy specimens using the more widely accepted Gleason score, and showed that the risk of PCa death was very high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 cancers (Table 10) (18,19) (LE: 3).

This paper also showed that Gleason 6-10 tumours carry a continuously increasing risk of ending the patient’s life for up to 15 years of follow-up after conservative management. The cancer-specific survival curves for this group of patients have been published in a recent discussion article on different methods of assessing outcome in treatment for localised PCa (18).

Table 10: The 15-year risk of dying from PCa in relation to Gleason score at diagnosis in patients with localised disease aged 55-74 years (17,18)

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Risk of cancer death* (%)</th>
<th>Cancer-specific mortality† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>4-7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>6-11</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>18-30</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>42-70</td>
<td>76</td>
</tr>
<tr>
<td>8-10</td>
<td>60-87</td>
<td>93</td>
</tr>
</tbody>
</table>

* The figures on the risk of cancer death differ for different age groups and represent the true risk in the studied population (taking actual competing mortality from other causes into consideration).
† The cancer-specific mortality compensates for differences in competing mortality and indicates the outcome if the patient actually lived for 15 years.

Three randomised clinical trials have reported long-term follow-up of patients randomised to WW or radical prostatectomy: the first was in the pre-PSA screening era (19); the second was at the beginning of PSA screening (20); and the third was a recent study, the results of which have been published in 2012 (21).

Between 1967 and 1975, the Veterans Administration Cooperative Urological Research Group randomised 142 patients affected by clinical localised PCa. The study was underpowered to detect treatment differences (22).

Between 1989 and 1999, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomised 695 patients with clinical stage T1-T2 to WW (n = 348) or radical prostatectomy (n = 347) (Table 11) (30). This study began after PSA screening was introduced into clinical practice, but only 5% of men were diagnosed by screening. After a median follow-up of 12.8 years, this study showed a significant decrease in cancer-specific mortality, overall mortality, metastatic risk progression and local progression in patients treated with radical prostatectomy versus WW (LE: 1b).

Table 11: Outcome of Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) at 15 years of follow-up (median of 12.8 years) (20)

<table>
<thead>
<tr>
<th></th>
<th>RP (N = 347) % (n)</th>
<th>WW (N = 348) % (n)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-specific mortality</td>
<td>14.6 (14)</td>
<td>20.7 (20.7)</td>
<td>0.62 (0.56-0.69)</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>46.1 (46.1)</td>
<td>57.2 (57.2)</td>
<td>0.75 (0.61-0.92)</td>
<td>0.007</td>
</tr>
<tr>
<td>Metastatic progression</td>
<td>21.7 (21.7)</td>
<td>33.4 (33.4)</td>
<td>0.59 (0.45-0.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Local progression</td>
<td>21.5 (21.5)</td>
<td>49.3 (49.3)</td>
<td>0.34 (0.26-0.45)</td>
<td></td>
</tr>
</tbody>
</table>

RP = radical prostatectomy; WW = watchful waiting.

Subgroup analysis showed that the overall difference was not modified by PSA level (below or above 10 ng/mL) or by the Gleason score (below 7 or above) at the time of diagnosis. However, age at that the time of randomisation had a profound impact, the benefit on overall survival and metastases free survival being only seen for those below 65 years of age.

The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT) recruited 731 men with clinically organ confined prostate cancer to the arms of radical prostatectomy or WW (21). Inclusion criteria were clinically organ confined PCa (cT1-2cN0cM0) with a PSA < 50 ng/mL,
patient age < 75 years and a life expectancy > 10 years. It has to be considered that 50% of the men had a non-palpable PCa, which was only the case in 12% of the patients in the SPCG-4 trial (20). Both prostate biopsy and radical prostatectomy specimens were pathohistologically assessed by a reference pathologist.

After a mean follow-up of 10 years, no statistically significant between both treatment arms could be demonstrated with regard to overall mortality (47% versus 49.9%, p = 0.22) and PCa-specific survival (5.8% versus 8.4%, p = 0.09). There were also no statistically significant differences concerning overall survival between both treatment groups when considering patient age, Gleason Score, performance status, and Charlson comorbidity score. Only patients exhibiting a pre-treatment PSA serum concentration > 10 ng/ml or high risk PCa experienced a statistically significant benefit concerning overall survival with a relative risk reduction of mortality of 33% (p = 0.02) and 31% (p < 0.01), respectively. In the pooled analysis a relative risk reduction and an absolute risk reduction of 31% and 10.5%, respectively, was identified for patients with intermediate/high risk PCa (p < 0.01). Patients who underwent radical prostatectomy also experienced a statistically significant reduction concerning the development of bone metastases (4.7% versus 10.6%, p < 0.01).

No data are available comparing WW and radiotherapy. Some data are available for hormonal treatment. For patients who choose deferred treatment, there appears to be a modest risk of disease progression, although shorter cancer-specific survival times have been reported after deferred therapy compared with immediate hormone therapy, in presumed localised PCa (not using PSA for staging) after 15 years of follow-up (22). In contrast to Lundgren et al. (22), the report of the Casodex Early Prostate Cancer Trialists’ Group programme showed a higher mortality in a group of men with localised PCa treated with bicalutamide, 150 mg/day, than in those who received placebo (23).

Conclusions on deferred treatment

Clinical stage T1c currently represents 40-50% of new cases of PCa (24). The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of PSA screening and ‘multicore’ schemes of prostate biopsy.

The SPCG-4 study demonstrated significant advantages for RP over WW, but only 5% of those studied were PSA-screened patients.

During the past 20 years, there appears to have been a shift towards higher Gleason scoring levels (25), even in cases evaluating microscopic foci of PCa. Some tumours previously given a Gleason score of 6 (3 + 3) might be scored today as 7 (3 + 4) or higher.

The lead time in PSA screening is about 10 years (26,27). It is therefore possible that cancer-related mortality from untreated, non-screen-detected PCa in patients with contemporary Gleason scores of 6 might be as low as 10% at 20-year follow-up (28).

The comparison of immediate hormonal treatment to WW in localised PCa remain controversial and may be associated with an increased mortality with bicalutamide.

It appears that many small localised well-differentiated tumours will not progress, and radical therapy may lead to substantial overtreatment with resulting effects on the patients’ quality of life and treatments costs. This has been further confirmed by a recent analysis at 5 and 10 years of 19,639 patients > 65 years from the SEER database not given curative treatment. Based on comorbidities (Charlson score), most men with a Charlson score ≥ 2 died from competing causes at 10 years, whatever their initial age (below or above 65 years). However, men with no or just one comorbidity had a low risk of death at 10 years, especially for well or moderately differentiated lesions (29). In men with a Charlson score ≥ 2, tumour aggressiveness had little impact on overall survival, suggesting that perhaps these patients could have been spared the biopsies and diagnosis of cancer. This strengthens the major role of initial comorbidity evaluation, leading to an individual survival probability, before embarking an individual on any form of medical intervention such as biopsies or treatment (30).

8.2.2 Active surveillance

Active surveillance was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined very low-risk PCa, without giving up radical treatment, as happens with WW. Currently, the only data available is data from non-mature randomised clinical trials of active surveillance, with a follow-up of less than 10 years. Active surveillance can therefore only be proposed for highly selected low-risk patients, particularly as the data indicate there is a significant risk of tumour progression after conservative treatment for some patients with apparently localised PCa. This conclusion is also supported by other studies, which have shown that patients with a life expectancy > 10 years have a higher mortality rate from PCa in the absence of curative treatment. These studies include the Johansson series, which showed that there is a higher risk of dying from PCa in patients surviving more than 15 years with well- and moderately differentiated tumours at diagnosis.
In the light of these findings, it is essential that a more precise selection of candidates for active surveillance is carried out.

A multicentre clinical trial of active surveillance versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025. Choo, Klotz and co-workers were the first to report on a prospective active surveillance protocol (32,33). The most advanced cohort to date was reported last year by Klotz (43). A total of 450 patients with clinical stage T1c or T2a, PSA \( \leq 10 \) ng/mL were enrolled with an overall Gleason score \( \leq 6 \) (PSA \( \leq 15 \)), with patients > 70 years having a Gleason score \( \leq 7 \) (3 + 4). Initially, six biopsies were performed, followed by the usual extended 12-core protocol during the study. At a median follow-up of 6.8 years, the 10-year overall survival was 68%. At 10 years, the disease-specific survival was 97.2%, with 62% of men still alive on active surveillance. Subsequently, 30% of patients underwent a radical treatment for the following reasons: 48% for a PSA doubling time < 3 years; 27% for Gleason score progression on repeat biopsies; and 10% because of patient preference.

A variety of additional studies on active surveillance in clinically organ confined disease (Tables 12 and 13) have now been published. All have confirmed that, in well-selected patients with very low-risk disease, there was a very low rate of progression and cancer-specific death, with only a few patients required delayed radical intervention. However, an extended follow-up is necessary to obtain definitive results. Thus, active surveillance might mean no treatment at all for patients older than 70 years, while in younger patients, it might mean a possible treatment delayed for years. The repeated biopsies that are part of active surveillance might then become important for their potential side effect on nerve preservation if surgery is subsequently considered.

### Table 12: Clinical trials of AS for organ-confined PCa: inclusion criteria

<table>
<thead>
<tr>
<th>N</th>
<th>Median age</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| 321   | 64         | Gleason \( \leq 3+3 \), PSAd \( \leq 0.15 \) ng/mL, T1-T2a, \( \leq 33% \) biopsies+,
|       |            | \( \leq 50% \) cores                                                   |
| 616   | 66         | Gleason \( \leq 3+3 \), PSA \( \leq 10 \) ng/mL, PSAd \( \leq 0.2 \) ng/mL, T1C-T2,
|       |            | \( \leq 2 \) biopsies +                                                  |
| 326   | 67         | Gleason \( \leq 3+4 \), PSA \( < 15 \) ng/mL, T1-T2a,Nonx,M0MX \( \leq 2a \),
|       |            | \( \leq 50\% \) biopsies +                                              |
| 230   | 64         | Gleason \( \leq 6 \), PSA \( < 10 \) ng/dL, T1a-T2, \( \leq 2 \) biopsies+,
|       |            | \( \leq 20\% \) cores +                                               |
| 453   | 70         | Gleason \( \leq 6 \), PSA \( < 10 \) ng/mL, (up to 1999: Gleason \( \leq 3+4 \), PSA
|       |            | \( < 15 \) ng/mL) \( < 3 \) biopsies +,
|       |            | \( < 50\% \) each core                                                 |
| 769   | 66         | Gleason \( \leq 3+3 \), PSAd \( < 0.15 \) ng/mL, T1, \( \leq 2 \) biopsies+,
|       |            | \( \leq 50\% \) cores +                                              |
| 238   | 64         | Gleason \( \leq 3+3 \), PSA \( < 10 \) ng/mL, T1-T2a, \( \leq 3 \) biopsies+,
|       |            | \( \leq 50\% \) cores +                                              |

**OS = overall survival; CSS = cancer-specific survival; PFS = progression-free survival.**

### Table 13: Clinical trials of AS for organ-confined PCa: main results

<table>
<thead>
<tr>
<th></th>
<th>Progression</th>
<th>RP (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median follow-up (months)</td>
<td>Biopsy (%)</td>
<td>PSA / PSA DT</td>
</tr>
<tr>
<td>Dall’Era</td>
<td>47</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Van den Berg</td>
<td>52</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Van As</td>
<td>22</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Soloway</td>
<td>32</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Klotz</td>
<td>82</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Tosoain</td>
<td>32</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Adamy</td>
<td>22</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

Different series have identified several eligibility criteria for enrolment (41):

- clinically confined PCa (T1-T2);
- Gleason score < 7 for most studies;
- PSA < 10-15 ng/mL.

Limited tumour volume is defined by a low number of involved cores and a low tumour length on each involved core. The role of other tools, e.g. MRI, to better define acceptable lesions remains controversial, except
probably for anterior lesions (42). The PCA3 level may become a practical tool in the future (43).

Active surveillance is based on repeated DRE, PSA and most importantly repeated biopsies, usually every year. The place of early repeated biopsy has become an important part of the selection process, based on the risk of under-detection of grade 4 (35,40,44,45).

The criteria for active treatment are less well defined (5), but most groups have used:

- PSA doubling time with a cut-off value ranging between ≤ 2 and ≤ 4 years. This criterion is becoming questionable because of a weak link between PSA doubling time and grade progression on repeated biopsy (46).
- Gleason score progression to ≥ 7 during follow-up systematic biopsies, at intervals ranging from 1-4 years.
- Patient’s request mainly based on anxiety. This is a significant factor (36) and might affect up to 10% of treated patients. No data is available regarding active surveillance. However, data from the SPCG-4 trial has suggested that, based on self-administered questionnaires 87% of the included patients, the treatment group always reported inferior well-being, depression and psychological status, but this difference was never significant (47).

8.3 Deferred treatment for locally advanced PCa (stage T3-T4, Nx-N0, M0)

The literature reporting on deferred treatment for locally advanced PCa is sparse. There are no randomised studies that compare more aggressive treatments, such as radiotherapy or surgery, with or without hormones.

Most patients whose disease progresses after deferred treatment of locally advanced PCa will be candidates for hormone therapy. There are reports from non-randomised studies showing that hormone treatment may safely be delayed until metastatic progression occurs, as no survival advantage was noted between patients treated with immediate orchectomy compared with delayed treatment (48,49).

In a prospective randomised clinical phase III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0 PCa were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic disease progression or occurrence of serious complications (50,51). After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% confidence interval [CI]: 1.05-1.48; non-inferiority p > 0.1) favouring immediate treatment, seemingly due to fewer deaths of non-prostatic cancer causes (p = 0.06). The time from randomisation to progression of hormone-refractory disease did not differ significantly nor did prostate cancer-specific survival. The median time to the start of deferred treatment after study entry was 7 years. In this group, 126 patients (25.6%) died without ever needing treatment (44% of deaths in this arm). The conclusion drawn from this study is that immediate ADT resulted in a modest but statistically significant increase in overall survival, but no significant difference in PCa mortality or symptom-free survival. This raises the question of the usefulness of such a small statistical benefit.

Furthermore, the authors identified significant risk factors associated with a significantly worse outcome: in both arms. Patients with a baseline PSA > 50 ng/mL were at a > 3.5-fold higher risk of dying of PCa than patients with a baseline PSA ≤ 8 ng/mL. If the baseline PSA was between 8 ng/mL and 50 ng/mL, the risk of PCa death was approximately 7.5-fold higher in patients with a PSA doubling time < 12 months than in patients with a PSA doubling time > 12 months. The time to PSA relapse following a response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA may also reflect disease aggressiveness.

However, when early and delayed treatments were compared in a large randomised trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormone therapy was demonstrated (62), comparable with the results of the Lundgren et al. study mentioned above (22) (LE: 1b). In addition, a comparison of bicalutamide, 150 mg/day, with placebo showed that progression-free survival (PFS) was better with early treatment in patients with locally advanced PCa (23) (LE: 1b).

Fifty selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 PCa were followed up for 169 months (53). The 5- and 10-year cancer-specific survival rates were 90% and 74%, respectively, and the likelihood of being without treatment at 5 and 10 years was 40% and 30%, respectively. The authors concluded that WW might be a treatment option for selected patients with non-poorly differentiated T3 tumours and a life expectancy of less than 10 years (LE: 3).

8.4 Deferred treatment for metastatic PCa (stage M1)

There are only very sparse data on this subject. The only candidates for such treatment should be asymptomatic patients with a strong wish to avoid treatment-related side-effects (LE: 4). As the median survival time is about 2 years, the time without any treatment (before symptoms occur) is very short in most cases. The MRC trial highlighted the risk of developing symptoms (pathological fractures, spinal cord compression), and even death from PCa, without receiving the possible benefit from hormone treatment (52,54) (LE:1b). If a deferred treatment policy is chosen for a patient with advanced PCa, close follow-up must be possible.
8.5 Summary of deferred treatment for prostate cancer

### 8.5.1 Indications

<table>
<thead>
<tr>
<th>Stages</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Well and moderately differentiated tumours. In younger patients with a life expectancy of more than 10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended.</td>
</tr>
<tr>
<td>T1b-T2b</td>
<td>Well and moderately differentiated tumours. In asymptomatic patients with a life expectancy of &lt; 10 years.</td>
</tr>
</tbody>
</table>

### 8.5.2 Options

<table>
<thead>
<tr>
<th>Stages</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1b-T2b</td>
<td>Patients who are well informed and have well-differentiated PCa and a life expectancy of 10-15 years. All patients not willing to accept side-effects of active treatment. Well-informed, asymptomatic patients with high PSA levels for whom cure is unlikely.</td>
</tr>
<tr>
<td>T3-T4</td>
<td>Asymptomatic patients with well or moderately differentiated cancer, PCa and a short life expectancy. PSA &lt; 50 ng/mL and PSA doubling time &gt; 12 months.</td>
</tr>
</tbody>
</table>

### 8.6 References


9. TREATMENT: RADICAL PROSTATECTOMY

9.1 Introduction

The surgical treatment of prostate cancer (PCa) consists of radical prostatectomy (RP), which involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. In men with localised PCa and a life expectancy ≥ 10 years, the goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency (1). There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone (2). Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes (3). An estimation of life expectancy is paramount in counselling a patient about surgery (4).

Currently, RP is the only treatment for localised PCa to show a benefit for OS and cancer-specific survival (CSS), compared with conservative management, as shown in one prospective randomised trial (5). After a follow-up of 15 years, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality: RR=0.75 (0.61 to 0.92). According to a post hoc statistical sub-group analysis, the number to treat (NNT) to avert one death was 15 overall and 7 for men younger than 65 years of age. Radical prostatectomy...
was also associated with a reduction in prostate cancer-specific mortality: RR=0.62 (0.44 to 0.87). This OS and CSS benefit could not be reproduced for the overall study population in another prospective randomised trial. After a median follow-up of 10 years, the PIVOT trial showed that RP did not significantly reduce all-cause mortality: HR=0.88 (0.71 to 1.08); p=0.22, nor did RP significantly reduce prostate cancer mortality: HR=0.63 (0.36 to 1.09); p=0.09. According to a preplanned sub-group analysis among men with low-risk tumours (n=296), RP non-significantly increased all-cause mortality: HR=1.15 (0.80 to 1.66). Among men with intermediate-risk tumours (n=249), RP significantly reduced all-cause mortality: HR=0.69 (0.49 to 0.98). Among men with high-risk tumours (n=157), RP non-significantly reduced all-cause mortality: HR=0.40 (0.16 to 1.00). Among men with PSA > 10, RP significantly reduced all cause mortality: HR=0.67 (0.48 to 0.94).

Surgical expertise has decreased the complication rates of RP and improved cancer cure (6-10). If performed by an experienced surgeon, the patient’s subsequent quality of life should be satisfactory. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can decrease positive surgical margin rates and improve cancer control with RP (11,12).

Radical retropubic prostatectomy (RRP) and perineal prostatectomy are performed through open incisions, and more recently, minimally invasive laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic prostatectomy (RALP) have been developed. RALP is displacing RRP as the gold standard surgical approach for clinically localised PCa in the United States and is also being increasingly used in Europe and other parts of the world. This trend has occurred despite the paucity of high-quality evidence to support its superiority over more-established treatment modalities. Recent in-depth systematic reviews of the literature have compared the results of RRP versus LRP/RALP.

Robot-assisted laparoscopic prostatectomy is associated with less blood loss and transfusion rates comparable to RRP, and there appear to be minimal differences between the two surgical approaches in terms of overall post-operative complications. Positive surgical margin rates are at least equivalent to RARP, but firm conclusions about biochemical recurrence and other oncologic end-points are difficult to draw due to the relatively short follow-up in the published literature and the fact that the overall experience with RARP in locally advanced PCa is still limited. RARP may offer advantages in postoperative recovery for urinary continence and erectile function, although most published studies addressing these outcomes suffer from methodological limitations. There is a need for well-controlled comparative outcomes studies of RP surgery following best practice guidelines.(13-17).

9.2  Low-risk, localised prostate cancer: cT1-T2a and Gleason score 2-6 and prostate-specific antigen < 10 ng/mL

Patients with low-risk, localised PCa should be informed about the results of two randomised trials comparing retropubic RP versus watchful waiting (WW) in localised PCa. In the SPCG-4 study, the survival benefit was similar before and after 9 years of follow-up and was also observed in men with low-risk PCa, and was confined to men < 65 years of age. In the PIVOT-trail, a preplanned sub-group analysis of men with low-risk tumours, showed that RP did not significantly reduce all-cause mortality.

9.2.1 Stage T1a-T1b prostate cancer

Stage T1a PCa is defined as an incidental histological finding of cancer in ≤ 5% of resected prostatic tissue [transurethral resection of the prostate (TURP) or open adenectomy]. Stage T1b PCa is defined as > 5% cancer. Published series have shown a pT0 stage in 4-21% and an organ-confined stage in 47-85% of patients at subsequent RP (18).

A Swedish register-based study of 23,288 men with incidental PCa detected at TURP or open adenoma enucleation, mostly the prostate-specific antigen (PSA) era, showed a 10-year PCa mortality of 26.6%. There were no details of the PSA level or Gleason score, nor the numbers of cases with cT1a or cT1b PCa (19). Other older studies have shown that, even though the risk of disease progression of untreated T1a PCa after 5 years is only 5%, these cancers can progress in about 50% of cases after 10-13 years (20). Thus, it was believed that, in younger patients with a life-expectancy of ≥ 15 years, the chance of disease progression was real. In contrast, most patients with T1b tumours were expected to show disease progression after 5 years, and aggressive treatment was often warranted (20). Patients with T1b lesions were offered RP when they had a life expectancy of ≥ 10 years.

Nevertheless, it remains unclear whether these findings would still be valid in the PSA era. In a recent analysis of T1a/b PCa:

- The only significant predictors of the presence of residual cancer at RRP were PSA measured before and after surgery for benign prostatic hyperplasia (BPH) and Gleason score at surgery for BPH.
- The only independent predictors of biochemical recurrence after RRP were PSA measured after
surgery for BPH and Gleason score at surgery for BPH.

• The stage (cT1a or cT1b) lost its significance in predicting the above-mentioned outcomes.

A predictive model has been proposed, which incorporates the PSA level before and after surgery and the Gleason score at surgery for BPH. The model has a predictive accuracy of 83.2% for estimating residual tumour and 87.5% for estimating biochemical progression, but needs external validation before it can be used in daily practice (18).

Systematic prostate biopsies of the remnant prostate may be useful in detecting residual cancer or concomitant peripheral zone cancer, or to ascertain a more correct tumour grade. Radical prostatectomy may be difficult after thorough TURP, when almost no residual prostate is left behind (21).

9.2.2 Stage T1c and T2a prostate cancer
Clinically unapparent tumour identified by needle biopsy because of an elevated PSA (cT1c) has become the most prevalent type of PCa. In an individual patient, it is difficult to differentiate between clinically insignificant and life-threatening PCa. Most reports, however, stress that cT1c tumours are mostly significant and should not be left untreated because up to 30% of cT1c tumours are locally advanced at final histopathological analysis (22). The proportion of insignificant tumours varies between 11% and 16% (23,24). Increasing the number of biopsies may carry the risk of detecting a higher number of insignificant cancers. However, a recent study has shown that increasing the number of biopsies to 12 did not increase the number of insignificant tumours (25). The major problem is how to recognise those tumours that do not need RP. The biopsy findings and the free PSA ratio are helpful in predicting insignificant disease (26). Partin tables may help better selection of patients who require surgical treatment, because of their ability to provide an estimation of the final pathological stage (27). Other authors have suggested the incorporation of biopsy information, such as the number of cores or the percentage of cores invaded (28). When only one or a few cores are invaded and the percentage of invasion in one core is limited, the chance of finding an insignificant PCa is more likely, certainly when the lesion is of low Gleason score (29). It might be reasonable to follow-up some patients whose tumours are most likely to be insignificant.

In general, however, RP should be advocated for patients with T1c tumours, bearing in mind that significant tumours will be found in most of these individuals. Stage T2a patients with a 10-year life expectancy should be offered RP because 35-55% of them will have disease progression after 5 years if not treated. If active monitoring is proposed for low-grade T2 cancer, it should be remembered that preoperative assessment of tumour grade by needle biopsy is often unreliable (30).

Extended pelvic lymph node dissection (eLND) is not necessary in low-risk, localised PCa, because the risk for positive lymph nodes does not exceed 5% (31).

9.3 Intermediate-risk, localised prostate cancer: cT2b-T2c or Gleason score = 7 or prostate-specific antigen 10-20 ng/mL
Patients with intermediate-risk, localised PCa should be informed about the results of two randomised trials comparing RRP vs. WW in localised PCa. In the SPCG-4 study, the survival benefit was similar before and after 9 years of follow-up and was confined to men < 65 years of age. The number needed to treat to avert one death was 15 overall and seven for men < 65 years of age. In the PIVOT-trial, a preplanned sub-group analysis of men with intermediate-risk tumours, RP did significantly reduce all-cause mortality. Radical prostatectomy is one of the recommended standard treatments for patients with intermediate-risk PCa and a life expectancy of > 10 years (32). The prognosis is excellent when the tumour is confined to the prostate, based on pathological examination (33,34). A policy of WW has been proposed for some patients with intermediate-risk localised tumours (35). However, when the tumour is palpable or visible on imaging and clinically confined to the prostate, disease progression can be expected in most long-term survivors. The median time to progression of untreated T2 disease has been reported as 6-10 years. Stage T2b cancer confined to the prostate, but involving more than half a lobe or both lobes, will progress in > 70% of patients within 5 years (36). These data have been confirmed by a large RCT which included mostly T2 PCa patients and compared RP and WW. The results showed a significant reduction in disease-specific mortality in favour of RP (5). Another large RCT corroborated these results (6).

An eLND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 5% (31). In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes. Limited LND should no longer be performed, because this misses at least half of the nodes involved.
9.3.1 **Oncological results of radical prostatectomy in low- and intermediate-risk prostate cancer**

The results achieved in a number of studies involving RP are shown in Table 14.

**Table 14: Oncological results of RP in organ-confined disease**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Year of RP</th>
<th>Median follow-up (mo)</th>
<th>10-year PSA-free survival (%)</th>
<th>10-year cancer-specific survival (%)</th>
<th>15-year cancer-specific survival (%)</th>
<th>25-year cancer-specific survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isbarn et al. (2009)</td>
<td>436</td>
<td>1992-97</td>
<td>122</td>
<td>60</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han et al. (2001)</td>
<td>2404</td>
<td>1982-99</td>
<td>75</td>
<td>74</td>
<td>96</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Hull et al. (2002)</td>
<td>1000</td>
<td>1983-98</td>
<td>53</td>
<td>75</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porter et al. (2006)</td>
<td>752</td>
<td>1954-94</td>
<td>137</td>
<td>71</td>
<td>96</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>Stephenson et al. (42)</td>
<td>6398</td>
<td>1987-2005</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td>88</td>
</tr>
</tbody>
</table>

The first externally validated nomogram predicting PCa-specific mortality after RP for patients treated in the PSA era was published in 2009. The nomogram predicts that few patients die from PCa within 15 years of RP, despite the presence of adverse clinical features. This nomogram can be used in patient counselling and clinical trial design (42).

9.4 **High-risk localised and locally advanced prostate cancer: cT3a or Gleason score 8-10 or prostate-specificantigen > 20 ng/mL**

The widespread use of PSA testing has led to a significant migration in stage and grade of PCa, with > 90% of men in the current era diagnosed with clinically localised disease (27). Despite the trends towards lower-risk PCa, 20-35% of patients with newly diagnosed PCa are still classified as high risk, based on either PSA > 20 ng/mL, Gleason score > 8, or an advanced clinical stage (43). Patients classified with high-risk PCa are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP (44).

There is no consensus regarding the optimal treatment of men with high-risk PCa. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.

9.4.1 **Locally advanced prostate cancer: cT3a**

Stage T3a cancer is defined as cancer that has perforated the prostate capsule. In the past, locally advanced PCa was seen in about 40% of all clinically diagnosed tumours. This figure is lower today, although its management remains controversial. Surgical treatment of clinical stage T3 PCa has traditionally been discouraged (45), mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse (46,47). Several randomised studies of radiotherapy combined with ADT versus radiotherapy alone have shown a clear advantage for combination treatment, but no trial has ever proven combined treatment to be superior to RP (48). Another problem is “contamination” by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal therapy (HT) in most series reporting the treatment of clinical T3 PCa. In recent years, there has been renewed interest in surgery for locally advanced PCa, and several retrospective case series have been published. Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease (49-51).
Over-staging of cT3 PCa is relatively frequent and occurs in 13-27% of cases. Patients with pT2 disease and those with specimen-confined pT3 disease have similarly good biochemical and clinical PFS (50,51). In 33.5-66% of patients, positive section margins are present, and 7.9-49% have positive lymph nodes (52). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or HT (50,51). Nevertheless, excellent 5-, 10- and 15-year OS and CSS rates have been published (Table 15). These rates surpass radiotherapy-alone and are no different from radiotherapy combined with adjuvant HT (48).

The problem remains the selection of patients before surgery. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease (27,52). In addition, nodal imaging with CT, and seminal vesicle imaging with MRI, or directed specific puncture biopsies of the nodes or seminal vesicles can help to identify those patients unlikely to benefit from a surgical approach (53). Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. Increased overall surgical experience must contribute to decreased operative morbidity and to better functional results after RP for clinical T3 cancer (50,54). It has been shown that continence can be preserved in most cases, and in selected cases, potency can also be preserved (55).

Table 15: OS and CSS rates for locally advanced PCa.

<table>
<thead>
<tr>
<th>Reference</th>
<th>no. of patients</th>
<th>Median and/or mean follow-up</th>
<th>BPFS (%)</th>
<th>CSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerber et al.</td>
<td>242</td>
<td>Mean, 39 months Median, 26 months</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>Ward et al.</td>
<td>841</td>
<td>Median, 10.3 years</td>
<td>58 (PSA &gt; 0.4)</td>
<td>95</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>200</td>
<td>Mean, 70.6 months (cT3a only)</td>
<td>59.5 (PSA &gt; 0.2)</td>
<td>99</td>
</tr>
</tbody>
</table>

BPFS = biochemical progression-free survival

**9.4.2 High-grade prostate cancer: Gleason score 8-10**

Although most poorly differentiated tumours extend outside the prostate, the incidence of organ-confined disease is 26-31%. Patients with high-grade tumours confined to the prostate at histopathological examination still have a good prognosis after RP. Furthermore, one-third of patients with a biopsy Gleason score ≥ 8 may in fact have a specimen Gleason score ≤ 7 with better prognostic characteristics. The PSA value and percentage of positive prostate biopsies may help to select men with high-grade PCa who are most likely to benefit from RP (56).

**9.4.3 Prostate cancer with prostate-specific antigen > 20 ng/mL**

Yossepowitch et al. have reported the results of RP as monotherapy in men with PSA > 20 ng/mL, in a cohort with mostly clinically organ-confined tumours, and found a PSA failure rate of 44% and 53% at 5 and 10 years, respectively (44). D’Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP (57). Spahn et al. published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively (58). In the same analysis, they demonstrated that the combination of PSA > 20 ng/mL with cT3 stage and/or biopsy Gleason score 8-10 significantly lowered CSS. More recently, Gontero and co-workers described a subanalysis of the same patient cohort. Ten-year CSS was 80%, 85% and 91% in patients with PSA > 100 ng/mL, 50.1-100 ng/mL and 20.1-50 ng/mL, respectively. These results argue for aggressive management with RP as the initial step (59).

Extended LND should be performed in all high-risk cases, because the estimated risk for positive lymph nodes is 15-40% (31). Limited LND should no longer be performed, because it misses at least half the nodes involved.

**9.5 Very-high-risk, localised prostate cancer: cT3b-T4 N0 or any T, N1**

**9.5.1 cT3b-T4 N0**

Men with very-high-risk PCa generally have a significant risk of disease progression and cancer-related death
if left untreated. Very-high-risk PCa presents two specific challenges. There is a need for local control as well as treatment of any microscopic metastases that are likely to be present but undetectable until disease progression.

The optimal treatment approach therefore often necessitates multiple modalities. The exact combinations, timing and intensity of treatment continue to be strongly debated. A recent US study has shown that 72 patients who underwent RP for cT4 disease had better survival than those who received HT or radiotherapy alone, and comparable survival to men who received radiotherapy plus HT (60). Another study has compared the outcomes of RP in very-high-risk PCa (T3-T4 N0-N1, N1, M1a) with those in localised PCa. The two groups did not differ significantly in surgical morbidity except for blood transfusion, operative time, and lymphoceles, which showed a higher rate in patients with advanced disease. Overall survival and CSS at 7 years were 76.69% and 90.2% in the advanced disease group and 88.4% and 99.3% in the organ-confined disease group, respectively (61).

Provided that the tumour is not fixed to the pelvic wall, or there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with very-high-risk PCa and low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.

9.5.2 Any T, N1

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Clinical lymph node-positive (N+) disease will mostly be followed by systemic disease progression, and all patients with significant N+ disease ultimately fail treatment.

Nevertheless, the combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% (62,63). Most urologists are reluctant to perform RP for clinical N+ disease, or cancel surgery if a frozen section shows lymph node invasion. However, a retrospective observational study has shown a dramatic improvement in CSS and OS in favour of completed RP vs. abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and the abandonment of RP in N+ cases may not be justified (64). These findings have been corroborated in a contemporary retrospective analysis (65). Radical prostatectomy resulted in superior survival of patients with N+ PCa after controlling for lymph node tumour burden. The findings from these studies support the role of RP as an important component of multimodal strategies of N+ PCa.

The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only (66,67). In patients who prove to be pN+ after RP, early adjuvant HT has been shown to improve CSS and OS significantly in a prospective randomised trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more eLND. The benefits should be judged against the side effects of long-term HT. Follow-up of PSA and delayed start of HT in patients with rising PSA level is therefore an acceptable option in selected cases. Interestingly, maximal local control with radiotherapy of the prostatic fossa appears to be beneficial in PCa patients with pN+ after RP, treated adjuvantly with continuous ADT (68).

9.6 Indication and extent of extended pelvic lymph node dissection

Although it is generally accepted that eLND provides important information for prognosis (number of nodes involved, tumour volume within the lymph node, and capsular perforation of the node) that cannot be matched by any other current procedure, consensus has not been reached about when eLND is indicated and to what extent it should be performed. When making such decisions, many physicians rely on nomograms based on preoperative biochemical markers and biopsies (27).

According to these nomograms, patients with PSA < 10 ng/mL and biopsy Gleason score < 7 have a low risk of lymph node metastasis, and therefore, eLND might not be beneficial. However, the fact that most nomograms are based on a limited eLND (obturator fossa and external iliac vein) probably results in underestimation of the incidence of patients with positive nodes (31). Lymphography studies have shown that the prostate drains not only to the obturator and external iliac lymph nodes but also to the internal iliac and presacral nodes. Performing eLND results in removal of all lymph nodes in these particular anatomical regions, producing a higher yield of excised lymph nodes (mean: 20 nodes) compared with limited LND (mean: 8-10 nodes).

In patients with PSA < 10 ng/mL and Gleason score ≥ 7, the incidence of nodal involvement has been reported as 25% (69). Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (70,71). Clearly, the removal of a greater number of nodes results in improved staging. In the largest study of its kind, a cut-off ≤ 2 vs. > 2 affected nodes was shown to
be an independent predictor of CSS (66).

9.6.1 **Extent of extended lymph node dissection**

Extended LND includes removal of the nodes overlaying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. Some lymph node mapping studies have advocated extending the template to include the common iliac lymph nodes up to the ureteric crossing. With this template, 75% of all anatomical landing sites are cleared (72). For eLND to be representative, a mean of 20 lymph nodes should be removed (73). It is recommended that the nodes should be sent in separate containers for each region for histopathological analysis, because this will usually be associated with a higher diagnostic gain by the uropathologist.

9.6.2 **Therapeutic role of extended lymph node dissection**

Besides being a staging procedure, pelvic LND/eLND can be curative, or at least beneficial, in a subset of patients with limited lymph node metastases (74-76). In some series, the number of nodes removed during lymphadenectomy has correlated significantly with time to progression (77). In one population-based study with a 10-year follow-up, patients undergoing excision of at least four lymph nodes (node-positive and node-negative patients) or > 10 nodes (only node-negative patients) had a lower risk of PCa-specific death at 10 years than those who did not undergo lymphadenectomy (78). Further studies should confirm these results.

9.6.3 **Morbidity**

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended vs. limited LND, threefold higher complication rates have been reported by some authors (79). Complications consist of lymphocoeles, lymphoedema, deep venous thrombosis, and pulmonary embolism. Other authors, however, have reported more acceptable complication rates (80,81).

9.6.4 **Conclusions extended lymph node dissection**

| Extended LND may play a role in the treatment of a subset of intermediate-risk cases with > 5% nomogram predicted risk of positive lymph nodes, and in all high-risk cases. |
| Extended LND may increase staging accuracy and influence decision making with respect to adjuvant therapy. The number of lymph nodes removed correlates with time to progression. |
| Surgical morbidity must be balanced against the therapeutic effects, and decisions need to be made based on an individual cases. |

9.7 **Summary of radical prostatectomy and eLND in high-risk localised disease**

| RP is a reasonable treatment option in selected patients with cT3a PCa, Gleason score 8-10 or PSA > 20. Furthermore, RP is optional in highly selected patients with cT3b-4 N0 or any cT N1 PCa in the context of a multimodality approach. |
| Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances. |
| If RP is performed, pelvic eLND must be performed, because lymph node involvement is common. |
| The patient must be informed about the likelihood of a multimodal approach. In case of adverse tumour characteristics (positive section margin, extraprostatic extension, or seminal vesicle invasion), adjuvant radiotherapy may reasonably be used after recuperation from surgery. |
| When nodal involvement is detected after surgery, adjuvant ADT may be selected. |
| Extended LND is not necessary in low-risk, localised PCa, because the risk for positive lymph nodes does not exceed 5%. |
| Extended LND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 5%, as well as in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15-40%. |
| Limited LND should no longer be performed, because it misses at least half the nodes involved. |

RP = radical prostatectomy; PCa = prostate cancer; eLND = extended lymph node dissection; ADT = androgen-deprivation therapy.
9.8 Neoadjuvant hormonal therapy and radical prostatectomy

Neoadjuvant or up-front HT is defined as therapy given before definitive local curative treatment (e.g., surgery or radiotherapy). PCa is an androgen-dependent tumour, therefore, neoadjuvant hormonal therapy (NHT) is an appealing concept. Attempts to decrease the size of the prostate before RP were first reported by Vallett as early as 1944 (82). In a recent review and meta-analysis, the role of NHT and prostatectomy has been studied (83). NHT before prostatectomy did not improve OS or disease-free survival (DFS), but did significantly reduce positive margin rates [relative risk (RR): 0.49; 95% confidence interval (CI): 0.42-0.56, P < 0.00001], organ confinement (RR: 1.63; 95% CI: 1.37-1.95, P < 0.0001) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, P < 0.02). Thus, the absence of improvement in clinically important outcomes (OS, disease-specific survival or biochemical DFS) was demonstrated despite improvements in putative pathological surrogate outcomes, such as margin-free positive status. This calls into question the use of these pathological markers of treatment outcomes as valid surrogates for clinically relevant outcomes.

Further studies are needed to investigate the application of HT as both neoadjuvant treatment and with chemotherapy in early disease. More information is also needed to evaluate these agents in terms of side effects and quality of life, which was lacking in most studies presented in this review.

Further cost analyses should be undertaken to update the data. A recent Cochrane review and meta-analysis have studied the role of adjuvant HT following RP: the pooled data for 5-year OS showed an odds ratio (OR) of 1.50 and 95% CI: 0.79-2.84. This finding was not statistically significant, although there was a trend favouring adjuvant HT. Similarly, there was no survival advantage at 10 years. The pooled data for DFS gave an overall OR of 3.73 and 95% CI: 2.3-6.03. The overall effect estimate was highly significant (P < 0.00001) in favour of the HT arm.

It is noteworthy that the Early Prostate Cancer Trialists’ Group (EPC) trial was not included in the Cochrane review. The third update from this large randomised trial of bicalutamide, 150 mg once daily, in addition to standard care in localised and locally advanced, non-metastatic PCa was published in November 2005 (84). Median follow-up was 7.2 years. There was a significant improvement in objective PFS in the RP group. This improvement was only significant in the locally advanced disease group [hazard ratio (HR): 0.75; 95% CI: 0.61-0.91]. There was no significant improvement in OS in the RP-treated groups (localised and locally advanced disease). In the WW group, there was an OS trend in favour of WW alone in the localised disease group (HR: 1.16; 95% CI: 0.99-1.37).

9.8.1 Summary of neoadjuvant and adjuvant hormonal treatment and radical prostatectomy

| NHT before RP does not provide a significant OS advantage over prostatectomy alone. |
| NHT before RP does not provide a significant advantage in DFS over prostatectomy alone. |
| NHT before RP does substantially improve local pathological variables such as organ-confined rates, pathological down-staging, positive surgical margins, and rate of lymph node involvement. |
| Adjuvant HT following RP shows no survival advantage at 10 years. |
| Adjuvant HT following RP: the overall effect estimate for DFS is highly significantly (P < 0.00001) in favour of the HT arm. |

9.9 Complications and functional outcome

The postoperative complications of RP are listed in Table 16. The mortality rate is 0-1.5% (81); urinary fistulae are seen in 1.2-4% of patients (85); and urinary incontinence persists after 1 year in 7.7% (86). In men undergoing prostatectomy, the rates of postoperative and late urinary complications are significantly reduced if the procedure is performed in a high-volume hospital and by a surgeon who performs a large number of such procedures (87-89).

Erectile dysfunction used to occur in nearly all patients, but this can be avoided by using nerve-sparing techniques in early-stage disease (90). Patients who benefit from nerve-sparing RP may have a higher chance of local disease recurrence and should therefore be selected carefully.
### Table 16: Complications of RP

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative death</td>
<td>0.0-2.1</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.0-11.5</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>0.0-5.4</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>0.0-8.3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.8-7.7</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>Urine leak, fistula</td>
<td>0.3-15.4</td>
</tr>
<tr>
<td>Slight stress incontinence</td>
<td>4.0-50.0</td>
</tr>
<tr>
<td>Severe stress incontinence</td>
<td>0.0-15.4</td>
</tr>
<tr>
<td>Impotence</td>
<td>29.0-100.0</td>
</tr>
<tr>
<td>Bladder neck obstruction</td>
<td>0.5-14.6</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>0.0-0.7</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>2.0-9.0</td>
</tr>
</tbody>
</table>

### 9.10 Summary of indications for nerve-sparing surgery* (100-104)

<table>
<thead>
<tr>
<th>Reference name</th>
<th>Sofer (91)</th>
<th>Walsh (92)</th>
<th>Alsikafi (93)</th>
<th>Graefen (94)</th>
<th>Bianco (95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative selection criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage &gt; T2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PSA &gt; 10</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy Gleason score 7</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy Gleason score 8-10</td>
<td>+</td>
<td></td>
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<tr>
<td>Partin tables</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Side with &gt; 50% tumour in biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Side with perineural invasion</td>
<td>+/-</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Intra-operative selection criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side of palpable tumour</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side of positive biopsy</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration of lateral pelvic fascia</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Adherence to neurovascular bundles</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Positive section margins</td>
<td>24%</td>
<td>5%</td>
<td>11%</td>
<td>15.9%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Clinical criteria used by different authors when NOT to perform a nerve-sparing RP

Nerve-sparing RP can be performed safely in most men undergoing RP (96,97). In the past decade, a dramatic shift towards lower-stage tumours has become evident. More importantly, men are younger at the time of diagnosis and more interested in preserving sexual function. Nevertheless, clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT3 PCa, cT2c, any Gleason score > 7 on biopsy, or more than one biopsy > 6 at the ipsilateral side. Partin tables help to guide decision making (27).

If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle (NVB). Alternatively, the use of intraoperative frozen-section analysis can help guide these decisions. This is especially helpful in patients with a lesion palpable close to the capsule during nerve-sparing RP. A wedge of the prostate can then be resected and inked differently. In case carcinoma is adherent to the capsule on frozen section analysis, the NVB is resected; otherwise, the NVB remains in situ. In patients with intraoperatively detected tumour lesions during nerve-sparing, planned RP, frozen-section analysis objectively supports the decision of secondary NVB resection, as well as preservation (98).

The patient must be informed before surgery about the risks of nerve-sparing surgery, the potency rates achieved, and the possibility that, to ensure adequate cancer control, the nerves may be sacrificed despite any preoperative optimism favouring the potential for their salvage.
The early administration of intracavernous injection therapy could improve the definitive potency rates (99,100). Finally, the early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. A placebo-controlled prospective study has shown no benefit from daily early administration of vardenafil vs. on-demand vardenafil in the postoperative period (101), whereas another placebo-controlled prospective study has shown that sildenafil has a significant impact on return of normal spontaneous erections (102).

9.11 Conclusions and recommendations for radical prostatectomy

<table>
<thead>
<tr>
<th>Indications</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with low and intermediate risk localised PCa (cT1a-T2b and Gleason score 2-7 and PSA ≤ 20 ng/mL) and life expectancy &gt; 10 years.</td>
<td>1b</td>
</tr>
<tr>
<td>Optional</td>
<td></td>
</tr>
<tr>
<td>Patients with stage T1a disease and a life expectancy &gt;15 years or Gleason score 7.</td>
<td>3</td>
</tr>
<tr>
<td>Selected patients with low-volume, high-risk, localised PCa (cT3a or Gleason score 8-10 or PSA &gt; 20 ng/mL).</td>
<td>3</td>
</tr>
<tr>
<td>Highly selected patients with very-high-risk, localised PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.</td>
<td>3</td>
</tr>
<tr>
<td>Short-term (3 months) or long-term (9 months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is NOT recommended for the treatment of stage T1-T2 disease.</td>
<td>1a</td>
</tr>
<tr>
<td>Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score &lt; 7 and PSA &lt; 10 ng/mL or see Partin tables/nomograms).</td>
<td>3</td>
</tr>
<tr>
<td>Unilateral nerve-sparing procedures are an option in stage T2a-T3a disease.</td>
<td>4</td>
</tr>
</tbody>
</table>

9.12 References


10. TREATMENT: DEFINITIVE RADIOTHERAPY

10.1 Introduction

There have been no randomised studies comparing RP with either external-beam radiotherapy (EBRT) or brachytherapy for localised PCa. The National Institutes of Health (NIH) consensus statement in 1988 (1) stated that external irradiation offers the same long-term survival results as surgery; moreover, EBRT provides a quality of life (QoL) at least as good as that following surgery (2). A more recent systematic review has provided a more sophisticated overview of outcomes from reports that meet the criteria for stratifying patients by risk group, standard outcome measures, numbers of patients, and minimum median follow-up period (3). Radiotherapy continues to be an important and valid alternative to surgery as the sole form of curative therapy.

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for external-beam radiotherapy, and all centres that are unable to offer this should have a plan to introduce it as a routine method for the definitive treatment of prostate cancer.

In addition to external irradiation, transperineal low-dose or high-dose rate brachytherapy are widely used. In localised and locally advanced PCa, several randomised phase III trials conducted by the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) have established the indications for the combination of external irradiation and ADT.

Whatever the technique used, the choice of treatment - after the appropriate assessment of the extent of the tumour - must be based on a multidisciplinary approach and should take the following into account:

- 2009 TNM classification.
- Gleason score, defined using an adequate number of core biopsies (at least 12).
- Baseline prostate-specific antigen (PSA).
- Age of the patient.
- Patient's comorbidity, life expectancy, and QoL.
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings.
- National Comprehensive Cancer Network (NCCN) and/or D'Amico prognostic factor classification (4).

Additional information on the various aspects of radiotherapy in the treatment of PCa is available in an extensive published overview (5).

10.2 Technical aspects: three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated external-beam radiotherapy (IMRT)

Anatomic data acquired by scanning the patient in a treatment position are transferred to the three-dimensional treatment planning system, which visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field by means of portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. Three-dimensional CRT improves local control through dose escalation, without significantly increasing the risk of morbidity.

It is possible to use IMRT with linear accelerators equipped with the latest multileaf collimators and specific software. At the time of irradiation, a multileaf collimator automatically - and in the case of IMRT continuously - adapts to the contours of the target volume seen by each beam; this allows for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves, which are particularly useful as a means of sparing the rectum. To date, no randomised trials have been published.
comparing dose escalation using IMRT and 3D-CRT.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear (6).

Another evolving technique for the delivery of IMRT is tomotherapy, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning. Preliminary data suggest that this technique is feasible in PCa treatment (7).

Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists, and computer scientists.

10.3 Radiotherapy for localised prostate cancer

10.3.1 Dose escalation

Before the advent of 3D-CRT, radiotherapy doses to the prostate were usually in the order of 64 Gy in 2-Gy fractions, or equivalent. With 3D-CRT, and more recently IMRT, dose escalation beyond this limit has been possible. Several randomised studies have shown that dose escalation (range 76-80 Gy) has a significant impact on the 5-year survival without biochemical relapse (8-14). These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant hormone therapy (see below) has varied.

To date, no trials have yet shown that dose escalation results in an OS benefit, but the trials have shown a remarkable consistency in that they have all reported improvements in freedom from biochemical progression in patients treated with dose-escalated radiotherapy:

- The M.D. Anderson study compared 78 Gy with 70 Gy conventional radiotherapy. It included 305 stage T1-3 patients with a pre-treatment PSA level of more than 10 ng/mL, with a median follow-up period of 9 years. At 10 years after treatment, 16% of the high-risk patients treated with 70 Gy had died of disease, in comparison with 4% of patients treated with 78 Gy (P = 0.05), a percentage similar to that for patients with higher PSA values, 15% vs. 2% (P = 0.03) (8).

- The PROG 95-09 study evaluated 393 T1b-T2b patients, 75% of whom had a Gleason score ≤ 6 and a PSA level < 15 ng/mL. The patients were randomly assigned to receive an initial boost to the prostate alone, using conformal protons, of either 19.8 Gy or 28.8 Gy, and then 50.4 Gy to a larger volume. With a median follow-up period of 8.9 years, there was a significant difference in the 10-year American Society for Radiation Oncology (ASTRO) biochemical failure rate, at 32.4% for conventional-dose treatment (70.2 Gy) and 16.7% for high-dose treatment (79.2 Gy) (P < 0.0001). The difference persisted when only low-risk patients (58% of the total) were examined: 28.2% for conventional and 7.1% for high-dose treatment (P < 0.0001) (9).

- The MRC RT01 study, comparing a dose of 64 Gy with 74 Gy, both with neoadjuvant hormonal therapy, in 843 men with T1b-T3b disease, showed an 11% difference in the 5-year biochemical disease-free survival (BDFS) in favour of dose-escalated radiotherapy (P = 0.0007) (15).

- The Dutch randomised phase III trial comparing 68 Gy with 78 Gy showed a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose of radiotherapy (P = 0.02) (11).

- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in men with localised prostate cancer, in 306 patients with a pelvic lymph node involvement risk of < 10% (Partin) or pN0, with no hormonal therapy allowed before, during, or after radiotherapy. With a median follow-up period of 61 months, better 5-year biological outcomes were seen in favor of dose-escalated radiotherapy (P = 0.036) (12).

In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT + hormone therapy (expert opinion). Currently, it is not possible to make different recommendations by risk group, as there is evidence from these randomised trials for an impact of dose-escalation in low-risk, medium-risk, and high-risk patients, although probably of different magnitudes (10).

10.3.2 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

Several randomised trials have shown clearly that in at least some patients with nonmetastatic prostate cancer, radiotherapy alone is inferior to the combination of radiotherapy plus ADT:

- EORTC study 22863 recruited 415 patients diagnosed with T1-2 grade 3 World Health Organization (WHO) or T3-4 N0 M0 and any histological grade, and compared radiotherapy plus adjuvant ADT with radiotherapy alone. Androgen deprivation treatment was allowed in cases of relapse. A total of 82% of patients were diagnosed as T3, 10% as T4, and 89% as N0. Hormonal treatment consisted of oral cyproterone acetate (CPA) 50 mg three times daily for 1 month, beginning 1 week before the start of radiotherapy, and goserelin acetate (Zoladex), 3.6 mg subcutaneously every 4 weeks for 3
years, starting on the first day of radiotherapy. The pelvic target volume received was 50 Gy, and the prostatic target volume was 20 Gy. With a median follow-up period of 66 months, the combination therapy compared with radiotherapy alone yielded significantly better survival (78% vs. 62%; P = 0.001) (16). At a median follow-up of 9.1 years, the 10-year OS remained significantly higher at 58.1% versus 39.8% (P < 0.0001), as did the clinical PFS at 47.7% vs. 22.7% (P < 0.0001). The 10-year cumulative incidences of PCa mortality were 11.1% vs. 31% (P < 0.0001), and the 10-year cumulative incidences of cardiovascular mortality were 11.1% vs. 8.2% (P = 0.75) (17).

- **RTOG study 8531** recruited 977 patients diagnosed with T3-4 N0-1 M0, or pT3, after RP. Androgen deprivation therapy was begun in the last week of irradiation and continued up to relapse (Group I) or was started at recurrence (Group II). A total of 15% of patients in Group I and 29% in Group II had undergone RP, and 14% of patients in Group I and 26% in Group II were pN1. Goserelin acetate, 3.6 mg subcutaneously, was administered every 4 weeks. The pelvis was irradiated with 45 Gy, while the prostatic target received 20-25 Gy. Patients diagnosed with stage pT3 received 60-65 Gy. With a median follow-up time of 7.6 years for all patients, the 10-year OS was significantly greater for the adjuvant arm, at 49% vs. 39% (P = 0.002) (18).

- **RTOG study 86-10** included 471 patients with bulky (5 x 5 cm) tumours T2-4 N0-X M0. Androgen deprivation therapy was administered at 2 months before irradiation and during irradiation, or in the case of relapse in the control arm. Thirty-two percent of the patients were diagnosed as having T2, 70% as having T3-4, and 91% with N0. The hormone treatment consisted of oral flutamide (Eulexin), 250 mg three times daily, and goserelin acetate (Zoladex), 3.6 mg every 4 weeks by subcutaneous injection. The pelvic target volume received 45 Gy and the prostatic target volume received 20-25 Gy. The 10-year OS estimates were 43% for ADT plus irradiation vs. 34% for hormonal treatment, although the difference was not significant (P = 0.12). There was a significant improvement in the 10-year disease-specific mortality (23% vs. 36%; P = 0.01), disease-free survival (11% vs. 3%; P < 0.0001) and in the biochemical failure rate (65% vs. 80%; P < 0.0001), with the addition of ADT having no statistical impact on the risk of fatal cardiac events (19).

- **A phase III randomised trial** including 206 patients with a PSA level of at least 10 ng/mL (maximum 40 ng/mL), a Gleason score of at least 7 (range 7-10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with 6 months of ADT. After a median follow-up period of 7.6 years, intermediate-risk or high-risk patients without moderate or severe comorbidity who had been randomly assigned to receive 3D-CRT + ADT showed a 13% improvement in the OS rate (P < 0.001) (20).

- **The RTOG 94-08 trial**, including 1979 patients with T1b-T2b and PSA < 20 ng/mL, showed that adding a complete androgen blockade for 2 months before and 2 months during conventional lower-dose radiotherapy (66 Gy) significantly improved the 10-year OS rate (62% vs. 57%; P = 0.03) (13). These trials included patients with a wide range of clinical risk factors, most of whom were thought to be at high risk of disease progression, usually by virtue of their clinical stage, but in some instances because of their PSA level or Gleason grade. The most powerful conclusion from these studies comes from the EORTC 22863 study, which is the basis for the combination of radiotherapy and ADT in patients with locally advanced (T3-T4) nonmetastatic prostate cancer. Whether these results should be applied to patients with all stages of prostate cancer is unclear.

- **EORTC trial 22991**, comparing 3D-CRT with or without IMRT with a choice of three levels of dosage (70 Gy, 74 Gy, or 78 Gy), with or without 6 months of neoadjuvant and concomitant hormonal therapy, was closed in April 2008 after recruiting 800 patients; the results are awaited.

10.3.2.1 Duration of adjuvant or neoadjuvant ADT in combination with radiotherapy.

Several phase III trials have attempted to define the optimum timing and/or duration of ADT in combination with radiotherapy.

- **The EORTC-22961 randomised phase III trial**, comparing 36 months of hormonal treatment plus radiotherapy with 6 months of hormonal treatment plus radiotherapy in 970 patients, showed that increased hormonal treatment improved OS in patients with high-risk PCa after 5 years (14). The 5-year overall mortality rates for short-term and long-term suppression were 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79; P = 0.65 for non-inferiority).

- **The Trans-Tasman Oncology Group (TROG) randomised trial** compared no neoadjuvant ADT with 3 months or 6 months of neoadjuvant ADT with goserelin and flutamide starting 2 months before radiotherapy, or 6 months of ADT with the same regimen starting 5 months before RT, in 818 men with T2b-T4 N0 M0 prostate cancer. While 3 months of ADT improved the biochemical PFS in comparison with radiotherapy alone, 6 months additionally improved the prostate cancer-specific survival and OS (21).
• The RTOG 94-13 randomised trial used a 2 × 2 design comparing whole-pelvic with prostate-only radiotherapy (see below) and neoadjuvant with adjuvant ADT in 1323 patients with stages T1c-T4 N0 M0 prostate cancer, and found no differences in the PFS. The report does, however, describe interactions between the timing of ADT and the radiotherapy volume, in subgroup analyses (22).

• The RTOG 92-02 study compared 4 months of neoadjuvant ADT (2 months before and during radiotherapy) with the same plus an additional 24 months of adjuvant ADT in 1554 men with T2c-T4 prostate cancer and reported improvements in local progression, disease-free survival, biochemical survival, and metastasis-free survival in patients treated with additional adjuvant ADT. However, an OS benefit was restricted to men with a Gleason score of 8-10 in the subgroup analysis (23).

10.3.2.2 Combined dose-escalated RT and ADT
Zelefsky et al. (24) reported a retrospective analysis of 2251 patients with T1-3 N0-X M0 PCa consisting of 571 low-risk patients (22.4%), 1074 intermediate-risk patients (42.1%), and 906 high-risk patients (35.5%), according to the National Comprehensive Cancer Network classification. Three-dimensional conformal radiotherapy or IMRT were administered to the prostate and seminal vesicles only. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years using image-guided IMRT. Androgen deprivation therapy by complete androgen blockade with a luteinising hormone-releasing hormone (LHRH) agonist plus oral antiandrogen was administered, at the discretion of the treating physician, to 1249 patients (49%), including 623 high-risk patients (69%), 456 intermediate-risk patients (42%), and 170 low-risk (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before radiotherapy and continued during radiotherapy. The end points were 10-year biochemical disease-free survival and distant metastasis-free survival. With an 8-year median follow-up period, the 10-year biochemical disease-free survival in each risk group was significantly improved by dose escalation: 84% (> 75.6 Gy) vs. 70% for low-risk patients (P = 0.04), 76% (> 81 Gy) vs. 57% for intermediate-risk patients (P = 0.0001), and 55% (> 81 Gy) vs. 41% for high-risk patients (P = 0.0001). The 6-month ADT also influenced the biochemical disease-free survival in intermediate-risk and high-risk patients, with 55% vs. 36% for high-risk patients (P < 0.0001). In the multivariate analysis, a dose greater than 81 Gy (P = 0.027) and ADT (P = 0.052) were found to be significant predictive factors for distant metastasis-free survival, but none of these parameters influenced PCa mortality or OS. There were very low rates of grade 3-4 acute or late toxicity (25).

10.3.2.3 Proposed EBRT treatment policy for localised prostate cancer

Low risk. Intensity-modulated radiotherapy with escalated dose and without androgen deprivation therapy is an alternative to brachytherapy (see below).

Intermediate risk. In patients who are suitable for ADT, combined IMRT with short-term ADT (4-6 months) (26,27). In patients who are unsuitable for ADT (e.g., due to comorbidities) or unwilling to accept it (e.g., to preserve their sexual health), IMRT at an escalated dose (80 Gy) or a combination of IMRT and brachytherapy is recommended.

High risk (T1-2 N0-X M0 with either a baseline PSA value > 20 ng/mL and/or a Gleason score of 8-10) plus short-term ADT, suggested by the Boston and 94-08 RTOG trials, did not show any impact on OS in the high-risk cohort. The high risk of relapse outside the irradiated volume makes a combined modality approach mandatory, consisting of dose-escalated IMRT including the pelvic lymph nodes plus long-term ADT. The duration of ADT has to take into account WHO performance status, comorbidities, and the number of poor prognostic factors: cT stage (> T2c), Gleason score 8-10, and PSA > 20 ng/mL.

10.3.3 The role of radiotherapy in locally advanced PCa: T3-4 N0, M0

The incidence of locally advanced PCa has declined as a result of individual and mass screening. Pelvic lymph node irradiation is optional for N0 patients, but the results of radiotherapy alone are very poor (28). The randomised trials discussed above clearly established that, in patients with locally advanced disease who are treated with radiotherapy, the addition of ADT results in better outcomes. However, some clinicians considered that the benefits were due to the earlier use of ADT and questioned the benefits of radiotherapy itself in this context. Three trials have established that in locally advanced disease, radiotherapy is effective and that combined radiotherapy plus ADT is clearly superior to ADT alone.

The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study included 1,205 patients with T3-4 (n = 1057) or T2, PSA > 40 ng/mL (n = 119), or T2, PSA > 20 ng and Gleason > 8 (n = 25) and N0-X M0 PCa, who were randomly assigned to lifelong ADT (bilateral orchidectomy or LHRH agonist), with or without radiotherapy (65-70 Gy to the prostate, with or without 45 Gy to the pelvic lymph nodes). With a median follow-up period of 6 years, the...
In practice, however, this has the disadvantage that dose distributions from protons are highly contrast, photon beams continue to deposit energy until they leave the body, including an exit dose. Their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to In theory, proton beams are an attractive alternative to photon-beam radiotherapy for PCa, as they deposit their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

In practice, however, this has the disadvantage that dose distributions from protons are highly sensitive to changes in internal anatomy, such as might occur with bladder or rectal filling, and prostate proton therapy is usually delivered with lateral beams. It is also possible that high linear energy transfer (LET)
radiotherapy using protons or carbon ions might offer inherent biological advantages over photons, which have a greater capacity for DNA damage dose for dose.

Only one randomised trial has incorporated proton therapy in one arm: the Loma Linda/Massachusetts General Hospital trial compared standard-dose conformal radiotherapy with dose-escalated radiotherapy using protons for the boost dose (9). This trial cannot, however, be used as evidence for the superiority of proton therapy per se, as its use here could be viewed simply as a sophisticated method of dose escalation. A randomised trial comparing equivalent doses of proton-beam therapy with IMRT is needed in order to compare the efficacy of protons vs. photons; a study of this type is under consideration by the RTOG.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing (40); the other study suggested a clearer advantage for protons (41). Further studies are clearly needed. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy. Theoretically, proton therapy may be associated with a lower risk of secondary cancers in comparison with IMRT because of the lower integral dose of radiation, but there are no data from patients treated for PCa to support this.

Carbon ions offer similar theoretical advantages to those of protons as an alternative to photon-beam therapy. In a phase II study, 175 patients with T1-3, N0-1, M0 PCa were treated with carbon ions at a dosage equivalent to 66 Gy in 20 fractions over 5 weeks (42). The treatment appeared to be well tolerated, with no RTOG grade 3 or 4 bowel or genitourinary toxicity, and an overall 4-year biochemical disease-free rate (BDFR) of 88% (41). As with protons, a randomised trial comparing carbon ions with IMRT and using equivalent doses is required.

10.5 Transperineal brachytherapy

Transperineal brachytherapy is a safe and effective technique. There is a consensus on the following eligibility criteria:

- Stage cT1b-T2a N0, M0.
- A Gleason score ≤ 6 assessed on an adequate number of random biopsies.
- An initial PSA level of ≤ 10 ng/mL.
- ≤ 50% of biopsy cores involved with cancer.
- A prostate volume of < 50 cm³.
- An International Prostatic Symptom Score (IPSS) ≤ 12 (43).

Patients with low-risk PCa are the most suitable candidates for low-dose-rate (LDR) brachytherapy. Further guidelines on the technical aspects of brachytherapy have been published recently and are strongly recommended (44).

In 1983, Holm et al. described the transperineal method with endorectal sonography, in which the patient is positioned in a dorsal decubitus gynaecological position (45). Implantation is undertaken with the patient under general anaesthesia or spinal block, and involves a learning curve for the whole team: the surgeon for delineation of the prostate and needle placement, the physicist for real-time dosimetry, and the radiation oncologist for source loading. The sonography probe introduced into the rectum is fixed in a stable position.

There have been no randomised trials comparing brachytherapy with other curative treatment modalities, and outcomes are based on nonrandomised case series. The results of permanent implants have been reported from different institutions, with a median follow-up ranging from 36 to 120 months (46). The recurrence-free survival after 5 and 10 years has been reported to range from 71% to 93% and from 65% to 85%, respectively (47-54). A significant correlation has been shown between the implanted dose and recurrence rates (55). Patients receiving a D90 of > 140 Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years than patients who received less than 140 Gy (92% vs. 68%). There is no benefit from adding neoadjuvant or adjuvant ADT to LDR brachytherapy (46).

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implantation transurethral resection of the prostate (TURP; required in up to 8.7% of cases), and incontinence (0-19%) (56). A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity (57). This observation requires further study in a larger number of patients. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for benign prostatic hyperplasia increases the risk of post-implantation incontinence and urinary morbidity.

The incidence of grade III toxicity is less than 5%. Erectile dysfunction develops in about 40% of the patients after 3-5 years. In a recent retrospective analysis of 5,621 men who had undergone LDR brachytherapy (58), the urinary, bowel, and erectile morbidity rates were 33.8%, 21%, and 16.7%, respectively, with invasive procedure rates of 10.3%, 0.8%, and 4%, respectively.

In patients with permanent implants, iodine-125 in granular form is the radioactive element of
reference, while palladium-103 may be used for less differentiated tumours with a high doubling time. The doses delivered to the planning target volume are 144 Gy for iodine-125 and 125 Gy for palladium-103. A Gleason score of 7 is still a "grey area," but patients with a Gleason score of 4 + 3 showed no difference in outcome (59).

A small randomised trial has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice (60).

In cases of intermediate-risk or high-risk localised PCa, brachytherapy in combination with supplemental external irradiation (61) or neoadjuvant hormonal treatment (62) may be considered. The optimum dose of supplemental EBRT is unclear. A randomised trial comparing 44 Gy with 20 Gy of EBRT plus palladium-103 brachytherapy closed early, showing no difference in the biochemical outcomes (63).

Nonpermanent transperineal interstitial prostate brachytherapy using a high-dose-rate iridium-192 stepping source and a remote afterloading technique can be applied with a total dose of 12-20 Gy in two to four fractions, combined with fractionated external radiotherapy of 45 Gy (64). Higher doses of supplemental EBRT than this may best be delivered with IMRT; a report from Memorial Sloan-Kettering indicates that this approach is safe and feasible (65).

Recent data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) (66). In a retrospective analysis of modern series (67,68), BDFS rates of 85.8%, 80.3%, and 67.8% in men with low-risk, intermediate-risk, and high-risk PCAs, respectively, were reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar with high-dose EBRT and high-dose-rate (HDR) brachytherapy, in terms of diarrhoea and insomnia (69). However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs. 34%). A single randomised trial of EBRT vs. EBRT plus HDR brachytherapy has been reported (70). A total of 220 patients with organ-confined PCAs were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical relapse-free survival (P = 0.03). There were no differences in the rates of late toxicity. Patients randomly assigned to EBRT plus brachytherapy had a significantly better QoL as measured by their Functional Assessment of Cancer Therapy-Prostate (FACT-P) score at 12 weeks. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to the uncommon fractionation used (70). There is still a need to compare dose-escalated EBRT plus hormone therapy, with the same following by a brachytherapy boost, in intermediate-risk and high-risk patients.

For T1-2 N0 M0 disease, the 5-year biochemical failure rates are similar for permanent seed implantation, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and radical prostatectomy, according to a study of 2991 patients diagnosed with T1-2 consecutive localised PCAs treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Center, with a minimum follow-up period of 1 year (66).

### 10.6 Late toxicity

Patients must be informed about the potential late genitourinary or gastrointestinal toxicity that may occur, and also about the impact of irradiation on erectile function. Late toxicity was analysed using a dose of 70 Gy in prospective EORTC randomised trial 22863 (1987-1995) (71), in which 90% of patients were diagnosed as having stage T3-4. A total of 377 patients (91%) out of 415 enrolled were evaluable for long-term toxicity, graded according to a modified RTOG scale. Eighty-six patients (22.8%) had grade 2 urinary or intestinal complications or leg oedema, 72 of whom had grade 2 (moderate) toxicity, while 10 had grade 3 (severe) toxicity and four died due to grade 4 (fatal) toxicity. Although four (1%) late treatment-related deaths occurred, the long-term toxicity was limited, with a grade 3 or 4 late complication rate of less than 5% being reported (Table 17). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT and IMRT.
Table 17: Incidence of late toxicity by Radiation Therapy Oncology Group (RTOG) grade (from EORTC trial 22863)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any significant toxicity (≥ grade 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cystitis</td>
<td>18</td>
<td>4.7</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Haematuria</td>
<td>18</td>
<td>4.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary stricture</td>
<td>18</td>
<td>4.7</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>18</td>
<td>4.7</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Overall GU toxicity</td>
<td>47</td>
<td>12.4</td>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>Proctitis</td>
<td>31</td>
<td>8.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
<td>14</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Overall GI toxicity</td>
<td>36</td>
<td>9.5</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Leg oedema</td>
<td>6</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall toxicity*</td>
<td>72</td>
<td>19.0</td>
<td>10</td>
<td>2.7</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; GU = genitourinary.

* Overall toxicity included GU and GI toxicity and leg oedema. As most patients had more than one type of toxicity, the overall toxicity does not result from simple addition.
† Two of the grade 4 patients were irradiated with cobalt-60.

Note: there was no other significant (≥ grade 2) toxicity among patients irradiated with cobalt-60 (n = 15), except for two patients with grade 4 GU (stated above) and only one patient with grade 2 GI toxicity.

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients (2). A recent meta-analysis has shown that the 1-year rates of probability for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing radical prostatectomy, and 0.25 after standard radical prostatectomy.

When studies with more than 2 years of follow-up were selected (i.e., excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches (72).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (73,74). In a retrospective evaluation of 30,552 and 55,263 men who had undergone either EBRT or RP, the risk of being diagnosed with rectal cancer increased 1.7-fold in comparison with the surgery group (73). Another analysis (74) showed that the relative risk of developing bladder cancer increased by 2.34-fold in comparison with a healthy control population. On the other hand, a re-analysis of SEER data including more than 100,000 patients demonstrated a risk of about 0.16% (i.e., 160 cases per 100,000 patients) of radiation-induced malignant tumours (75).

Corresponding data on late toxicity have also been reported by the Memorial Sloan-Kettering Cancer Center group, from their experience in 1571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of 10 years (75). Both acute gastrointestinal and genitourinary toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) grade 2 or more gastrointestinal toxicity was 5% with IMRT, in comparison with 13% with 3D-CRT. The incidence of grade 2 or higher late genitourinary toxicity was 20% in patients treated with 81 Gy, in comparison with 12% in patients treated with lower doses. The overall incidence of grade 3 gastrointestinal toxicity was 1%, and grade 3 genitourinary toxicity was 3%. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity, but, interestingly, with dose escalation, genitourinary toxicity may become the predominant type of morbidity (76).

10.6.1 Immediate (adjuvant) postoperative external irradiation after radical prostatectomy

Extracapsular invasion (pT3), Gleason score ≥ 7, and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after 5 years (77,78). Three prospective randomised trials have assessed the role of immediate postoperative radiotherapy (adjuvant radiotherapy, ART). EORTC study 22911 (79), with a target sample size of 1005 patients, compared immediate postoperative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as having pT3 pN0 with risk.
The most suitable candidates for immediate radiotherapy may be those with multifocal positive surgical margins and a Gleason score > 7. The conclusions of ARO trial 96-02 (n = 385) appear to support those of the EORTC study. After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical PFS of 72% vs. 54%, respectively (P = 0.0015). However - of major interest, and in contrast to other studies - randomisation of the patients was carried out after they had achieved an undetectable PSA level following RP (< 0.1 ng/mL), and only pT3 tumours were included. This finding indicates that adjuvant radiotherapy works even in the setting of an undetectable PSA after RP and additional risk factors (81). Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, P = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; P = 0.023) (82).

Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins and a Gleason score > 7. The conclusions of ARO trial 96-02 (n = 385) appear to support those of the EORTC study. After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical PFS of 72% vs. 54%, respectively (P = 0.0015). However - of major interest, and in contrast to other studies - randomisation of the patients was carried out after they had achieved an undetectable PSA level following RP (< 0.1 ng/mL), and only pT3 tumours were included. This finding indicates that adjuvant radiotherapy works even in the setting of an undetectable PSA after RP and additional risk factors (81). Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, P = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; P = 0.023) (82).

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The role of short-term hormone therapy in combination with radiotherapy is being investigated in the European Organization for Research and Treatment of Cancer (EORTC) 22043 randomised trial.

Decision-making on whether to proceed with adjuvant RT for high risk PCa - pT3-4 pN0 M0 with undetectable PSA - after radical prostatectomy, or to postpone RT as an early salvage procedure in case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before radical prostatectomy that adjuvant radiotherapy may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of radiotherapy when it is used and provides justification when it is not, and this will help the discussion between the physician and the patient.

### 10.7 Guidelines for definitive radiotherapy

<table>
<thead>
<tr>
<th>Guideline</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>In localised prostate cancer, T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended, even for young patients who decline surgical intervention.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>For high-risk patients, long-term ADT before and during radiotherapy is recommended, as it results in increased overall survival.</td>
<td>2a</td>
<td>B</td>
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<tr>
<td>In patients with locally advanced prostate cancer (T3-4, N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>In patients with cT1-T2a, Gleason score &lt; 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.</td>
<td>2a</td>
<td>B</td>
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<tr>
<td>In patients with pathological tumour stage T3 N0 M0, immediate postoperative external irradiation after RP may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In patients with pathological tumour stage T2-3 N0 M0, salvage irradiation is indicated in case of persisting PSA or biochemical failure, but before the PSA level rises above 0.5 ng/mL.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>In patients with locally advanced prostate cancer, T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>In a subset of patients with T2c-T3 N0-X and a Gleason score of 2-6, short-term ADT before and during radiotherapy can be recommended, as it may favourably influence the overall survival.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In patients with very high-risk prostate cancer, c-pN1 M0, with no severe comorbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended, as it will improve the overall survival, disease-specific failure rate, metastatic failure rate, and biochemical control.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

**CRT** = conformal radiotherapy; **IMRT** = intensity-modulated radiotherapy; **ADT** = androgen deprivation therapy; **EBRT** = external beam radiation therapy; **PSA** = prostate specific antigen; **TURP** = transurethral resection of the prostate; **IPSS** = international prostatic symptom score; **RP** = radical prostatectomy; **TURP** = International Prostate Symptom Score.

### 10.8 References


11. EXPERIMENTAL LOCAL TREATMENT OF PROSTATE CANCER

11.1 Background
Besides radical prostatectomy (RP), external beam radiation and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) have emerged as alternative therapeutic options in patients with clinically localised PCa (1-4).

Although HIFU is still considered to be an experimental treatment, CSAP has been recognised as a true therapeutic alternative according to the guidelines of the American Urological Association. Both HIFU and CSAP have been developed as minimally invasive procedures, which have potentially the same therapeutic efficacy as established surgical and non-surgical options, with reduced therapy-associated morbidity.

11.2 Cryosurgery of the prostate (CSAP)
Cryosurgery uses freezing techniques to induce cell death by:
• dehydration resulting in protein denaturation;
• direct rupture of cellular membranes by ice crystals;
• vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consequent ischaemia;
• apoptosis (1-4).

Freezing of the prostate is ensured by placement of 12-15 17G-cryoneedles under TRUS guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle.

11.2.1 Indication for CSAP
Patients who are ideal candidates for CSAP are those who have organ-confined PCa and those identified as
having minimal tumour extension beyond the prostate (1-3). The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobes under the pubic arch. PSA serum levels should be < 20 ng/mL, and the biopsy Gleason score should be < 7. It is important that patients with a life expectancy > 10 years should be fully informed that there are no data, or only minimal data, on the long-term outcome for cancer control at 10 and 15 years.

11.2.2 Results of modern cryosurgery for PCa

When comparing treatment modalities, it is important to bear in mind that, in modern RP patients with clinically organ-confined PCa, there is a very low risk (2.4%) of dying from PCa at 10 years after surgery (5). Therapeutic results have improved over time with enhanced techniques, such as gas-driven probes and transperineal probe placement, as used in third-generation cryosurgery (6-11).

An objective assessment of PSA outcome is not easily performed because some institutions use PSA values < 0.1 ng/mL as an indicator of therapeutic success, whereas others use the American Society of Therapeutic Radiology and Oncology (ASTRO) criteria, which requires three consecutive increases in PSA level.

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, biochemical disease-free survival (BDFS) at 5 years is 60% and 36% for low-risk and high-risk patients, respectively (6,7).

Long et al. (6) have performed a retrospective analysis of the multicentre, pooled, CSAP results of 975 patients stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL at a mean follow-up of 24 months, the 5-year actuarial BDFS rate was:

- 76% and 60%, respectively, for the low-risk group;
- 71% and 45%, respectively, for the intermediate-risk group;
- 61% and 36%, respectively, for the high-risk group.

However, according to a recent meta-analysis of 566 cryosurgery-related publications, there were no controlled trials, survival data or validated biochemical surrogate end-points available for analysis (12).

Cryosurgery showed progression-free survival (PFS) of 36-92% (projected 1- to 7-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72-87% of cases, but no biopsy data were available for the currently used third-generation cryotherapy machines.

With regard to third-generation cryosurgery, clinical follow-up is short, with a 12-month PSA follow-up carried out in only 110/176 (63%) patients (6-11). Eighty of these (73%) patients still had a PSA nadir < 0.4 ng/mL, whereas 42/65 (64.6%) low-risk patients remained free from biochemical progression using the 0.4 ng/mL cut-off.

Longer follow-up has been reported by Bahn et al. (9), who have analysed the therapeutic results of 590 patients undergoing CSAP for clinically localised and locally advanced PCa. At a PSA cut-off level of < 0.5 ng/mL, the 7-year BDFS for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively.

Nerve-sparing cryosurgery, as reported recently (13), must still be considered an experimental therapeutic option. Nerve-sparing surgery was performed in nine patients with unilateral PCa confirmed on repeated biopsies; CSAP was carried out on the side of the positive biopsy, whereas the negative biopsy side was spared from freezing.

11.2.3 Complications of CSAP for primary treatment of PCa

Erectile dysfunction occurs in about 80% of patients and remains a consistent complication of the CSAP procedure, independent of the generation of the system used. The complication rates described in third generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% (6-11). The development of fistula is usually rare, being < 0.2% in modern series. About 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.

Quality of life and sexuality following CSAP have been investigated in a clinical phase II trial recruiting 75 men (14). Quality-of-life analysis by the prostate-specific FACT-P questionnaire showed that most subscales return to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes are seen when comparing data at 36 months with those at 12 months. With regard to sexuality, 37% of men were able to have intercourse 3 years after CSAP.

In a recent, prospective, randomised clinical trial, 244 men with newly diagnosed organ-confined PCa were randomised to receive either external beam radiation therapy (EBRT) or to undergo CSAP (15). After a follow-up of 3 years, sexual function was significantly less impaired in the EBRT group.
11.2.4 **Summary conclusions for CSAP**

Patients with low-risk PCa (PSA < 10 ng/mL, < T2a, Gleason score < 6) or intermediate-risk PCa (PSA > 10 ng/mL, or Gleason score > 7, or stage > 2b) represent potential candidates for CSAP.

Prostate size should be < 40 mL at the time of therapy.

Long-term results are lacking, whereas 5-year BDFS rates are inferior to those achieved by RP in low-risk patients. Patients must be informed accordingly.

11.3 **HIFU of the prostate**

HIFU consists of focused ultrasound waves emitted from a transducer, which cause tissue damage by mechanical and thermal effects as well as by cavitation (16). The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis.

HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position. The procedure is time-consuming, with about 10 g prostate tissue treated per hour.

In a 2006 review, 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters (12). No controlled trial was available for analysis, and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy.

11.3.1 **Results of HIFU in PCa**

As with CSAP, it appears to be difficult to interpret oncological outcome in patients undergoing HIFU because various PSA thresholds are defined, and no international consensus exists on objective response criteria. The results of HIFU are limited, with outcome data from < 1,000 PCa cases published in the literature.

According to the review mentioned above (12), HIFU showed PFS (based on PSA ± biopsy data) of 63-87% (projected 3-5-year data), but median follow-up in the studies ranged from 12-24 months only.

In one of the largest single-centre studies, 227 patients with clinically organ-confined PCa were treated with HIFU, and their outcome data were analysed after a mean follow-up of 27 months (range: 12-121 months) (17). The projected 5-year BDFS was 66%, or only 57% if patients had exhibited a pre-therapeutic PSA value of 4-10 ng/mL. Incontinence and bladder neck stricture decreased over time from 28% and 31% to 9% and 6%, respectively. In one of the studies (18), a significant decrease in pre-treatment PSA serum levels from 12 to 2.4 ng/mL was observed. However, 50% of the 14 patients demonstrated positive prostate biopsies during follow-up. In another study (19), a complete response rate (i.e., PSA < 4 ng/mL) and six negative biopsies were achieved in 56% of the patients.

Thüroff et al. (19) have summarised the efficacy results of a European multicentre study comprising the data of 559 patients with mainly low- and intermediate-risk PCa, and have reported a negative biopsy rate of 87.2% in 288 men with a follow-up of at least 6 months. A PSA nadir after 6 months’ follow-up could be determined in 212 patients, and was 1.8 ng/mL. However, following the initial procedure, it could be demonstrated that the PSA nadir might be reached in 12-18 months.

Blana et al. have reported the results of 146 patients undergoing HIFU with a mean follow-up of 22.5 months (20). The mean PSA level at initiation of therapy was 7.6 ng/mL; the PSA nadir achieved after 3 months was 0.07 ng/mL. However, after 22 months, the median PSA level was 0.15 ng/mL. Of the 137 men available for analysis, 93.4% demonstrated a negative control biopsy. The PSA nadir appeared to be strongly associated with treatment failure (21) (P < 0.001). Patients with a PSA nadir of 0.0-0.2 ng/mL had a treatment failure rate of only 11% compared with 46% in patients with a PSA nadir of 0.21-1.00 ng/mL, and 48% with a PSA nadir of > 1.0 ng/mL. Recently, the group has updated its results, with a total of 163 men treated for clinically organ-confined PCa. Within the 4.8 ± 1.2 years of follow-up, the actuarial DFS rate at 5 years was 66%, with salvage treatment initiated in 12% of patients (22).

In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU (23). Biochemical failure was defined as the PSA nadir + 2 ng/mL, according to the Phoenix guidelines with regard to radiotherapy. After a median follow-up of 24 months, the BDFS was 72% for the entire cohort. The BDFS in patients with stage T1c, T2a, T2b, T2c and T3 groups at 5 years was 74%, 79%, 72%, 24% and 33%, respectively (P < 0.0001). The BDFS in patients in the low-, intermediate- and high-risk groups at 5 years was 84%, 64% and 45%, respectively (P < 0.0001). The BDFS in patients treated with or without neoadjuvant hormonal therapy at 7 years was 73% and 53% (P < 0.0001), respectively. Postoperative erectile dysfunction was noted in 33 out of 114 (28.9%) patients who were preoperatively potent.

In a recent retrospective study, 137 patients with PCa underwent HIFU (24). After a median follow-up of 36 months, 22% of the patients relapsed according to the Phoenix criteria. The 5-year DFS rate was 78% based on these criteria, and 91%, 81% and 62% in the low-, intermediate- and high-risk group, respectively. Urge incontinence (16 cases) and dysuria (33 cases) occurred after removal of the urethral catheter in 11.8% and 24.1%, respectively.
To evaluate whether the location (apex/midgland/base) of PCa influences the risk of incomplete transrectal HIFU ablation, Bouiter et al. (25) analysed 99 patients who underwent PCa HIFU ablation (Ablatherm; EDAP, Vaulx-en-Velin, France) with a 6-mm safety margin at the apex, and had systematic biopsies at 3-6 months after treatment. After treatment, residual cancer was found in 36 patients (36.4%) and 50 sextants (8.4%); 30 (60%) positive sextants were in the apex, 12 (24%) in the midgland, and eight (16%) in the base. Statistical analysis showed that the mean (95% CI) probability for a sextant to remain positive after HIFU ablation was 8.8% (3.5-20.3%) in the base, 12.7% (5.8-25.9%) in the midgland, and 41.7% (27.2-57.8%) in the apex. When a 6-mm apical safety margin was used, treatment-associated side effects, especially incontinence and erectile dysfunction, were fewer but residual cancer after HIFU ablation was significantly more frequent in the apex.

Komura et al. (26) have analysed the oncological outcome in 144 patients with T1/T2 PCa and a median follow-up of 47 (2-70) months. Thirty-nine percent patients relapsed and approximately 40% developed a clinical or subclinical urethral stricture postoperatively. Most interestingly, the 5-year DFS was significantly better in those with a stricture as compared to those without (78.2% vs. 47.8%, P < 0.001), indicating the need for more aggressive treatment especially at the apex of the prostate.

11.3.2 Complications of HIFU
Urinary retention appears to be one of the most common side effects of HIFU, developing in almost all patients, with the mean interval of catheterisation via a suprapubic tube varying between 12 and 35 days (16-18). Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common, and is sometimes even performed at the time of HIFU. Post-operative impotence occurs in 55-70% of patients.

Elterman et al. (27) have treated 95 patients with clinically organ-confined PCa using the Sonablate-500 device, and have evaluated the type and frequency of treatment-associated complications. With a minimum follow-up of 6 months, 17% (7/41) of the men had significant incontinence and 2% developed significant erectile dysfunction. Early and late subvesical obstruction necessitating surgical treatment occurred in 17 (17.9%) and 20 (21.1%) patients, respectively.

11.4 Focal therapy of PCa
During the past two decades, there has been a trend towards earlier diagnosis of PCa due to greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men with smaller tumours at an earlier stage, which occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease (28-30).

Most focal therapies to date have been achieved with ablative technologies; cryotherapy, HIFU or photodynamic therapy. So far, three groups have proposed that non-diseased prostate tissue be left untreated in the hope and expectation that genitourinary function might be preserved and the tumour treated adequately (31-33). Although focal therapy is currently not the standard for men with organ-confined PCa, it is the therapeutic approach with the most important future potential.

11.4.1 Pre-therapeutic assessment of patients
The high number of random and systematic errors associated with TRUS-guided biopsy regimens means that this procedure is not sufficiently accurate for selecting candidates for focal therapy. The current standard for characterising men considering focal therapy is transperineal prostate biopsy using a template-guided approach (34,35). When used with a 5-mm sampling frame, this approach can rule in and rule out PCa foci of 0.5 and 0.2 mL volume, with 90% certainty (36). Thus, the exact anatomical localisation of the index lesion - defined as the biologically most aggressive - can be accurately determined.

11.4.2 Patient selection for focal therapy
The primary objective of treatment must be the eradication of measurable and biologically aggressive disease. However, although treatment is usually intended to be one-off, patients should know that further treatment might be necessary in the future.

Based on published data, the following criteria identify possible candidates for currently ongoing trials of focal treatment:
- Candidates for focal therapy should ideally undergo transperineal template mapping biopsies. However, a state-of-the-art multifunctional MRI with TRUS biopsy at expert centres may be acceptable.
- Focal therapy should be limited to patients with a low to moderate risk. The clinical stage of the tumour should be < cT2a and the radiological stage < cT2b.
- Patients with previous prostate surgery should be counselled with caution because no data on
functional and oncological outcomes are available. Patients who have undergone radiation therapy of the prostate are not candidates for focal therapy.

- Patients must be informed that the therapy is still experimental and that there is a possibility of repeat-treatment.

11.5 Summary of experimental therapeutic options to treat clinically localised PCa

**Conclusion**

All other minimally invasive treatment options - such as HIFU microwave and electrosurgery - are still experimental or investigational. For all of these procedures, a longer follow-up is mandatory to assess their true role in the management of PCa.

**Recommendation**

In patients who are unfit for surgery, or with a life expectancy < 10 years CSAP has evolved from an investigational therapy to a possible alternative treatment for PCa.

Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.

11.6 References


12. HORMONAL THERAPY; RATIONALE AND AVAILABLE DRUGS

12.1 Introduction
In 1941, Huggins and Hodges assessed the effect of surgical castration and oestrogen administration on the progression of metastatic prostate cancer (PCa). They demonstrated for the first time the responsiveness of PCa to androgen deprivation (1,2). Since then, androgen-suppressing strategies have become the mainstay of management of advanced PCa. More recently, there has been a move towards the increasing use of hormonal treatment in younger men with earlier disease (i.e. non-metastatic) or recurrent disease after definitive treatment, either as the primary single-agent therapy or as a part of a multimodality approach (3).

However, even if hormonal treatment effectively palliates the symptoms of advanced disease, there is currently no conclusive evidence to show that it extends life.

12.1.1 Basics of hormonal control of the prostate
Prostate cells are physiologically dependent on androgens to stimulate growth, function and proliferation. Testosterone, although not tumorigenic, is essential for the growth and perpetuation of tumour cells (4). The testes are the source of most androgens, with adrenal biosynthesis providing only 5-10% of androgens (i.e. androstenedione, dihydroepiandrosterone and dihydroepiandrosterone sulphate).

Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. Hypothalamic luteinising hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). Luteinising hormone stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cell, testosterone is converted to 5-α-dihydrotestosterone (DHT) by the enzyme 5-α-reductase; DHT is an androgenic stimulant about 10 times more powerful than testosterone. Meanwhile, circulating testosterone is peripherally aromatised and converted to oestrogens, which together with circulating androgens, exert a negative feedback control on hypothalamic LH secretion.

If prostate cells are deprived of androgenic stimulation, they undergo apoptosis (programmed cell death). Any treatment that results ultimately in suppression of androgen activity is referred to as androgen deprivation therapy (ADT).

12.1.2 Different types of hormonal therapy
Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens by surgical or medical castration or inhibiting the action of circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens. In addition, these two methods of androgen deprivation can be combined to achieve what is commonly known as complete (or maximal or total) androgen blockade (CAB).

12.2 Testosterone-lowering therapy (castration)
12.2.1 Castration level
Surgical castration is still considered the ‘gold standard’ for ADT, against which all other treatments are
rated. Removal of the testicular source of androgens leads to a considerable decline in testosterone levels and induces a hypogonadal status, although a very low level of testosterone (known as the 'castration level') persists.

The standard castrate level is < 50 ng/dL. It was defined more than 40 years ago, when testosterone level testing was limited. However, current testing methods using chemiluminescence have found that the mean value of testosterone after surgical castration is 15 ng/dL (1.7 nmol/L) (5). This has led to a revisiting of the current definition of castration, with many authors suggesting a more appropriate level is < 20 ng/dL (0.1 nmol/L).

12.2.2 Bilateral orchiectomy
Bilateral orchiectomy, which is either total or subcapsular (i.e. with preservation of tunica albuginea and epididymis), is a simple and virtually complication-free surgical procedure. It is easily performed under local anaesthesia (6) and is the quickest way to achieve a castration level, usually within less than 12 hours.

The main drawback of orchiectomy is that it may have a negative psychological effect: some men consider it to be an unacceptable assault on their manhood. In addition, it is irreversible and does not allow for intermittent treatment.

12.3 Oestrogens
Oestrogens have several mechanisms of action:
- down-regulation of LHRH secretion;
- androgen inactivation;
- direct suppression of Leydig cell function;
- direct cytotoxicity to the prostate epithelium (in-vitro evidence only) (7).

12.3.1 Diethylstilboesterol (DES)
Diethylstilboesterol (DES) is the most commonly used oestrogen in PCa. Early studies by the Veterans Administration Co-operative Urological Research Group (VACURG) tested oral DES at a dosage of 5 mg/day. However, this dosage was associated with high cardiovascular morbidity and mortality, due to first-pass hepatic metabolism and formation of thrombogenic metabolites. Lower oral doses of 1 mg/day and 3 mg/day were therefore tested and were both found to provide a therapeutic efficacy similar to that of bilateral orchiectomy. However, 3 mg daily of DES was still associated with high cardiotoxicity. Although 1 mg daily of DES resulted in much fewer adverse cardiovascular events than 5 mg daily of DES, the side-effects were still significantly greater than with castration. Recently, there has been renewed interest in using oestrogens (8).

12.3.2 Renewed interest in oestrogens
There are three main reasons for a renewed interest in using oestrogens to treat PCa:
1. Oestrogens suppress testosterone levels and do not seem to lead to bone loss and cognitive decline (9) as do LHRH agonists (LE: 3).
2. In phase II trials for castration refractory PCa (CRPC), oestrogenic compounds (DES, DES-diphosphate) have induced prostate-specific antigen (PSA) response rates as high as 86%.
3. Discovery of a new oestrogen receptor-® (ER-®), possibly involved in prostate tumorigenesis (7).

12.3.3 Strategies to counteract the cardiotoxicity of oestrogen therapy
Two strategies have been used to try and neutralise the cardiotoxicity associated with oestrogen therapy, which is its main disadvantage:
- parenteral route of administration - so avoiding first-pass hepatic metabolism;
- concomitant use of cardiovascular-protective agents.

The Scandinavian Prostatic Cancer Group Study 5 is a large prospective randomized trial which compared a parenteral oestrogen (polyoestradiol phosphate) with CAB (orchiectomy, or an LHRH agonist + flutamide). No difference was observed in disease or overall survival between the treatment groups nor was there any increase in cardiovascular mortality. However, in the oestrogen-treated group, there was a significantly higher incidence of non-fatal adverse cardiovascular events, particularly ischaemic and heart decompensation events (10).

In addition, thromboembolic complications have been observed in trials evaluating the combination of DES, 1 mg/day or 3 mg/ day, with either a low dose of warfarin sodium, 1 mg/day, or a low dose of aspirin, 75-100 mg/day, for the prevention of cardiovascular toxicity (11,12).

12.3.4 Conclusions
Diethylstilboesterol is an effective form of hormonal therapy comparable to that of bilateral orchiectomy (8) (LE:1a). However, there is still concern about the significant cardiovascular side-effects of DES, even at lower
dosages. Further data are needed before oestrogens can be re-admitted into clinical practice as a standard first-line treatment option.

12.4 LHRH agonists

Long-acting LHRH agonists have been used in advanced PCa for more than 15 years and are currently the main forms of ADT (3). They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release leading to the ‘testosterone surge’ or ‘flare-up’ phenomenon, which begins 2-3 days later and lasts for about 1 week. No significant difference in efficacy has been observed between the different drugs. But the different drugs have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection. It is important to carefully follow the directions for using a particular drug to avoid any misuse.

12.4.1 Achievement of castration levels

Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors, suppressing pituitary LH and FSH secretion and testosterone production. Testosterone levels decrease to castration levels usually within 2-4 weeks (13). However, about 10% of patients treated with LHRH agonists fail to achieve castration levels (14). This proportion rises to 15% if the castration threshold is defined as 20 ng/dL. A recent meta-analysis evaluating single-therapy ADT for advanced PCa suggested that LHRH agonists have a similar efficacy compared to orchiectomy or DES (8) (LE: 1a) when 2-year survival was the target outcome. This finding raises the question about the clinical impact of changing the definition of the castrate testosterone level from 50 ng/dL to 20 ng/dL. In addition, although only based on indirect comparison, the LHRH agonists seemed equally effective whatever their formulation (8) (LE: 3).

12.4.2 Flare-up phenomenon

Today, LHRH agonists have become the ‘standard of care’ in hormonal therapy. The main concerns are the potentially detrimental effects associated with ‘flare phenomenon’ in advanced disease, namely increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and fatal cardiovascular events due to hypercoagulation status.

A recent review (15) concluded that clinical flare needs to be distinguished from the more common biochemical flare (i.e. increasing levels of PSA), and even from asymptomatic radiographic evidence of progression. Patients at risk are usually patients with high-volume, symptomatic, bony disease, which account for only 4-10% of M1 patients. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely suppress the risk. Anti-androgens should be started on the same day as the LHRH analogue and should be continued for a 2-week period. The overall clinical impact of this initial flare is unknown.

Some mini-flares have also been observed with the long-term use of LHRH agonists. The clinical impact is unknown but it has been suggested a mini-flare is associated with a negative impact on overall survival (see Section 15).

12.5 LHRH antagonists

In contrast to LHRH agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. This seemed to be a more desirable mechanism of action and has made LHRH antagonists very attractive to use. However, practical shortcomings have limited clinical studies, as many LHRH antagonists have been associated with serious and life-threatening histamine-mediated side-effects and, until recently, no depot formulation was available.

12.5.1 Abarelix

Two published phase III trials compared abarelix, with an LHRH agonist, (16), and with CAB (17), in patients with metastatic or recurrent PCa. Both trials showed no difference in achieving and maintaining castration levels of testosterone and in reducing serum PSA, without any biochemical ‘flare up’ phenomenon in the abarelix arm. Data on survival end-points and long-term safety are not yet available.

The US Food and Drug Administration have recently licensed the clinical use of abarelix in metastatic and symptomatic PCa, for which no other treatment option is available. However, based on prolonged analysis, the FDA has issued a warning about allergic reactions with the long-term use of abarelix, which has resulted in suspension of its further development.
12.5.2 Degarelix
Degarelix is another LHRH antagonist in a monthly subcutaneous formulation. Based on a large, randomized, non-inferiority, dose-finding study (n = 610) the standard dosage of degarelix should be 240 mg the first month, followed by 80 mg monthly injections. More than 95% of patients achieved a castrate level at day 3, which was associated with a quick decline in PSA (as early as day 14). No allergic reaction was observed. The main specific side-effect of degarelix was a painful injection (moderate or mild) reported in 40% of patients, mainly after the first injection. An extended follow-up has been recently published (median 27.5 months), suggesting that degarelix might result in better progression-free survival compared to monthly leuprolelin (18).

12.5.3 Conclusions
Overall, this new family of agents seems appealing, but their advantages over LHRH agonists are far from proven. The use of LHRH antagonists is limited by a monthly formulation. Suppression of the initial flare-up with monotherapy is only clinically relevant in a few, symptomatic, metastatic patients.

12.6 Anti-androgens
These oral compounds are classified according to their chemical structure as:
- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.
Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal anti-androgens. In addition, steroidal anti-androgens have progestational properties leading to a central inhibition. As a consequence, non-steroidal antiandrogens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

12.6.1 Steroidal anti-androgens
These compounds are synthetic derivatives of hydroxyprogesterone. Since steroidal antiandrogens lower testosterone levels, the main pharmacological side-effects are loss of libido and erectile dysfunction, while gynaecomastia is quite rare. The non-pharmacological side-effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

12.6.1.1 Cyproterone acetate (CPA)
Cyproterone acetate was the first anti-androgen to be licensed and is the most widely used. However, it is the least studied.

The most effective dose of CPA in monotherapy is still unknown. Although CPA has a relatively long half-life (31-41 hours), it is usually administered in two or three fractionated doses of 100 mg each (19). There has been only one randomized trial (20) comparing CPA with standard medical castration, suggesting a poorer OS compared to LHRH analogs. Although there are other studies in CPA monotherapy, methodological limitations prevent firm conclusions being made from their results about the relative efficacy of CPA and castration. The only comparative study on anti-androgens as monotherapy was recently published by the EORTC, comparing CPA to flutamide in metastatic PCa. No difference in cancer-specific survival and OS at a median follow-up of 8.6 years was observed, although the study was underpowered (21) (LE: 1b).

12.6.1.2 Megestrol acetate and medroxyprogesterone acetate
Very limited information is available on these two compounds. But the overall poor efficacy (22) has prevented them from being recommended for either primary- or second-line hormonal therapy.

12.6.2 Non-steroidal anti-androgens
The use of non-steroidal anti-androgens as monotherapy has been promoted on the basis of improved quality of life (QoL) and compliance compared to castration. They do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are preserved (23). Although they have not been directly compared in a monotherapy setting, the severity of pharmacological side-effects, namely gynaecomastia, breast pain and hot flashes, appears similar for the three available non-steroidal anti-androgens. However, there are differences in non-pharmacological side-effects, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide (24). All three agents share a common liver toxicity and liver enzymes must be monitored regularly.

12.6.2.1 Nilutamide
There are no comparative trials of nilutamide monotherapy with castration or with other anti-androgens. Non-pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, hepatotoxicity, and interstitial pneumonitis. Even if exceptional, interstitial pneumonitis is potentially
life-threatening and is specific to nilutamide. Nilutamide is not licensed for monotherapy.

12.6.2.2 Flutamide
Flutamide was the first non-steroidal anti-androgen available for clinical use. Although it has been studied as monotherapy for more than 20 years, there are no dose-finding studies against a currently accepted end-point (e.g. PSA response). Flutamide is a pro-drug, and the half-life of the active metabolite is 5-6 hours, so it must be administered three times daily. The recommended daily dosage is 750 mg (19). The non-pharmacological side-effects of flutamide are diarrhoea and hepatotoxicity (occasionally fatal).

12.6.2.3 Bicalutamide
Dose-finding studies of bicalutamide
The dosage licensed for use in CAB is 50 mg/day, and 150 mg dosage for monotherapy. The non-pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens (25-27), prophylactic radiotherapy (28), or treatment with surgical mastectomy or radiotherapy (29). However, bicalutamide clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists (30,31).

12.7 New compounds
Our knowledge of castration resistant prostate cancer (CRPC) remains incomplete, but is starting to become clearer (5,6). It is thought that castrate resistant disease is mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see chapter . . . ). This has led to the development of two new major compounds targeting the androgen axis: abiraterone acetate and lenzaalutamide.

12.7.1 Abiraterone acetate
Abiraterone acetate is a CYP17 inhibitor. It represents an improvement of ketoconazole, which is no longer used or available. By blocking CYP17, abiraterone acetate significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level as inside the cancer cells (intracrine mechanism). In castrate resistant prostate cells, the intracellular androgen level is increased compared to androgen sensitive cells, suggesting an adaptive mechanism, through an increase of androgen biosynthesis (32) enzymes.

12.7.2 Lenzaalutamide
Lenzalutamide (previously known as MDV 3100) is a novel anti-androgen with a higher affinity compared to bicalutamide. It blocks the transfer of ARs to the nucleus so that no agonist-like activity should ever occur. In contrast, currently available drugs still permit the transfer of ARs to the nucleus. The ability of lenzaalutamide to block AR transfer is important because over-expression of the AR has been observed in CRPC.

Both drugs have been developed for use in CRPC after docetaxel has been used. Abiraterone acetate and Lenzaalutamide have shown a significant overall improvement in survival (33,34). Detailed results of both drugs are presented in chapter 20. Both drugs represent an outstanding opportunity for the future treatment of CRPC and confirm that the CRPC status is far from being a hormonal-resistant status.

12.8 References


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536685/


13. METASTATIC PROSTATE CANCER - HORMONAL THERAPY

13.1 Prognostic factors
The M1 population is heterogeneous (Table 18). Various prognostic factors have been suggested, including general prognostic factors, such as pain, ECOG score, Gleason score or biological information (haemoglobin level, CRP level, alkaline phosphatase), which still need to be confirmed in large trials. The most convincing data come from the large SWOG 8894 trial. Patients who have only nodal metastases or pelvic and axial bone...
metastases have been classified as having minimal disease, compared to those with visceral metastases or appendicular bone metastases, leading to a median overall survival of 58 and 30 months, respectively (1). An updated more precise classification has been published (2), which discriminates patients into three groups according to survival, with a median OS of 54, 30 and 21 months, respectively.

Table 18: Prognostic factors for the heterogeneous M1 population for patients with advanced prostate cancer (2)

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial bone metastasis and/or nodes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicular bone or visceral metastasis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance status &lt; 1</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status ≥1</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gleason score &lt; 8</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score ≥ 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &lt; 65</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA ≥ 65</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13.2 First-line hormonal treatment

Primary androgen deprivation therapy (ADT) is the standard of care, usually with a long-lasting LHRH analogue or antagonist (3). Orchidectomy is still a valid option provided it has been accepted by the patient. There is not yet any convincing data to choose between an LHRH analogue or antagonist, except in patients with an impending spinal cord compression for whom a bilateral orchidectomy or an LHRH-antagonist should be considered first.

13.2.1 Prevention of flare-up

When choosing an LHRH analogue, an initial testosterone flare-up is likely. It is important to prevent a flare in symptomatic patients or in patients for whom a clinical flare might lead to severe complications. However, there is little data to support the long-term impact of preventing a flare-up, as has been suggested (4).

The concomitant administration of an anti-androgen is used to prevent testosterone flare-up. It has been suggested that giving an anti-androgen at the same time as the LHRH analogue may be sufficient to prevent flare-up rather than giving an anti-androgen for some days before treatment is started with an LHRH analogue (5). However, there has been no trial specifically designed to decide the best choice of anti-androgen or modality.

13.3 Combination therapies

13.3.1 Complete androgen blockade (CAB)

Although castration reduces serum testosterone levels by up to 95%, an intraprostatic androgen stimulus is sustained by the conversion of circulating androgens of adrenal origin into DHT within the prostate cells. However, the action of the adrenal androgens can be blocked by adding an anti-androgen to either surgical or pharmacological castration, a concept known as complete (or maximal or total) androgen blockade (CAB).

The many studies comparing CAB with monotherapy have produced conflicting results (6). The largest randomized trial compared surgical castration, with or without flutamide, in 1286 M1b patients. No difference was observed between both groups (1). According to the most recent systematic reviews and meta-analyses, at a follow-up of 5 years, CAB appears to provide a small survival advantage (< 5%) versus monotherapy (7-10) (LE: 1a). However, some of the largest trials included were methodologically flawed (61). It remains debatable whether this small advantage, if any, is useful in everyday clinical practice, as the survival benefit seems limited to patients taking non-steroidal anti-androgens (12) and only appears after 5 years of follow-up.

Gastrointestinal, ophthalmological and haematological side effects are worse with CAB. Although LHRH analogues and non-steroidal anti-androgens have the highest estimated quality-adjusted survival, there is an incremental cost of more than US$1 million per quality-adjusted life-year for CAB over orchidectomy alone.

13.3.2 Non-steroidal antiandrogen (NSAA) monotherapy

13.3.2.1 Nilutamide

There are no comparative trials of nilutamide monotherapy with castration or with other anti-androgens. Nilutamide is not licensed for monotherapy.
13.3.2.2 Flutamide
Early phase II trials suggested the efficacy of flutamide monotherapy in advanced PCa. The main advantage suggested was the preservation of sexual function in up to 80% of patients with no pre-treatment erectile dysfunction. This finding has not been confirmed in the EORTC trial 30892 (13), in which as few as 20% of men treated with flutamide maintained sexual activity for up to 7 years.

In the only published RCT, there was no significant difference in OS for flutamide monotherapy compared to castration in M1b patients with a PSA < 100 ng/mL (14). At a higher PSA, flutamide was inferior. However, the trial was underpowered. Results are still awaited from an ongoing Swedish study, which randomized 700 patients with M1 PCa to flutamide, 250 mg three times daily, or CAB (15).

13.3.2.3 Bicalutamide
Dose-finding studies established that bicalutamide, 150 mg once daily, was chosen for further evaluation, as both primary and adjuvant monotherapy (16). It has been compared to medical or surgical castration in two large prospective RCTs with identical study designs, including a total of 1435 patients with locally advanced M0 or M1 PCa (17). A pooled analysis showed:

- In M1 patients, there was an improvement in OS with castration, although the difference in median survival between the groups was only 6 weeks (17).
- In M0 patients (n = 480), no significant difference was noted in OS (18) based on the Kaplan-Meier test, with median survival being 63.5 months in the bicalutamide arm compared with 69.9 months in the castration one.

In two smaller RCTs, high-dose bicalutamide was compared with CAB. In the first trial (251 patients with predominantly M1 stage), there was no apparent difference in OS (19). In the second trial (220 patients with M0 and M1 stage), there was no difference in OS for well-differentiated tumours (G1) or tumours that were only moderately differentiated (20) (G2) (LE: 1b). However, both studies were underpowered and the first study has not yet been fully published.

High-dose bicalutamide has emerged as an alternative to castration for highly selected, well-informed patients with M1 PCa with a low PSA (21). However, the expected benefit of bicalutamide for QoL compared with castration is far from being proven.

13.3.3 Intermittent versus continuous ADT
For reasons we are beginning to understand, long-term CAB, which stimulates prostate cell apoptosis, fails to eliminate the entire malignant cell population. Thus, after a variable period (averaging 24 months), the tumour inevitably relapses, characterized by a castrate-independent state of growth. Experimental data indicate that castrate-independent progression may begin early after the administration of hormonal therapy, coinciding with the cessation of androgen-induced differentiation of stem cells (22). It has therefore been suggested that stopping androgen deprivation prior to progression of androgen-independent cells would mean any subsequent tumour growth would be solely sustained by the proliferation of androgen-dependent stem cells. The stem cells should therefore be susceptible once again to androgen withdrawal. Thus, intermittent androgen blockade (IAD) would delay the emergence of the androgen-independent clone. It should be noted that this rationale has been developed mainly through models (e.g. the Shionogi model), which may be significantly different to the behaviour of total tumour in men. Other possible benefits of IAD include the preservation of QoL in off-treatment periods and a reduction in the cost of treatment.

A detailed systematic review was recently published (23). It concluded that intermittent IAD was feasible and accepted by patients. However, RCTs are required to clarify the potential survival benefit suggested by animal models.

Overall, nine RCTs are underway, only some of which have published findings. Most of the trials have included a mixed patient population of both locally advanced and metastatic disease, with two trials including only metastatic patients. Results from one of the largest trials (SWOG 9346) (n = 1535), which included only randomized metastatic patients, has been presented, but is not yet published (24). Few fully published trials are available. All the trials that have published results have reported similar findings, except for one trial, allowing the inclusion of abstract-only references.

13.3.3.1 Summary of important trial results in IAD in locally advanced or metastatic PCas
Research in mixed populations of locally advanced and metastatic PCas (25-27):
- There has never been a suggestion of decreased survival using IAD. To date, the largest first fully...
published trial (n = 766) was carried out by the South European Uroncological (SEUG) Group (28) with 30% M1. The primary end-point was time to progression. After a median follow-up of 51 months, there was no difference in either time to progression (HR: 0.81; p = 0.11) or OS (HR: 0.99). The metastatic status and PSA at randomization were associated with specific death rates. No overall QoL benefit was seen, except for more frequent side effects in the CAB-treated group.

- However, there was a clear benefit for improved sexual function in the IAD group versus the CAB group, with 28% sexually active vs 10% at 15 months after randomization, respectively. After a median of 7 years’ follow-up, it should be highlighted that both the IAD treatment arm and the continuous treatment arm showed similar non-significant specific death increases. The second largest study (27) randomized 554 out of 852 patients with either M1 disease (50%) or a locally advanced disease. After a median follow-up of 65 months, no significant difference was observed in the median PFS (34.5 months in the IAD group vs 30.2 months in the CAB group, p = 0.29) in either the total study population or in the N+ or M1 subgroup populations. The median OS was 45 months in both groups.

Research in M1b patients:
- The only published trial on M1b patients included a very small number of patients (n = 341) (29). Again, neither OS nor PFS were different between both arms. However, this trial was clearly underpowered.
- Detailed results are awaited from the SWOG trial 9346, which randomized 1134 men out of 3040 men with stage D2 PCa to intermittent and continuous ADT. This is the largest trial that has been conducted in PCa and findings were first presented at ASCO in 2012. It is a non-inferiority trial, which means that for the first time IAD was presented as being not ‘non inferior’ compared to continuous ADT (median OS 5.1 years for IAD compared to 5.8 years for the continuous treatment arm). Although not yet published, results from this trial have raised the question for the first time of the safety of IAD in metastatic situations (24).
- In 1386 patients relapsing after radiotherapy, the randomized JPR.7 trial has shown no difference in OS after a median follow up of 6.9 years, suggesting that this treatment modality might become the standard for those requiring ADT treatment. The median OS were 8.8 years in the IAD compared to 9.1 years in the continuous treatment arm (HR = 1.02; 0.86-1.21) (30).

IAD regimen of fixed 6-month periods of CAB treatment and surveillance:
An alternative IAD regimen using fixed 6-month periods of CAB treatment and surveillance has been published (31). The results are limited by the small number of patients (n = 129). There was no difference observed in OS, cancer-specific survival or PFS after a mean 44.8 months of follow up.

13.3.3.2 Potential benefits of IAD
Intermittent androgen deprivation has not been shown to be associated with prolonged hormone-sensitive status or an increase in OS. However, this modality is well accepted by patients, urologists and oncologists. Although the QoL benefit is less than expected or absent, except in a few studies (30,32,33), IAD is better tolerated and sometimes benefits sexual functioning (26,28). Other possible long-term benefits, which are not clearly proven, include bone protection (34,35) and/or a protective effect against metabolic syndrome. Testosterone recovery is seen in most studies (23), leading to an intermittent castration (not just an intermittent treatment delivery).

13.3.3.3 Optimal threshold for stopping or resuming ADT
The optimal thresholds at which ADT must be stopped or resumed are empirical (23). The best candidates for IAD have still not been completely defined (23,35), but are probably patients with locally advanced or relapsing disease, provided a perfect response is obtained (see below). Nevertheless, several points are clear (23,36).
- Because IAD is based on intermittent castration, only drugs leading to castration are suitable for use in IAD.
- It is unclear if an LHRH agonist may be used alone, as published experiences are based on CAB. An LHRH antagonist might be a valid alternative, provided clear results are obtained from RCTs.
- The initial (induction) cycle must last between 6 and 9 months, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
  - well-informed and compliant patient
  - no clinical progression, i.e. a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease, or 0.5 ng/mL in relapsing disease.
- Strict follow-up must be applied once treatment has stopped, with clinical examination every 3-6 months. The more advanced the disease, the closer should be the follow-up. The PSA level should be measured by the same laboratory to ensure standardization of testing.
In conclusion, IAD is currently widely offered to patients with PCa in various clinical settings and its status should no longer be regarded as investigational (LE: 2). Future publication of the results from the SWOG 9346 may change guidance on the use of IAD in M1B patients.

13.3.4 Immediate versus deferred ADT
There is no discussion regarding symptomatic patients. However, it is still unclear when it is the most appropriate time to introduce hormonal therapy in asymptomatic patients with metastatic PCa. Should hormonal therapy be introduced immediately or deferred until there are signs and symptoms of clinical progression? The controversy has arisen because of the lack of properly conducted RCTs. Published studies have not included enough patients and have been underpowered, with heterogeneity of patient enrolment (i.e. locally advanced, nodal and metastatic stages of disease), and with variation in the hormonal treatments given and in the follow-up schedules and modalities used.

A report by the Agency for Health Care Policy and Research (AHCPR) indicated a possible survival advantage for early ADT in single studies in which hormonal treatment was the primary therapy (37). Furthermore, androgen suppression was shown to be the most cost-effective therapy if it was begun after patients had experienced symptoms from metastatic disease (38). The Cochrane Library review extracted four good-quality RCTs; these were namely VACURG I and II studies, the MRC trial and the ECOG 7887 study, which were all conducted in the pre-PSA era. The studies included patients with advanced PCa, who had received early versus deferred ADT, either as primary therapy or adjuvant to radical prostatectomy (39).

In M1a/b patients only, no improvement in OS was observed, although early ADT significantly reduced disease progression and complication rates due to progression. However, the results were different in locally advanced situations with a relatively small benefit in OS. There was an absolute risk reduction of 5.5% after 10 years (39), while another review reported an OS benefit (+10%) and SS (+20%) (40), especially in combination with a local treatment. In the PSA era, the EORTC 30891 study (41) has clarified the results a small benefit in OS, but not for cancer-specific survival. Furthermore, only young patients with a high PSA are likely to clearly benefit.

Based on a systematic review of the literature, recently published ASCO guidelines on initial hormonal treatment for androgen-sensitive, metastatic, recurrent or progressive PCa concluded that no recommendation can be made about when to start hormonal therapy in advanced asymptomatic PCa, (42). The ESMO guidelines do not make any statement (43).

For asymptomatic metastatic patients, an active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective.

The detailed discussion on immediate or deferred ADT combined with surgery or radiation therapy is discussed in Sections 8.3 and 10.3.

13.4 Indications for hormonal therapy
Table 19 lists the indications for hormonal therapy.

Table 19: Indications for hormonal therapy in metastatic patients

<table>
<thead>
<tr>
<th>Castration</th>
<th>Benefits</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 symptomatic</td>
<td>To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis)</td>
<td>1b</td>
</tr>
<tr>
<td>M1 asymptomatic</td>
<td>Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications</td>
<td>1b</td>
</tr>
</tbody>
</table>
An active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective

### Anti-androgens

**Short-term administration**
- To reduce the risk of the ‘flare-up’ phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist (91,92)

**Long-term administration**
- It may be sufficient to give an anti-androgen for 3 weeks of concomitant use, starting treatment on the same day as LHRH analogue treatment is started, or for up to 7 days before the first LHRH analogue injection

### Intermittent treatment

**Threshold to start and stop ADT**
- The threshold is empirically chosen. However, it should reproduce what has been used in clinical trials. In trials, treatment is usually stopped when the PSA level is < 4 ng/mL (M1) and < 0.5-4 ng/mL (relapsing)

**Drug**
- LHRH analogue + flare-up prevention OR combined treatment

**Population:**
- Metastatic patients: asymptomatic, motivated, with a clear PSA response after the induction period.
- Relapsing after radiotherapy: patients with a clear response after the induction period

### 13.5 Contraindications for various therapies (Table 20)

**Table 20: Contraindications for various therapies.**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral orchiectomy</td>
<td>Psychological reluctance to undergo surgical castration</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>Known cardiovascular disease</td>
</tr>
<tr>
<td>LHRH agonists alone</td>
<td>Patients with metastatic disease at high risk for clinical ‘flare-up’ phenomenon</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>Localised PCa as primary therapy</td>
</tr>
</tbody>
</table>

### 13.6 References


* Based on one published trial in M1b patients only and two published cohorts in mixed populations.


http://www.asco.org/ASCOv2/meetings/abstracts/?view=abst_detail_view&confID=114&abstractID=92516


http://www.asco.org/ASCOv2/meetings/abstracts/?view=abst_detail_view&confID=47&abstractID=33936


http://www.asco.org/ASCOv2/meetings/abstracts/?view=abst_detail_view&confID=102&abstractID=77775


14. MANAGEMENT OF PROSTATE CANCER IN OLDER MEN

14.1 Introduction
Prostate cancer is the most prevalent cancer in men, with a median age at diagnosis of 68 years. Two-thirds of prostate cancer-related deaths occur in men aged ≥ 75 years (1). Older men tend to have larger tumours of a higher grade than younger patients (2,3). Treatment decisions for older men should take into consideration the risk of dying from PCa (which depends on the grade and stage of the tumour), potential adverse effects of treatment, and patient preference. Interventions that might decrease health-related quality of life (HRQoL) without prolonging survival should be avoided. Evidence suggests that in both the USA (4) and Europe (5) older patients are under-treated: only a minority of older adults with localised prostate cancer receive curative treatment. However, curative treatment should neither be denied where appropriate, nor limited to androgen deprivation therapy (ADT).

Life expectancy is a major determinant of the potential for benefit from therapy. The International Society of Geriatric Oncology (SIOG) Prostate Cancer Working Group recommends that the decision-making process for treating older men with PCa should be based on a systematic evaluation of health status, most importantly comorbidities, dependence status, and nutritional status (6). These factors influence patient survival and can also affect the ability to tolerate treatment-related side-effects (6).

For localised disease, treatment benefit is usually considered to be seen only beyond 10 years, which leads to a treatment frontier of 75 years. This should be reconsidered, given that Walter (7) has shown that survival probability is linked not only to legal age, but more importantly to overall health status. For example, a healthy 80-year-old senior can expect a median 10.8 years of survival, compared to 6.7 years for a vulnerable, and 3.3 years for a frail senior. At 85 years of age, healthy seniors can expect to survive 8 years. These figures date back 10 years, and are likely to have increased with life expectancy.

Comorbidity is a major predictor of PCa mortality. Tewari et al. demonstrated that comorbidity evaluated by the Charlson index was the strongest predictor of death from causes other than PCa in men with localised PCa treated with RP (8). This was recently confirmed in a cohort of patients from the Surveillance, Epidemiology and End Results (SEER) database, all of whom had treatment-resistant PCa. At 10 years, most men with a Charlson score ≥ 2 died from competing causes, irrespective of age or tumour aggressiveness (9). Currently the Cumulative Illness Score Rating-Geriatrics (CISR-G) is the best available tool for assessing the risk for death unrelated to PCa. Whereas the Charlson index considers only potentially lethal comorbid conditions, the CISR-G also rates nonlethal conditions according to their severity and level of control (10,11).

Level of dependence in daily activities is another factor that influences survival in senior adult patients (12,13). Dependence can be evaluated using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales. The ADL scale rates an ability to accomplish basic activities of daily living, while the IADL scale rates activities that require a higher level of cognition and judgement (for example the ability to manage money or medication, or to use transportation or the telephone).

Malnutrition has also been shown to be associated with an increased mortality rate in senior patients (14). Nutritional status can be estimated by the variation of weight during the previous 3 months:
• good nutritional status < 5% of weight loss;
• risk of malnutrition - weight loss 5-10%;
• severe malnutrition - weight loss > 10%.

Evaluation of comorbidity, dependence and malnutrition is recommended by The SIOG Prostate Cancer Working Group in order to classify patients into one of 4 groups:
1. ‘Fit’ or ‘healthy’ older men should receive the same standard treatment as younger patients.
2. ‘Vulnerable’ patients (i.e. reversible impairment) should receive standard treatment after resolution of any geriatric problems through geriatric interventions.
3. ‘Frail’ patients (i.e. irreversible impairment) should receive an adapted treatment.
4. Patients who are ‘too sick’ with ‘terminal illness’ should receive only symptomatic palliative treatment (6).

“Fit” and “vulnerable” older men with localised PCa in the high-risk group defined by D’Amico et al. (18), with a chance of surviving for more than 10 years are likely to benefit from curative treatment. Older men in the low risk and possibly intermediate risk classification are most likely to benefit from a watchful-waiting approach. The urological approach in older men with PCa should be the same as in younger patients, based on existing recommendations (15-17). Older men with PCa should be managed according to their individual health status which is mainly driven by the severity of associated comorbid conditions and not according to chronological age.

14.2 Treatment-related complications
The risk of short-term postoperative complications appears to be related more to the severity of comorbidities than chronological age. Conversely, the risk of long-term incontinence after RP is more influenced by increasing age than comorbidity (19,20). EBRT has similar outcomes in terms of cancer control and treatment related comorbidities in both older and younger patients, assuming a dose of ≥ 70Gy using intensity modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT). Brachytherapy might be a suitable option in older patients, but survival benefit in older men with low risk disease has not been established. Urinary, bowel, and erectile complications after brachytherapy increase significantly with both increasing age and severity of comorbidities (15). For those with locally advanced disease, a combined modality of EBRT and long term hormonal treatment must be considered. The drawback of ADT in older patients has been discussed earlier (see Chapter 14). Cardiac status should be specially checked if ADT is considered, as it might be associated with increased morbidity, but not mortality. Comorbidity by itself could also be a discriminating factor, as suggested recently in localised high risk patients (21).

In patients with non-metastatic localised PCa unsuitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation (22,23). In the case of locally advanced T3-T4 disease immediate ADT can be of benefit in patients with PSA > 50ng/mL and PSA doubling time of < 12 months (22,23). ADT is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG Prostate Cancer Working Group recommends evaluation of bone mineral status and prevention of osteoporosis. All men receiving ADT should receive calcium and vitamin D supplementation. The routine use of bisphosphonates to prevent skeletal complications in patients undergoing ADT is not recommended unless there is a documented risk for fracture or castration-resistant PCa with skeletal metastasis (6). However, in a recent randomised trial Denosumab was shown to improve metastases free survival in patients without distant metastases and rising PSA (29.5 months vs 25.2 months, p = 0.0028) and increase time to first bone lesion (33.2 months vs 29.5 months, p = 0.0032) (24).

In metastatic castration-resistant prostate cancer (CRPC), chemotherapy with docetaxel (75 mg/m² every 3 weeks) is the standard for fit and vulnerable older men. The tolerability of the docetaxel 3-weekly regimen has not been specifically studied in frail older men. In a retrospective analysis of 175 patients aged ≥ 75 years treated with docetaxel, patients with a good performance status responded to docetaxel therapy to a similar extent as younger patients. Docetaxel was generally well tolerated. The weekly regimen showed less febrile neutropenia than the 3-weekly regimen but a higher rate of fatigue, resulting in frequent treatment discontinuation (25). The place of weekly docetaxel in metastatic CRPC should be further evaluated. Palliative treatments in CRPC include palliative surgery, radiopharmaceuticals, EBRT, and medical treatments for pain and symptoms.

14.3 References


15. QUALITY OF LIFE OF PATIENTS WITH LOCALISED PROSTATE CANCER

15.1 Introduction
The increase in life expectancy of patients with localised PCa has made the quality of life (QoL) after treatment a key issue for PCa survivors. The term ‘health-related quality of life’ (HRQoL) is typically used to refer to the impact that disease and treatment have on a person’s well-being and physical, emotional and social functioning, including daily functioning (1-4). HRQoL is a patient-centred outcome, which is rated by the patient himself, particularly as physicians often underestimate the impact of disease and treatment on their patients’ lives (5).

In PCa, HRQoL is usually divided into PCa-specific and PCa-general issues. PCa-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel, and sexual functioning. PCa-general HRQoL refers to the generic issues of well-being, including physical, social, emotional, and cognitive functioning, vitality/fatigue, pain, general health status, global QoL and life satisfaction (6).

HRQoL is measured using standardised questionnaires, which collect patient-centric data and provide an objective assessment and perception of both generic and disease-specific domains. Several comprehensive HRQoL questionnaires have undergone validation and have been used to measure early stage PCa outcomes. The most frequently used questionnaires include the EPIC (Expanded Prostate Cancer Index Composite), the Symptom indexes constructed by Clark and Talcott, and the Prostate Module appendix for the EORTC-QLQ C30 (7-9).

Various forms of therapies have different impacts on HRQoL. A comparison of the most common contemporary therapies for localised PCa (radical prostatectomy, brachytherapy, external-beam radiation therapy and active surveillance) is necessary to inform patients about treatment options and to address individual patient preferences for the various possible outcomes. There is still very little objective data about HRQoL for PCa treatment, mainly because of a lack of prospective trials.

15.2 Active surveillance
Although active surveillance avoids treatment-related side effects, it carries an increased risk of psychological distress, which can have significant effects on the patient’s HRQoL. There are certain risk factors for patients who may not do well on active surveillance. These factors include the patient’s perception that the physician is making most of the decision-making, a poor physical health score, a high neuroticism (anxiety) score, and a high PSA value. All these factors were found to have significant positive associations with lower HRQoL scores in multivariate analysis (10). Anxiety and distress did not increase and remained low during the first 9 months of surveillance in men enrolled in the active surveillance PRIAS study (11). Additional research with a longer follow-up is needed to define the significance of negative effects of active surveillance on HRQoL (LE: 1b).

Data from an RCT on anxiety comparing WW and RP (13) found that depression, well-being and psychological status were not significantly different between treatment groups, even if they were systematically...
inferior in the treated group (LE: 1b).

Apart from psychological distress, men left without anticancer treatment may have a higher level of irritative-obstructive urinary symptoms compared to patients treated with RP or RT at 12–36 months of follow-up (14) (LE: 2b).

15.3 Radical prostatectomy
Several trials have shown that RP has a significant negative effect on multiple QoL domains, including a lower sexual function score, lower urinary function and incontinence scores, and a lower physical HRQoL (13,15-17).

In the Prostate Cancer Outcomes Study (PCOS), 8.7% of men at 24 months were bothered by a lack of urinary control and 41.9% reported that sexual function was a moderate-to-big problem in their daily lives (18). Sexual function and interest are the two prostate-specific domains that decline most after surgery and remain most affected after 1 year (19). The recovery of sexual dysfunction and urinary incontinence occurs over 2 to 3 years (20-22). Sanda et al. (15) recently reported that urinary incontinence was at its worst by 2 months after surgery, after which time it improved in most patients. At 1 year after RP, 26% of patients reported that sexual function was a ‘big problem’, while 76% reported that urinary incontinence was a ‘very small’ problem or ‘no problem at all’ (LE: 2a).

Although certain advances have been made that help diminish these side effects, such as nerve-sparing RP or robotic-assisted radical prostatectomy (RALP), their impact on HRQoL remain controversial. Preserving the neurovascular bundles reduces the incidence of impotence (15,23) and can also help to improve urinary function (22,24). Both RALP and open RP have demonstrated comparable functional outcomes and should therefore theoretically have similar HRQoL scores (25). Other general HRQoL domains that may be affected after surgery included pain and energy (18). Several studies have shown that pain and energy worsen immediately post-RP but usually improve by 12 months (20,22,26).

A new methodology for reporting outcomes after RP was proposed recently: the so-called trifecta (27) and pentafecta (28). The new method combines major outcomes, including continence, potency and cancer control (trifecta) and peri-operative complications and positive surgical margins rates (pentafecta). Pentafecta rates reflect post-operative patient expectations and satisfaction more accurately and can be used in counselling patients with clinically localised PCa. The use of trifecta and pentafecta outcomes in post-operative HRQoL assessment needs further validation.

15.4 External-beam radiation therapy (EBRT) and low-dose rate (LDR) brachytherapy
Patients undergoing EBRT and iodine-125 LDR brachytherapy may have urinary, sexual and bowel dysfunction following treatment (29). Both methods can result in irritative voiding symptoms, such as urgency, frequency, and urge incontinence, that negatively affect overall urinary function and HRQoL. The most predominant severe acute toxicity after LDR brachytherapy is urinary retention requiring catheterisation (30). Roeloffzen et al. (30,31) reported that acute urinary retention after LDR brachytherapy occurs in 8–10.2% of patients and has a significant negative impact on patients’ HRQoL up to 6 years after treatment, in terms of both global QoL measures and urinary symptom scores (LE: 3).

A prospective multicentre study showed that the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months (15). In the same study, patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence compared with baseline. Incontinence after LDR brachytherapy was reported by 4-6% of patients at 1-2 years after treatment. Eighteen percent of patients in the LDR brachytherapy group and 11% of those in the EBRT group reported moderate or worse distress from overall urinary symptoms at 1 year (15) (LE: 3).

It has been shown that both EBRT and LDR brachytherapy have a significant impact on the bowel and rectal HRQoL domains (15,32). Bowel/rectal problems appeared to have an overall impact almost as important as that of the urinary domain (33,34). The onset of symptoms occurred during or early after treatment, and sometimes persisted into follow-up. Sanda et al. reported rectal urgency, frequency, pain, fecal incontinence, or haematochezia-caused distress related to bowel function in 9% of patients at 1 year after EBRT or LDR brachytherapy (15). In a retrospective observational study of fecal incontinence in 143 men, who had received LDR brachytherapy for localised PCa, 13.2% (21) of patients at 2 years reported that faecal incontinence was impacting their ability to participate in daily activities (35). A multivariable analysis suggested that bowel and rectal symptoms were less profound after LDR brachytherapy than after EBRT (7) (LE: 2a).

Roeloffzen et al. (31) reported a statistically significant deterioration in HRQoL in patients treated with iodine-125 LDR brachytherapy at 6 years for urinary symptoms, bowel symptoms, pain, physical functioning, and sexual activity. However, most of these changes were not clinically relevant. HRQoL scores returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. The only clinically relevant changes occurred in emotional functioning and sexual activity. Worse bowel and urinary function may play a stronger role than sexual function in predicting a patient’s overall physical and emotional HRQoL (36). Contemporary treatment refinements, such as 3-D conformal or intensity-modulated radiotherapy (IMRT), may
be able to reduce the impact of EBRT on bowel symptoms, but this has not yet been shown in a multicentre setting.

Dietary intervention had no statistically significant positive impact on gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT (LE: 1b). Sanda et al. showed that adjuvant androgen suppression exacerbated the adverse effects of EBRT or LDR on sexuality and vitality (15). The negative effects of adjuvant hormonal therapy have been shown in some other studies (29,38). The significant worsening of bowel function with the addition of hormones to external radiotherapy was shown at 12 and 24 months after completion of radiotherapy (39).

Among general domains, fatigue was commonly reported following EBRT. However, provided that fatigue was temporary, it did not appear to be emotionally distressing to most men (40,41). Men treated with interstitial LDR brachytherapy appeared to show only slight declines in general HRQoL (42). Physical and functional status declines have been reported in the first few months after implant, but pretreatment levels of function are regained by most men at 1 year after implant (43).

15.5 Comparison of HRQoL between treatment modalities

The limitations of all published studies assessing QoL include the lack of randomisation to treatment and therefore the presence of selection bias, which may influence outcomes. Thus, information regarding comparative outcome relies largely on results from non-randomised observational cohorts. Treatment comparison requires a long follow-up, as measures of QoL may change with time. There are very few trials that are directly comparing different treatment modalities.

Studies addressing general HRQoL issues (general physical function, role function, social function, emotional well-being, body pain, general health, or vitality/energy) have found few differences across treatments for clinically localised disease (6,44). In longitudinal studies, both surgery- and radiotherapy-treated men have reported some declines in role function and vitality/energy shortly after treatment, with surgically treated men reporting the most dysfunction (26,40). However most men recovered function by 1 year after treatment.

The presence of comorbid psychiatric conditions (i.e. prior psychiatric history, alcohol abuse, drug abuse) and the experience of pain after treatment were considered to be certain risk factors for poor general HRQoL in men after treatment for localised prostate cancer (45-47).

The PCOS was the first reported prospective study presenting treatment-specific QoL outcomes for PCa patients at 5 years after initial diagnosis (18). The cohort consisted of men with newly diagnosed localised PCa treated with RP (n = 901) or EBRT (n = 286). At 5 years after diagnosis, overall sexual function declined in both groups to approximately the same level, mostly because of a continuing decline in erectile function among EBRT patients between years 2 and 5. However, erectile dysfunction was more prevalent in the RP group (79.3% vs 63.5%, respectively). Approximately 14-16% of RP and 4% of EBRT patients were incontinent at 5 years. Bowel urgency and painful haemorrhoids were more common in the EBRT group (LE: 2a).

Madalinska et al. evaluated the side effects of RP and EBRT in 278 patients from the ERSPC study at 6 and 12 months following treatment (33). RP patients reported significantly higher incidences of urinary incontinence (39-49%) and erectile dysfunction (80-91%) than radiotherapy patients (6-7% and 41-55%, respectively). Bowel problems (urgency) affected 30-35% of the EBRT group versus 6-7% of the RP group (LE: 2a).

Downs et al. measured the impact of LDR brachytherapy alone on general HRQoL and disease-specific HRQoL compared to patients treated with RP (48). The authors studied 419 men from the CaPSURE database, whose primary treatment was LDR brachytherapy (n = 92) or RP (n = 327). Patients treated with LDR brachytherapy or RP did not differ greatly in general HRQoL after treatment. Both treatment groups showed early functional impairment in most general domains, with scores returning to or approaching baseline in most domains at 18 to 24 months after treatment. Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0 to 6 months after treatment (84.5%) than patients treated with RP (63.3%). Urinary bother scores were not significantly different (67.7% vs 67.4%, respectively). Both treatment groups showed decreases in sexual function that did not return to pretreatment levels (LE: 2a).

A multicentre study that compared all three treatments (RP, EBRT, LDR brachytherapy) in a longitudinal prospective cohort was conducted by Talcott et al. (7). In 417 men, the authors assessed urinary, bowel and sexual function from before primary treatment to 24 months afterwards. Urinary incontinence increased sharply after RP, while bowel problems and urinary irritation-obstruction occurred after EBRT and LDR brachytherapy. Sexual function severely worsened immediately after surgery and then improved, while sexual function continued to decline after both radiation treatments. It has been shown that a surgical patient, who is impotent at 3 or 12 months after surgery, can expect to have a realistic hope of improvement while impotent EBRT patients probably should not. There was no change in urinary function and little change in overall bowel function after 12 months. The data showed that a patient with bowel dysfunction at 12 months after EBRT may expect modest improvement, with diverging trends for individual symptoms. Diarrhoea will continue to subside,
but there will be little change in tenesmus and rectal urgency, and episodes of rectal bleeding will become more prevalent (7) (LE: 2a).

A prospective, multicentre study of 435 patients with a longer follow-up of 36 months was reported by Pardo et al. (49). The study confirmed that there was a long-term change in adverse effects, e.g. an increase in urinary-related adverse effects after EBRT or sexual adverse effects with LDR brachytherapy, which tended to reduce any differences between treatments over time. However, these changes were only slight. In accordance with other reports, the RP-treated group showed greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive results compared with the LDR brachytherapy group. In patients with urinary irritative-obstructive symptoms at baseline, improvement was observed in 64% of those treated with nerve-sparing RP. Higher bowel worsening was observed in the ERBT group, with 20% of patients reporting bowel symptoms. Relevant differences between treatment groups persisted for up to 3 years of follow-up (49) (LE: 2a).

The American College of Surgeons Oncology Group phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial compared RP and LDR brachytherapy, but was closed after 2 years due to poor accrual. Crook et al. (50) recently reported the HRQoL at a mean of 5.3 years for 168 trial-eligible men, who either chose or were randomly assigned to RP or brachytherapy following a multidisciplinary educational session (50). There were no differences in bowel or hormonal domains. However, men treated with LDR brachytherapy scored slightly better in the urinary QoL domain (91.8 vs 88.1; p = 0.02) and sexual (52.5 vs 39.2; p = 0.001) domain, and in patient satisfaction (93.6 vs 76.9%; p < 0.001). It should be noted that treatment allocation was random in only 19% of cases (LE: 2a).

A population-based study investigated the relationship between presence of urinary, bowel or sexual dysfunction and global QoL in PCa survivors in Norway including men who did not have any active treatment. Men who had undergone RP reported more urinary incontinence (24%) than the other treatment groups, but had the lowest level of moderate or severe urinary irritative-obstructive symptoms. Men who from the ‘no treatment’ group had the highest level of moderate or severe irritative-obstructive urinary symptoms. Men who had undergone RT reported higher levels of irritative intestinal symptoms and faecal leakage compared with the RP group and the no-treatment group. In all treatment groups, poor sexual drive and poor erectile function were common, with men treated with RP reporting the highest prevalence of poor erectile function (89%). The presence of irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global QoL in multivariate analyses. The use of medication for erectile dysfunction was not significantly associated with global QoL (14) (LE: 2b).

The QoL of a patient’s spouse or partner may also be reduced as a result of their spouse or partner receiving treatment for PCa. In a prospective, multicentre, study of more than 1200 patients and 625 spouses or partners (15), distress associated with the patient’s erectile dysfunction was reported by 44% of partners in the RP group, 22% of those in the EBRT group and 13% of those in the LDR brachytherapy group. After RP, urinary incontinence was observed, but urinary irritation and obstruction improved, particularly in patients with large prostates. Treatment-related symptoms were made worst by obesity, large prostate size, high prostate-specific antigen score and older age (LE: 2a).

Malcolm et al. (51) reported a single-institution study comparing the outcomes of surgery (RP, RALP), LDR brachytherapy and cryosurgical ablation of the prostate (CSAP) with a relatively short follow-up of 24 months (51). The HRQoL of patients treated with LDR brachytherapy and CSAP was associated with higher urinary function and higher bother score compared to open RP and RALP. LDR brachytherapy was associated with a higher sexual function and higher bother score compared to all other treatment modalities. Unfortunately, the study used the UCLA-PCI questionnaire, which lacks items for evaluating irritative urinary symptoms, which are often observed in patients after LDR brachytherapy (48). This may have significantly compromised the results of the HRQoL assessment (LE: 3).

In conclusion, many men treated for clinically localised PCa will experience some post-treatment problems that may impact their daily lives. Each patient therefore has to determine which side effect profile (32) is most acceptable to them when making a decision about treatment.

15.6 References
### 16. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF PCA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Comment</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Watchful waiting</td>
<td>Standard treatment for Gleason score ≤ 6 and 7 adenocarcinomas and &lt; 10-year life expectancy.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Active surveillance</td>
<td>In patients with &gt; 10-year life expectancy, re-staging with TRUS and biopsy is recommended.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional in younger patients with a long life expectancy, especially for Gleason score ≥ 7 adenocarcinomas.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Optional in younger patients with a long life expectancy, in particular in poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Not an option.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Not an option.</td>
<td>C</td>
</tr>
<tr>
<td>T1b-T2b</td>
<td>Active surveillance</td>
<td>Treatment option in patients with cT1c-cT2a, PSA &lt; 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 biopsies positive, ≤ 50% cancer involvement of each biopsy.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with a life expectancy &lt; 10 years.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with a life expectancy &gt; 10 years once they are informed about the lack of survival data beyond 10 years.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients who do not accept treatment-related complications.</td>
<td></td>
</tr>
<tr>
<td>T1a-T2c</td>
<td>Radical prostatectomy</td>
<td>Optional in patients with pT1a PCa. Standard treatment for patients with a life expectancy &gt; 10 years who accept treatment-related complications.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Patients with a life expectancy &gt; 10 years who accept treatment-related complications.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Brachytherapy</td>
<td>Low-dose rate brachytherapy can be considered for low risk PCa patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.</td>
<td>A</td>
</tr>
<tr>
<td>T3-T4</td>
<td>Watchful waiting</td>
<td>Option in asymptomatic patients with T3, well-differentiated and moderately-differentiated tumours, and a life expectancy &lt; 10 years who are unfit for local treatment.</td>
<td>C</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional for selected patients with T3a, PSA &lt; 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy &gt; 10 years. Patients have to be informed that RP is associated with an increased risk of positive surgical margins, unfavourable histology and positive lymph nodes and that, therefore, adjuvant or salvage therapy such as radiation therapy or androgen deprivation might be indicated.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>T3 with &gt; 5-10 years of life expectancy. Dose escalation of &gt; 74 Gy seems to be of benefit. A combination with hormonal therapy can be recommended.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Symptomatic patients, extensive T3-T4, high PSA level (&gt; 25-50 ng/mL), PSA-Doubling Time (DT) &lt; 1 year. Patient-driven, unfit patients. Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation. NHT plus radical prostatectomy: no indication.</td>
<td>B</td>
</tr>
<tr>
<td>N+, M0</td>
<td>Watchful waiting</td>
<td>Asymptomatic patients. Patient-driven (PSA &lt; 20-50 ng/mL), PSA DT &gt; 12 months. Requires very close follow-up.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional for selected patients with a life expectancy of &gt; 10 years as part of a multimodal treatment approach.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Optional in selected patients with a life expectancy of &gt; 10 years, combination therapy with adjuvant androgen deprivation for 3 years is mandatory.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Standard adjuvant therapy in more than 2 positive nodes to radiation therapy or radical prostatectomy as primary local therapy. Hormonal therapy should only be used as monotherapy in patients who are unfit for any type of local therapy.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>No standard option. Patient-driven.</td>
<td>B</td>
</tr>
<tr>
<td>M+</td>
<td>Watchful waiting</td>
<td>No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Not a standard option.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Standard option. Mandatory in symptomatic patients.</td>
<td>A</td>
</tr>
</tbody>
</table>

**DT = doubling time; NHT = neoadjuvant hormonal treatment; IPSS = International Prostatic Symptom Score; PSA = prostatespecific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate**

### 17. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

#### 17.1 Definition
Curative treatment is defined as radical prostatectomy or radiotherapy, either by external beam radiation or an interstitial technique, or any combination of these. Alternative treatment options that are not fully established,
such as HIFU, do not have a well-defined, validated PSA-cut-point to define biochemical failure but do generally follow the outlines given below.

17.2 Why follow-up?
The first question to be answered is: ‘If failure after curative treatment is so common, are follow-up efforts worthwhile?’ The answer to this question is definitely ‘yes’. Recurrences will occur in a substantial number of patients who received treatment with intent to cure at various time points after the primary therapy.

The second question to be answered is: ‘What is the reason for follow-up?’ Reasons may vary depending on the treatment given, patient age, co-morbidity and the patient’s own wishes. In general, patients who receive curative therapy may be followed-up for any of the following reasons:

• good responsible patient care;
• possibility of second-line treatment with curative intent;
• possibility of early hormonal therapy after failure;
• as part of a study protocol.

Chapter 18 discusses treatment options after failure of primary therapy.

17.3 How to follow-up?
The procedures indicated at follow-up visits vary depending on the clinical situation. The examinations discussed below are routinely used for the detection of PCa progression or residual disease. The PSA level, and eventually DRE, are the only tests that need to be carried out routinely. A disease-specific history should be mandatory at every follow-up visit and should include psychological aspects, signs of disease progression, and treatment-related complications. The examinations used for the evaluation of treatment-related complications must be individualised and are beyond the scope of these guidelines. The examinations used most often for cancer-related follow-up after curative surgery or radiation treatment are discussed below.

17.3.1 PSA monitoring
The measurement of PSA level is a cornerstone in the follow-up after curative treatment. There is a difference in what can be expected after radical prostatectomy and radiotherapy, but PSA recurrence nearly always precedes clinical recurrence after either treatment, in some cases by many years (1-5). It is recommended that the finding of a single, elevated, serum PSA level should be re-confirmed before second-line therapy is started solely based on the PSA elevation.

17.3.2 Definition of PSA progression
The level of PSA at which to define treatment failure differs between radical prostatectomy cases and radiation treated cases. Following radical retropubic prostatectomy, two consecutive values of 0.2 ng/mL or greater appear to represent an international consensus defining recurrent cancer (6,7). Other authors have argued for an even higher cut-off of 0.4 ng/mL to better define patients with a high risk for clinical progression (5). It has been shown that patients with a PSA level between 0.1 ng/mL and 0.2 ng/mL after radical prostatectomy had neither clinical nor biochemical disease progression (8). Therefore, the use of an ultra-sensitive PSA assay is not justified for routine follow-up after radical prostatectomy (4). If ongoing randomised trials show that early adjuvant treatment after radical prostatectomy (given before PSA reaches > 0.2 ng/mL) improves survival, this issue should be reconsidered.

Following radiation therapy, until recently, the definition of biochemical relapse was three consecutive increases according to the recommendation of ASTRO from 1996 (9). At the 2006 RTOG-ASTRO Consensus conference a new definition of radiation failure was established with as the main aim to establish a better correlation between the definition and clinical outcome. The new definition of radiation failure is a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value) (10). This definition is applicable for patients treated with or without hormonal therapy.

After HIFU or cryotherapy, a variety of definitions for PSA-relapse have been used (11). Most of these are based on a cut-off of around 1 ng/mL, eventually combined with a negative post-treatment biopsy. As yet, none of these end-points have been validated against clinical progression or survival and therefore it is not possible to give firm recommendations on the definition of biochemical failure.

17.3.3 PSA monitoring after radical prostatectomy
PSA is expected to be undetectable within 6 weeks after a successful radical prostatectomy (12). A persistently elevated PSA level means that PSA-producing tissue remains in the body. In patients treated with radical prostatectomy, this is generally thought to be residual cancer due to either micrometastases that were not detected or undetectable beforehand, or residual disease in the pelvis possibly due to positive surgical margins.
A rapidly increasing PSA level (high PSA velocity, short PSA doubling time) indicates distant metastases, while a later and slowly increasing concentration of PSA is most likely to indicate local disease recurrence. The time to PSA recurrence and tumour differentiation are also important predictive factors distinguishing between local and systemic recurrence (13,14). Both local treatment failure and distant metastases have been shown to occur with undetectable PSA levels. This is very rare and occurs almost only in patients with unfavourable pathology (undifferentiated tumours) (15,16).

This means that, in patients with a relatively favourable pathology (< pT3, pN0, Gleason score < 8), PSA measurement, together with the disease-specific history, could stand as the single test in follow-up after radical prostatectomy.

17.3.4 PSA monitoring after radiation therapy
The PSA level falls slowly after radiotherapy compared with radical prostatectomy. The optimal cut-off value for a favourable PSA nadir after radiotherapy is somewhat controversial. Achieving a PSA nadir of less than 0.5 ng/mL seems to be associated with a favourable outcome (17). The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. A PSA rising more than 2 ng/mL above the nadir PSA is the current definition of biochemical failure after radiotherapy (10). Also, after radiotherapy, the PSA doubling time has been shown to correlate to the site of recurrence; patients with local recurrence had a doubling time of 13 months compared to 3 months for those with distant failure (18).

17.3.5 Digital rectal examination (DRE)
DRE is performed to assess whether or not there is any sign of local disease recurrence. It is very difficult to interpret the findings of DRE after curative therapy, especially after radiotherapy. A newly detected nodule should raise the suspicion of local disease recurrence.

As mentioned previously, a local disease recurrence after curative treatment is possible without a concomitant rise in PSA level (15,16). However, this has only been proven in patients with unfavourable pathology, i.e. those with undifferentiated tumours. Thus, PSA measurement and DRE comprise the most useful combination of tests as first-line examination in follow-up after radiotherapy or radical prostatectomy, but PSA measurement may well be the only test in cases with favourable pathology (19).

17.3.6 Transrectal ultrasonography (TRUS) and biopsy
TRUS and biopsy have no place in the routine follow-up of asymptomatic patients and nowadays only rarely after biochemical failure. TRUS cannot stand alone as a diagnostic tool, but must usually be combined with biopsy to establish the presence of local disease recurrence. The purpose of the investigation is to confirm a histological diagnosis of local disease recurrence. It is only warranted if the finding of a local recurrence affects the treatment decision (see Section 16 for a more detailed discussion).

17.3.7 Bone scintigraphy
The purpose of bone scintigraphy is to detect skeletal metastases. It is not recommended for the routine follow-up of asymptomatic patients, but may be indicated in individuals with elevated PSA levels for whom the findings will affect the treatment decision. It is also indicated in patients with symptoms arising from the skeleton, since metastatic disease may occur even if PSA is undetectable (15,16).

17.3.8 Computed tomography (CT) or magnetic resonance imaging (MRI)
CT or MRI have no place in the routine follow-up of asymptomatic patients. They may be used selectively in the evaluation after biochemical failure before treatment decisions are made (see Chapter 18).

17.4 When to follow-up?
Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. The patient should therefore be followed-up more closely during the first years after treatment when the risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at the following intervals: 3, 6 and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually. The purpose of the first clinic visit is mainly to detect treatment-related complications and to assist patients in coping with the new situation. Tumour or patient characteristics may allow alterations to this schedule. For example, patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimenconfined tumour. Obviously, advanced age or associated co-morbidity may make further follow-up in asymptomatic patients superfluous.
### 17.5 Guidelines for follow-up after treatment with curative intent

#### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.</td>
<td>B</td>
</tr>
<tr>
<td>After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.</td>
<td>B</td>
</tr>
<tr>
<td>After radiation therapy, a rising PSA level over 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.</td>
<td>B</td>
</tr>
<tr>
<td>Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.</td>
<td>B</td>
</tr>
<tr>
<td>Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases TRUS and biopsy are not necessary before second-line therapy.</td>
<td>B</td>
</tr>
<tr>
<td>Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be omitted if the serum PSA level is less than 20 ng/mL but data on this topic are sparse.</td>
<td>C</td>
</tr>
<tr>
<td>Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.</td>
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#### References


18. FOLLOW-UP AFTER HORMONAL TREATMENT

18.1 Introduction
A large proportion of patients treated with hormonal therapy have either metastatic or locally advanced tumours at diagnosis. This will affect the scheme of follow-up because biochemical failure is often associated with rapid symptomatic progression.

18.2 Purpose of follow-up
The main objectives of following-up these patients are to:
• monitor the response to treatment;
• ensure compliance with treatment;
• detect potential complications of endocrine therapy;
• guide the modalities of palliative symptomatic treatment at the time of CRPC.

It is important to be clear about which complementary investigations are helpful at different stages of the disease to avoid unnecessary patient examinations and excessive economic cost. In addition, strict recommendations for follow-up procedures are only useful if effective therapeutic strategies are available in cases of disease progression. To date, the issue of early versus late initiation of non-hormonal treatment in CRPC has still not been resolved, so follow-up should be performed on an individual basis. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up procedures following hormonal therapy.
18.3 Methods of follow-up

18.3.1 Prostate-specific antigen monitoring
Prostate-specific antigen is a good marker for following the course of metastatic PCa. The initial PSA level can be a reflection of the extent of metastatic disease, although some poorly differentiated tumours do not secrete PSA. In recent decades, the PSA value has been used to predict the duration of response to endocrine treatment, based on either the initial pre-treatment value or the PSA decrease during the first 3-6 months. However, the prognostic value of the pre-treatment PSA value is variably assessed in the literature and should not be used alone to predict the duration of treatment response (1).

Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa after hormonal treatment has been initiated. Patients with the lowest absolute value of serum PSA (< 0.2 ng/mL) have been shown to have the best survival compared to patients with a value of 0.2-4.0 ng/mL or > 4.0 ng/mL (2). Similar results have been seen in other studies of locally advanced and metastatic PCa (3-5). The PSA response has been shown to be equally important in patients treated with hormonal therapy, following a rising PSA after treatments with curative intent (radical prostatectomy, radiation therapy). Patients with the best response also had the best survival (6,7).

Despite its usefulness in determining treatment response in individual patients, the role of PSA as a surrogate end-point in clinical trials is more controversial (8). After the initial phase of response to endocrine treatment, patients should be regularly monitored to detect and treat any complications of endocrine escape. Clinical disease progression occurs after a median interval of about 12-18 months of treatment in patients with stage M1 disease. It is well established that regular PSA control in asymptomatic patients allows the earlier detection of biochemical escape because a rise in PSA level usually precedes the onset of clinical symptoms by several months. However, it must be stressed that the PSA level is not the absolute marker of escape and should not be used alone as a follow-up test. Clinical disease progression (usually bone pain) with normal PSA levels has been reported to occur.

18.3.2 Creatinine, haemoglobin and liver function monitoring
Creatinine monitoring has some value because it can detect upper urinary tract obstruction in cases of advanced cancer, which might need to be relieved by, for example, percutaneous nephrostomy or a JJ-stent.

Haemoglobin and liver function tests may suggest disease progression and/or toxicity of hormonal treatment, which can lead to interruption of hormonal treatment (i.e. liver toxicity from non-steroidal antiandrogens). It is important to remember that haemoglobin levels will decrease by about 20% with androgen deprivation (9).

Alkaline phosphatase and its bone-specific isoenzymes have the advantage of not being directly influenced by hormonal therapy compared with PSA. These markers may be used to monitor patients with stage M1b disease. It should be remembered that increases in serum alkaline phosphatase may be due to androgen-induced osteoporosis (10), and in this context, it may be helpful to determine the level of bone-specific alkaline phosphatase.

18.3.3 Bone scan, ultrasound and chest X-ray
In routine practice, asymptomatic patients with a stable PSA level should not undergo a bone scan at regular intervals, because disease progression is more reliably detected by PSA monitoring, which also has a lower cost (11,12).

Moreover, it is also sometimes difficult to interpret bone scans. Thus, in an asymptomatic patient, the therapeutic approach is not modified by the appearance of a new site of uptake or deterioration of pre-existing lesions. Recently, the PCWG2 has clarified the definition of bone scan progression as the appearance of at least two new lesions (13).

Clinical or laboratory suspicion of disease progression indicates the need for a chest X-ray or renal and hepatic ultrasound. Imaging modalities must also be guided by symptoms. However, these examinations are not recommended for routine use in asymptomatic patients. In CRPC disease, follow-up examinations should be individualised with the aim of maintaining the patient’s quality of life.

During long-term ADT, it may be necessary to introduce regular measurement of BMD (LE: 3), based on the initial T-score (14). Bone mineral density should be measured every 2 years if the initial T-score < 1.0, or every year if the T-score is between 1.0 and 2.5, in the absence of associated risk factors (LE: 4). Otherwise, active protective bone treatment should have started at the initiation of ADT (see Chapter 12).

18.4 Testosterone monitoring
Most PCa patients receiving LHRH analogues will achieve serum testosterone values at or below the castration level (< 20 ng/dL). However, about 13-38% of patients fail to achieve this therapeutic goal, while 2-17% of patients do not achieve a serum testosterone level below 50 ng/dL (15-17). Furthermore, up to 24% of men treated with LHRH analogues may experience testosterone surges (testosterone > 50 ng/dL) during long-term
treatment upon re-administration of the agonist drug, which is described as the ‘acute on-chronic effect’ or ‘breakthrough responses’ (16,18).

In view of these findings, the measurement of serum testosterone levels, as well as serum PSA levels, should be considered as part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. The first evaluation of testosterone level can be recommended at 1 month after initiating LHRH therapy to check the nadir testosterone level achieved before re-administration of the agonist drug. A 6-month testosterone level assessment may be performed to evaluate the effectiveness of treatment and to ensure the castration level is being maintained. If it is not being maintained, switching to another LHRH agent or surgical orchiectomy can be attempted. In patients with a rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

18.5 Monitoring of metabolic complications
Androgen deprivation therapy is beneficial in patients with prostate cancer, but has a greater range of complications than might be expected (see Chapter 12). The most common side-effects of low testosterone levels include hot flashes, lack of libido, erectile dysfunction, gynaecomastia and loss of bone mineral density. In addition, recent studies have suggested that men with low testosterone levels have a higher prevalence of metabolic complications (19), including insulin resistance, arterial stiffness, diabetes and metabolic syndrome. Research has shown that the metabolic syndrome is present in more than 50% of men undergoing long-term ADT, predisposing them to a higher cardiovascular risk (20). Men with metabolic syndrome are almost three times more likely to die of coronary heart disease and other cardiovascular diseases (21), which have now become the most common cause of death in prostate cancer patients, even exceeding prostate cancer mortality (22).

In view of these findings, a cardiology consultation may be beneficial in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months [LE: 3]). In selected cases, glucose tolerance testing may be required. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc.) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension (23,24). The patient’s GP or family physician should probably be more involved in those patients at risk of cardiovascular disease, including monitoring of fasting glucose, lipids profile and blood pressure, which is recommended in all patients receiving long-term ADT. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT (19,25).

Monitoring bone health is also important, particularly serum levels of Vitamin D and calcium. If needed, supplements should be given so that the patient receives a daily intake of at least 1200 mg/day of calcium and 1000 UI of vitamin D. Preventive therapy with bisphosphonates or denosumab should be considered in patients who have an initial T-score of less than -2.5 on dual-energy X-ray absorptiometry (DEXA), which is the definition of osteoporosis. However, optimal bone monitoring using DEXA is still controversial and should be prospectively evaluated. It is currently suggested that bone monitoring should be performed every 2 years after initiation of castration, provided there are no other risk factors (26), and every year if there are risk factors (27,28).

18.6 When to follow-up
After initiation of hormonal treatment, it is recommended that patients be followed-up at 3 and 6 months. These guidelines must be individualised, and each patient should be told to contact his physician in the event of troublesome symptoms.

18.6.1 Stage M0 patients
If there is a good treatment response, i.e. symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up visits are scheduled every 6 months.

18.6.2 Stage M1 patients
If there is a good treatment response, i.e. good symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up is scheduled every 3 to 6 months.

18.6.3 Castration-refractory PCa
Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualised follow-up scheme.
18.7 Guidelines for follow-up after hormonal treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tr>
<td>Patients should be evaluated at 3 and 6 months after the initiation of treatment.</td>
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<tr>
<td>As a minimum, tests should include serum PSA measurement, digital rectal examination (DRE), serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and the side-effects of the treatments given.</td>
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<tr>
<td>If patients undergo intermittent androgen deprivation, PSA and testosterone should be monitored in 3-month intervals during the treatment pause.</td>
<td>C</td>
</tr>
<tr>
<td>Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.</td>
<td>C</td>
</tr>
<tr>
<td>In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and should include as a minimum a disease-specific history, DRE and serum PSA determination.</td>
<td>C</td>
</tr>
<tr>
<td>In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements. The testosterone level should be checked, especially during the first year.</td>
<td>C</td>
</tr>
<tr>
<td>Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.</td>
<td>A</td>
</tr>
<tr>
<td>When disease progression occurs, or if the patient does not respond to the treatment given, the follow-up needs to be individualised.</td>
<td>C</td>
</tr>
<tr>
<td>In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient is castrated (at least T &lt; 50 ng/dL).</td>
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<tr>
<td>Routine imaging of stable patients is not recommended.</td>
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18.8 References


19. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENT WITH CURATIVE INTENT

19.1 Background
Primary curative procedures such as RP and RT are well-established therapeutic options in the management of localised PCa. Technical advances in surgery and RT have both improved the efficacy of treatment and reduced treatment-associated morbidity and toxicity.

Despite these improvements, however, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or RT develop local or distant recurrences, and second-line treatment is required in 16-35% of cases within 10 and 5 years of the initial therapy, respectively (1-6).

19.2 Definitions
19.2.1 Definition of treatment failure
Treatment failure was in the past defined as a recurrence identified during DRE or the development of metastatic disease. Currently, treatment failure is anticipated by a rising PSA level; Pound et al. (7) showed that no patients who were followed up for > 5 years developed a recurrence without a concomitant rise in PSA.

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. Following RRP, there is an international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL (6,8). However, the most appropriate definition of biochemical progression after RP is still unclear. A retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa (9) was used to determine the best PSA cut-off point for defining biochemical recurrence (BCR). Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively (9). These data indicate that only half of patients with a PSA of 0.2 ng/mL will show further progression, and they can therefore be managed initially by surveillance.

This finding has been confirmed with similar data reported by Stephenson et al. (10), who identified a PSA value of > 0.4 ng/mL, followed by another increase, as the best cut-off level for indicating the development of distant metastases. This level was estimated using definitions obtained from a retrospective review of patients who had developed distant metastases following RP.

After RT, three consecutive increases in PSA following a PSA nadir were considered to provide a reasonable definition of BCR, according to the American Society for Therapeutic Radiology and Oncology (ASTRO) (11). This definition of PSA failure after RT was updated at the RTOG-ASTRO Phoenix Consensus Conference to any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir (12).

A recent study by Kapadia et al. including 710 patients with PCa who were treated with RT with or without ADT showed biochemical failure (BCF) in 21% at a median follow-up of 42 months after EBRT. Biochemical failure was present in 8%, 15%, and 36% of low-risk, intermediate-risk, and high-risk patients, respectively. The authors also found that there was a stronger correlation between a short interval to BCF (defined as failure occurring within 18 months of completing EBRT and/or ADT) and a significantly increased rate of distant metastases, decreased CSS, and decreased OS (13).

19.2.2 Definition of recurrence
A recurrence of PCa can be defined as:
Following RP, PSA values > 0.2 ng/mL, confirmed by two consecutive measurements
Following RT, a PSA value of 2 ng/mL above the nadir after treatment

19.3 Local or systemic relapse

Once a PSA relapse has been diagnosed, it is extremely important to determine whether the recurrence has developed at local or distant sites. About 50% of patients who have undergone RRP will have local disease, while the remainder will have either distant disease alone or distant and local disease (11).

Several important parameters have been suggested in order to differentiate between local and distant relapse:
- Timing of the PSA increase after surgery.
- PSA velocity (PSAV).
- PSA doubling time (PSADT).
- Histopathological stage.
- Gleason score in the prostatectomy specimen.

Prostate-specific antigen increases developing within the first 2 years following surgery are more often associated with distant recurrences (12). It has been shown that a median PSADT of 4.3 months may be associated with distant relapse, whereas a median PSADT of 11.7 months is better predictive of local failure (14). Freedland et al. showed that clinical parameters, PSADT, pathological Gleason score, and time from surgery to BCR are important for stratifying patients into groups with varying levels of risk for prostate cancer-specific mortality (15). In patients who have undergone RP, there is apparently no indication for performing ultrasound-guided biopsies of the vesicourethral anastomosis in order to diagnose local relapse, as this method has low sensitivity and low predictive accuracy in patients with rising PSA levels < 1.0 ng/mL.

In patients who have undergone RT, any continuously rising PSA levels following a nadir after treatment indicate local recurrence, systemic metastatic spread, or a combination of the two (11,15,16). A late and slowly rising PSA level may be a sign of only local failure.

19.3.1 Ultrasensitive PSA

The introduction of ultrasensitive PSA testing has made it possible to screen patients after RP and predict the risk of BCF after surgery at an early stage. Ultrasensitive PSA testing allows more precise measurement of the PSA nadir after radical surgery; patients with a PSA nadir < 0.01 ng/mL developed an early relapse in 4% of cases; by contrast, those with a PSA nadir of 0.04 ng/mL or higher developed an early relapse in 89% of cases (17).

19.3.2 Definition of local and systemic failure

The definitions of local and systemic failure are as follows:
- Following RP, local failure is predicted with an 80% probability by a PSA increase 3 years after surgery, a PSADT > 11 months, a Gleason score < 7, and stage < pT3a pN0, pTx R1.
- Following RP, systemic failure is predicted with > 80% accuracy by a PSA increase at < 1 year after surgery, a PSADT of 4-6 months, a Gleason score of 8-10, and stage ≥ pT3b, pTx pN1.
- After RT, local failure is documented by a positive prostatic biopsy and negative imaging studies such as CT or MRI and bone scintigraphy. Prostatic biopsy after RT is considered necessary only if local procedures with curative intent, such as a salvage radical prostatectomy (SRP), are indicated in an individual patient.

19.4 Evaluation of PSA progression

Before extensive diagnostic work-up is carried out in patients with a PSA relapse following local treatment, men need to be stratified into those who are candidates for salvage therapy and those who are not. Any diagnostic procedures should only be performed if the results will have therapeutic consequences.

In recent years, most patients with PSA progression following initial therapy with curative intent have undergone physical and ultrasound examinations, as well as radiologic investigations or biopsies of the prostatic fossa and the vesicourethral anastomosis to confirm the recurrence suggested by serological studies. The diagnostic yield is very low in patients with asymptomatic PSA-only progression.

As mentioned above, according to Pound et al. (7), not all patients with BCF after RP also develop clinical recurrence. The authors evaluated the follow-up data for 1997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data have been confirmed by Boorjian et al. in a study including approximately 2400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only few of them died due to PCa (5.8%) (18).
Imaging studies are used to distinguish between local relapse and systemic relapse in order to select the most appropriate treatment modality. Unfortunately, most imaging studies are not sensitive enough to identify the anatomic location of relapsing PCa at PSA levels < 0.5–1.0 ng/mL.

### 19.4.1 Diagnostic procedures for PSA relapse following RP

Traditionally, bone scans and abdominal CT have been used to evaluate increases in the PSA level following primary treatment. Both imaging studies have low sensitivity and specificity, and can be safely omitted from the routine work-up for relapsing patients. Bone scans were examined in 144 patients presenting with PSA recurrences (20): 122 of the patients had undergone RP with no HT, and 22 had received either neoadjuvant or adjuvant ADT. In the first group, the lowest PSA associated with positive scintigraphy findings was 46 ng/mL, while in those who had received HT, the lowest PSA value was 15.47 ng/mL.

The probability of finding a positive bone scan remains < 5% until the serum PSA level reaches at least a value of 40 ng/mL. In other studies, patients with a true positive bone scan had an average PSA level of > 60 ng/mL and a PSAV of 22 ng/mL/year (21,22). Logistic regression analysis showed that PSA and PSAV were good predictors of bone scan results and that PSA was a good predictor of CT scan results. Johnstone et al. (22) found a slight difference between surgically treated patients and those who received RT: 5% and 30% of the bone scans, respectively, were positive.

In summary, bone scintigraphy and abdominal CT scan are of no additional diagnostic value unless PSA serum levels are > 20 ng/mL or PSAV is > 20 ng/mL/year.

The diagnostic accuracy of endorectal MRI (e-MRI) using a 1.5-Tesla machine was investigated in a series of patients with PSA relapse following RP (23). The mean total PSA was 1.23 ± 1.3 ng/mL. The data were compared with standard references for local recurrence, including prostatectomy bed biopsy results, choline PET results, PSA reduction or increase after pelvic RT, and PSA modification during active surveillance. The sensitivity, specificity, positive and negative predictive values, and accuracy were 61.4%, 82.1%, 84.4%, 57.5%, and 69.4%, respectively, for unenhanced e-MRI and 84.1%, 89.3%, 92.5%, 78.1%, and 86.1%, respectively, for enhanced e-MRI. The two methods showed a statistically significant difference in accuracy (chi-squared test = 5.33, $P = 0.02$) and sensitivity (chi-squared test = 9.00, $P = 0.0027$).

Although e-MRI appears to be sensitive and predictive in identifying local recurrences following RP, it does not currently appear capable of becoming a routine imaging modality to be performed in every case, as local vs. systemic relapse may be differentiated at PSA levels < 0.5 ng/mL. At this level of PSA, e-MRI is not sufficiently sensitive or accurate.

Positron-emission tomography has been successfully used in many human cancers for early identification of local or systemic recurrences. In PCa, there are few, even if promising, published data on the clinical efficacy of PET in detecting local recurrences after RP, especially when an increased PSA value is detected (24-28). Choline, as a component of the phosphatidyicholines, is highly increased in PCa and can be easily radiolabeled with either carbon-11 ($^{11}$C-choline) or fluorine-18 ($^{18}$fluorocholine).

Kotzerke et al. (24) reported a potential use of $^{11}$C-acetate PET as a new tool for diagnosing PCa recurrences, with an important impact on management as well. However, Cimitan et al. (25) suggested that in previously treated PCa patients with biochemical recurrences, $^{18}$F-choline PET/CT may not have a significant impact on therapeutic care until PSA increases to > 4 ng/mL, particularly in patients with well or moderately differentiated primary tumors (Gleason score < 7). Choline PET/CT may be helpful in selected patients with higher PSA levels and/or poorly differentiated PCa (Gleason score > 7), to exclude distant metastases when salvage local treatment is intended.

Pelosi et al. (29) reported that the sensitivity of $^{18}$F-choline PET/CT was 20%, 44%, and 80% in patients with PSA levels ≤ 1 ng/mL, 1-5 ng/mL, and > 5 ng/mL, respectively. Husarik et al. (30) evaluated the accuracy of PET/CT for detecting relapses following initial radical treatment for PCa. They confirmed that it is more accurate in patients with PSA levels > 2 ng/mL, regardless of the concomitant use of HT.

Giovacchini et al. (27) reported that PSAV was a predictor of positive $^{11}$C-choline PET/CT and that it can be used to stratify the risk of positive $^{11}$C-choline PET/CT in PCa patients with BCF. The authors concluded that a PSAV rate of > 1 ng/mL/year should be used to increase the rate of positive detection with $^{11}$C-choline PET/CT. The most recent series evaluating the role of $^{11}$C-choline PET/CT in men with biochemical failure after RP showed that metastases were more likely to be identified at higher PSA levels, with a detection rate ranging
from 20% to 36% in patients with PSA levels < 1 ng/mL and increasing to 63-83% in men with PSA levels > 3 ng/mL (31-33).

Recently, Giovacchini et al. (34), evaluating 109 patients with rising PSA levels and negative conventional imaging studies, concluded that $^{11}$C-choline PET/CT may be helpful for re-staging PCa, but it should not be used to guide therapy. The use of $^{11}$C-choline PET/CT in all men with a rising PSA level > 1 ng/mL would result in an 85% incidence of unnecessary examinations, a significant increase in medical costs, and no benefit for the individual patient.

Graute et al. (35) used $^{18}$F PET/CT to try to identify PSA threshold levels, as well as the PSAV, progression rate, and PSADT in relation to the detectability and localisation of recurrent lesions. ROC analysis identified the optimal threshold for distinguishing between PET-positive and PET-negative findings as 1.74 ng/mL (AUC 0.818), resulting in a sensitivity of 82% and a specificity of 74%. In that study, the sensitivity for tumor detection correlated with serum PSA levels, yielding sensitivities increasing from 20% in patients with PSA < 1 to 44% for PSA ≤ 5 ng/mL and 82% for PSA > 5 ng/mL.

Fuccio et al. (26) evaluated consecutive patients with biochemical recurrences (mean PSA value 3.3 ng/mL) after RP. Using $^{11}$C-choline PET/CT, they identified unknown bone lesions in 14.6% of the patients; 33% of these lesions did not reveal any structural change at CT. As previously reported in the literature, the advantage of choline PET/CT may be that it is able to detect bone marrow involvement in PCa patients at an early stage before and after therapy (36,37).

The effects of HT on radiolabeled choline uptake (especially in the skeleton) are of great importance and still under investigation. Giovacchini et al. (38) evaluated the influence of HT on the efficacy of choline PET. Although HT was significantly associated with an increased risk of positive choline PET/CT in the univariate analysis, the effects of ADT were no longer significant in the multivariate analysis.

As recently reported by Picchio et al. (39), routine use of $^{11}$C-choline PET/CT cannot be recommended for PSA values < 1 ng/mL, but a cut-off value for appropriate referral of patients for choline PET/CT imaging has yet to be defined. The accuracy of PET correlates with PSA values, PSADT, and other pathological features. Certainly, a PSADT < 3 months can be regarded as a strong predictor of PET positivity.

Panebianco et al. compared the accuracy of detecting local recurrence of PCa in patients with BCF using proton magnetic resonance spectroscopic imaging ($^{1}$H-MRSI) in comparison with combined dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) techniques with a 3 T magnet vs. $^{18}$F-choline PET/CT. $^{1}$H-MRS-DCEMR combined techniques may be a valid tool for detecting PCa recurrence and may be more accurate than PET/CT for identifying smaller lesions in patients with low biochemical alterations after RRP (0.2-2 ng/mL) (sensitivity 92% vs. 62%; specificity 75% vs. 50%; accuracy 89% vs. 60%) (40).

In summary, the role and diagnostic accuracy of $^{11}$C-choline PET/CT in men with rising PSA following RP depends on the absolute PSA value, PSADT, and PSAV. The higher the PSA level and the faster the PSADT, the better will be the predictive value of this imaging modality. However, even in patients with PSA values > 2 ng/mL and negative imaging studies, $^{11}$C-choline PET/CT is positive in only 28% of patients. It appears that there is an urgent need for well-conducted and histologically controlled trials to explore the potential role of $^{11}$C-choline PET/CT.

### 19.4.2 Diagnostic studies for PSA relapse following radiation therapy

With regard to PSA relapses following RT, routine prostate biopsy should no longer be performed for the evaluation of PSA-only recurrences, according to an ASTRO consensus recommendation (11). However, a prostate biopsy documenting local recurrence represents the main cornerstone in the decision-making process for SRP in patients with rising PSA levels following a nadir after RT (41). It is a general recommendation to wait about 18 months and 3 months after RT or seed implant and cryotherapy or high-intensity focused ultrasound (HIFU), respectively. Patients with rising PSA and a viable cancer on biopsy 2 years after RT have true locally recurrent disease and may be candidates for SRP.

The role of choline PET/CT to detect local or systemic recurrences in men with a PSA relapse following RT is still unclear and based on very few studies (42,43). No conclusive recommendations can therefore be made. The sensitivity and specificity of choline PET/CIT with regard to the detection of lymph node metastases are less reliable, and routine use of $^{11}$C-PET cannot therefore be recommended, especially for PSA values < 1 ng/mL.
The role of e-MRI, MRI spectroscopy, and dynamic contrast-enhanced MRI for the identification of locally recurrent PCa following RT was evaluated in a number of studies (44-46). These studies have demonstrated that locally recurrent PCa can be differentiated from benign nodules due to its low signal intensity on T2-weighted imaging. e-MRI and magnetic resonance spectroscopy were more sensitive than transrectal ultrasonography (TRUS) or TRUS-guided prostate biopsies for detecting viable PCa. e-MRI also contributed important information regarding the presence of extraprostatic extension and seminal vesicle invasion, with a sensitivity of 86% and a specificity of 96%. e-MRI is therefore strongly recommended in the diagnostic work-up of men with a PSA relapse after RT, who may be candidates for secondary local salvage therapy with curative intent.

19.5 Treatment of PSA-only recurrences
The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial. After RP, the therapeutic options are:

- Radiotherapy to the prostatic bed.
- (Complete) androgen deprivation (CAD, AD).
- Intermittent androgen deprivation (IAD).
- Combination of antiandrogens with 5-alfa-reductase inhibitors.
- Early chemohormonal approaches.

Following RT, the same therapeutic options may apply in relation to PSA recurrences. In addition, SRP, cryotherapy, or brachytherapy may be indicated in carefully selected patients.

19.5.1 Radiotherapy for PSA-only recurrence after RP
Three large randomised controlled trials in adjuvant radiation have been published (47-49). All three reported a BCR-free survival benefit with adjuvant RT of at least 15% at 5 and 10 years.

The largest trial (EORTC-22911, n = 1005) (47) and the smallest trial (ARO-96-02, n = 307) (49) trial were powered to detect a benefit in BCR-free survival, while metastasis-free survival was the primary end-point of the third trial (SWOG-S8794, n = 431) (48). The three trials had similar inclusion criteria. However, the EORTC trial also included pT2 R1 patients, while the other two trials allowed only pT3 cancers with or without positive resection margins. Quite a high proportion of patients in all three trials (63-68%) had positive surgical margins.

It should be noted that the postoperative PSA level before patients were randomly assigned to adjuvant RT differed among the three trials. In the German ARO-96-02 trial, only men with a PSA < 0.1 ng/mL were eligible for randomisation; in the EORTC trial, 11% of men had a PSA level > 0.2 ng/mL prior to randomisation, and 34% in the SWOG trial. Thus, a substantial number of men in the EORTC and SWOG trials received “salvage” radiotherapy (SRT) rather than “adjuvant” RT for a non-normalised PSA. It is therefore of interest that not all of the men in the nonadjuvant arms of the trials were treated with SRT by the time of a biochemical recurrence: delayed RT or SRT to the prostatic fossa was administered in 55% of men with a rising PSA level in the EORTC trial and to 33% of men in the SWOG trial. Thus, the trials were not able to evaluate whether adjuvant therapy was superior to salvage radiation as in the control arm; only half of the men received RT at the time of PSA recurrence.

The authors of the EORTC trial suggested that SRT may be equivalent to adjuvant therapy, provided that the PSA level is < 1 ng/mL (47). However, only the SWOG trial was powered to address the effect of delayed radiation, as it was the only trial with metastasis-free survival as the primary end-point. In the SWOG trial, men in the control arm were less likely to receive SRT (33%). However, it took a median follow-up of over 12 years before metastasis-free survival improved in the adjuvant treatment arm, suggesting that adjuvant therapy may not be helpful in men with a life expectancy of less than 10 years (48,49). Recently, it has been demonstrated that patients in the control group more often had a higher frequency of PCa with Gleason score 8-10 and were more likely not to receive ADT at the time of PSA relapse.

There have been many studies on the use of RT for PSA-only recurrences after RRP. As a result, there is a growing body of parameters for predicting the outcome that may help differentiate between the need for observation, RT, or HT. As confirmed by various studies, the pre-radiotherapy PSA level is critically important for optimal treatment results (41,44,45).

Cotter et al. analysed 4,036 patients with 11.3 years of follow-up who had been treated with RP for PCa, and found that SRT was associated with a significant reduction in all-cause mortality for men with either a PSADT of < 6 months or a PSADT of ≥ 6 months (50).
Siegmund et al. tried to define “what is the best time to treat” patients with biochemical recurrences after RP. They evaluated the biochemical response to SRT, without HT, in 301 patients, with a median follow-up of 30 months. In the multivariate logistic regression analysis evaluating factors influencing an undetectable PSA following SRT, only the pre-SRT PSA level (odds ratio 2.62, P = 0.001) and infiltration of the seminal vesicles (odds ratio 2.53, P = 0.02) were found to be independent predictive factors. The authors found that patients with a PSA level < 0.28 ng/mL before SRT had a better outcome than those with higher PSA levels and that they may have a chance of a long-term durable response without further treatment (51). Similarly, a major role for early SRT was reconfirmed by a systematic review by Ohri et al., who demonstrated that the biochemical recurrence-free survival (BCR-FS) increased along with the SRT dosage by 2.5% per Gy and decreased along with the pre-SRT PSA by 18.3% per ng/mL (P < 0.001) (52).

ASTRO has published a consensus paper recommending a dosage of at least 64 Gy when the PSA level is < 1.5 ng/mL after RRP (11).

Stephenson et al. evaluated prognostic models for predicting the outcome of SRT in a cohort of 1603 men with PSA progression after RP who underwent surgery in 17 North American tertiary referral centres. They identified a significant relationship between the PSA value at the time of RT and the therapeutic outcomes. Specifically, the 6-year BCR-FS estimates were 48% in men with PSA < 0.5 ng/mL and only 40%, 28%, and 18% in men with PSA levels of 0.51-1.0 ng/mL, 1.01-1.50 ng/mL, and > 1.50 ng/mL, respectively (53).

In the SWOG and EORTC nonadjuvant radiotherapy arms, the median intervals to SRT were 2.0 and 2.2 years, respectively. In the SWOG 8974 study, 23% of men had a PSA level > 1.5 ng/mL prior to SRT. In a subanalysis of the SWOG 8,974 trial, Swanson et al. (54) showed that men in all categories of post-prostatectomy PSA levels (< 0.2, 0.2-1.0, > 1.0 ng/mL) had improved metastasis-free survival after SRT. However, the therapeutic benefit was most evident in the presence of minimal PSA serum levels. These data suggest that, although less effective, SRT may help improve the metastasis-free survival.

In a multi-institutional, matched-control analysis of adjuvant and salvage postoperative RT for pT3-4 N0 PCa, Trabulsi et al. (55) demonstrated a BCR-FS advantage in favor of adjuvant RT vs. SRT. Interestingly, in a multivariable Cox regression analysis, adjuvant RT vs. SRT was not an independent predictor of metastatic PFS, after correction for adverse clinical and pathological factors.

Data have become available on overall survival and SRT. In a group of men with a median follow-up of 9 years after radical prostatectomy, the benefit of SRT for PCa-specific mortality was seen particularly in men with a PSADT of less than 6 months who had received SRT to the prostate fossa within 2 years after a rise in PSA (56). This suggests that local disease control may prolong the prostatic CSS in men formerly thought to be at risk for systemic disease progression and less likely to benefit from (salvage) RT.

Men with slowly progressing disease, although they are still at risk for systemic progression, may not benefit from SRT as they have a low risk for developing fatal PCa. Longer follow-up periods are certainly needed in order to answer this question.

19.5.1.1 Dose, target volume, toxicity
The three randomised trials on adjuvant RT all used dosages < 66 Gy, which is currently the most frequently used dosage for adjuvant and salvage RT. However, it is important to note that, as with dose escalation studies in primary radiation for PCa, an increased dose in the salvage setting may improve the biochemical response without worsening local toxicity (57,58). Dosages of up to 70 Gy have shown better BCR-free rates at higher dosages, with 66.8 Gy RT found to be the dosage required for 50% BCR-free survival. Even higher doses may be considered, particularly when using improved imaging techniques, such as fiducial markers (59). The finding that 9% of men develop a local recurrence after adjuvant radiation of 60 Gy provides support for an increase in the dosage and target volume (54).

Target volume delineation has been found to vary by up to 65% between different radiotherapists administering adjuvant or salvage radiation to the prostatic fossa (60-62). It is therefore important not to overlook local toxicity. In the EORTC 22911 study, 3.1% of men had to interrupt adjuvant RT because of local symptoms, mainly diarrhoea. Although grade 3 or 4 toxicity is rare for either adjuvant or SRT to the prostatic fossa, it was almost doubled in the adjuvant arm of the EORTC 22911 study (2.6% vs 4.2%) and the SWOG S8794 study, particularly with regard to urethral strictures (relative risk 9) and incontinence (relative risk 2.3).

19.5.2 Hormonal therapy
Systemic failure following RP is predicted with > 80% accuracy by a PSA relapse < 1 year, a PSADT of 4-6 months, Gleason score 8-10, and stage pT3b, pTx pN1. There is some evidence that early HT may help delay progression and possibly achieve a survival benefit (63,64).
19.5.2.1 Adjuvant hormonal therapy after RP

In the absence of randomised controlled trials for postoperative PSA recurrence, it is necessary to rely on retrospective data or to extrapolate data from other clinical settings, such as men with metastatic disease or locally advanced nonmetastatic disease. It is uncertain whether or not such data are relevant to men with rising postoperative PSA levels.

Two randomised studies have compared immediate HT (after diagnosis) with deferred HT (on progression) in patients with PCa. The Medical Research Council study in locally advanced or asymptomatic metastatic PCa and the EORTC study in newly diagnosed PCa (T0-4 N0 M0) illustrate that, although immediate HT after diagnosis may delay disease progression in men with PCa, this does not necessarily result in an improved CSS (65,66).

A survival advantage for immediate (adjuvant) ADT after RP has only been confirmed in patients with positive lymph node PCa in a single randomised study (63,64).

Mydin et al. concluded that early salvage HT based on PSA < 10 ng/mL and absent distant metastases improved the survival in patients with PCa after the failure of initial treatment with neoadjuvant HT plus RT (67).

Adjuvant bicalutamide (150 mg) was able to decrease progression in men with locally advanced PCa, but did not result in an OS benefit (68). Several retrospective analyses from the Mayo Clinic have shown that adjuvant HT after RP had a positive effect on the time to progression and cancer death in pT3b and N+ patients (69-71). However, large series from the Mayo Clinic with a median follow-up of 10.3 years show that adjuvant HT in surgically managed N+ patients decreased the risk of BCF and local recurrence, but did not have a significant impact on systemic progression or CSS (72). Another retrospective study with a median follow-up period of 5.2 years showed that immediate and delayed HT (at PSA recurrence) in surgically managed N+ patients provided similar outcomes (73).

An observational study has shown that deferred vs. immediate ADT in N+ men after RP may not significantly compromise survival. There was no statistically significant difference in the OS between the adjuvant ADT group and the non-ADT group. These results need to be validated in a prospective study (74).

19.5.2.2 Postoperative hormonal therapy for PSA-only recurrence

Androgen deprivation therapy

Although patients with postoperative PSA recurrences often undergo ADT before there is any evidence of metastatic disease, the benefit of this approach is uncertain. A retrospective study including 1,352 patients with postoperative PSA recurrence showed no significant difference in the time to clinical metastases with early ADT (after PSA recurrence, but before clinical metastases) vs. delayed ADT (at the time of clinical metastases). However, after risk stratification, it was found that early ADT was able to delay the time to clinical metastases in high-risk patients with a Gleason score > 7 and/or a PSADT < 12 months. ADT had no overall impact on the PCa-specific mortality (75).

It has been shown (76) that adjuvant ADT (within 90 days of surgery) slightly improved the CSS and systemic PFS after RP in a large group of high-risk PCa patients. The survival advantage was lost when ADT was administered later in the disease process, at the time of PSA recurrence or systemic progression. It should be emphasised that there was no advantage with regard to OS (83% in both groups) and that the differences in the CSS and systemic PFS were only 3% and 5%, respectively. In a retrospective study including 422 patients with postoperative PSA recurrences, 123 developed distant metastasis, of whom 91 patients with complete data received deferred ADT at the time of documented metastasis after RP. It was concluded that when closely followed up after PSA recurrence, patients may have an excellent response to deferred ADT and a long survival period, with a median failure time of 169 months from RP to death (77). These three studies are limited by their retrospective design and in assessing the side effects of long-term ADT. They do not allow any definitive conclusions to be drawn on the use of early HT in clinical practice.

Antiandrogens

Although gynecomastia and breast tenderness were the most predominant side effects of treatment for organ-confined and locally advanced PCa, the incidence of hot flushes, loss of libido, and impotence was significantly lower than expected for luteinising hormone-releasing hormone (LHRH) agonists and complete androgen deprivation (CAD) (78).

However, the OS did not differ between the groups (79). Low-dose flutamide (250 mg daily) is currently being investigated in men with PSA recurrences.
Intermittent androgen deprivation

Intermittent androgen deprivation (IAD) has been examined as a potential alternative to CAD in order to:

• Delay the time to androgen independence and hormone-refractory disease.
• Minimise side effects.
• Reduce the costs of prolonged therapies.

There are no long-term data from large-scale randomised controlled trials that can confirm the superiority of IAD over CAD for survival. Limited information suggests that IAD may result in a slight reduction of adverse effects (80). However, in the setting of PSA-only recurrences, there are no prospective randomised trials and no clinical studies with sufficient data on long-term efficacy to justify the routine clinical application of IAD, despite its potential benefits.

In the series in which PSA-only recurrences were treated with IAD (81-84), PSA threshold levels at study entry varied significantly, as did the PSA level at discontinuation of HT. Crook et al. randomly assigned 690 patients to IAD and 696 to CAD. There were no significant between-group differences with regard to adverse events; in the IAD group, full testosterone recovery occurred in 35% of patients, and testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent androgen deprivation provided potential benefits with respect to physical function, fatigue, urinary problems, hot flushes, libido, and erectile function (85).

Minimal androgen blockade

In some studies, finasteride and flutamide have been combined for the management of PSA-only recurrences, since the two agents work additively by blocking the intraprostatic conversion of testosterone to dihydrotestosterone (DHT) and blocking the intracytoplasmic DHT receptor (86-88). In the latest report (87), including 73 patients, administration of finasteride (10 mg/day) and low-dose flutamide (250 mg/day) resulted in a mean PSA nadir of 1.35 ng/mL within 6 months. However, only 62% of the patients studied reached a PSA nadir of < 0.2 ng/mL.

After a mean follow-up period of 15 months, none of the patients had progressed to traditional HT. However, longer follow-up of a larger patient cohort is needed, and randomised phase III trials using modern antiandrogens with fewer gastrointestinal and hepatic side effects are mandatory.

Hormonal therapy after RP combined with radiotherapy and/or chemotherapy

The addition of HT to SRT (n = 78) was not associated with any additional increase in the CSS (88). A phase II trial including 74 patients with postoperative PSA recurrences showed that combined treatment with SRT plus 2 years of CAD (castration + oral antiandrogen) had relatively minor long-term effects on quality of life (89). However, more efficacy data are needed and the potential increase in side effects should be considered when combining therapies. Results are eagerly awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting.

Radiotherapy and ADT in combination after local surgery are being investigated in a recently started, large, randomised, controlled study sponsored by the Medical Research Council. The study is addressing the timing of RT (adjuvant vs early salvage) and the duration of HT (none vs. short-term vs. long-term) used together with postoperative RT. The primary outcome measure will be CSS. Secondary outcome measures will include OS, ADT administered outside the protocol, and reported treatment toxicity. The study is also aiming to assess the long-term effect of RT after RP on sexual, urinary, and bowel function, and the long-term effect of ADT on sexual function and the overall quality of life (90).

Currently, it seems there is no indication for chemotherapy in patients with PSA-recurrence only. Chemotherapy should be considered as a treatment option for patients with castration-resistant PCa, but when a cytotoxic regimen should be initiated is still a matter of controversy (91).

19.5.3 Observation

Observation until the development of clinically evident metastatic disease may represent a viable option for patients with a Gleason score < 7, PSA recurrence > 2 years after surgery, and a PSADT of > 10 months. In these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years (7).
19.5.4 Management of PSA relapse after radical prostatectomy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Local recurrences are best treated by salvage RT with 64-66 Gy at a PSA serum level &lt; 0.5 ng/mL.</td>
<td>B</td>
</tr>
<tr>
<td>For patients with presumed local recurrence who are too unfit or who are unwilling to undergo RT, expectant management can be offered.</td>
<td>B</td>
</tr>
<tr>
<td>PSA recurrence indicative of systemic relapse is best treated by early ADT, resulting in a reduced frequency of clinical metastases.</td>
<td>B</td>
</tr>
<tr>
<td>LHRH analogues/antagonists/orchiectomy or bicalutamide (150 mg/day) can be used when there is an indication for HT.</td>
<td>A</td>
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ADT = androgen deprivation therapy; HT = hormone therapy; LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen; RT = radiotherapy.

19.6 Management of PSA failures after radiation therapy

In a review of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), including 2336 patients with PCa, Grossfeld et al. (92) demonstrated that 92% of patients who had initially been treated with RT received ADT for secondary treatment of PSA progression, with no salvage procedures. The mean time interval from biochemical to clinical progression is approximately 3 years. Therapeutic options in these patients are ADT or local procedures such as salvage RP, cryotherapy, and interstitial RT (41,93-101). Salvage radiotherapy has not gained widespread acceptance because of the morbidity associated with it - namely, urinary incontinence (UI), local recurrences, and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

19.6.1 Salvage radical prostatectomy

Previously, most series reporting on SRP have included patients treated in the pre-PSA era without modern radiotherapeutic techniques, when local recurrences were usually detected at a late stage. Complications associated with the procedure were therefore quite high, with up to 65% of patients suffering from treatment-related morbidity. Up to 60% of patients who underwent SRP had to undergo anterior or total exenteration for locally extensive disease, associated with a high rate of local recurrences and a mean time to progression of 1.3 years.

Recent reports analysing patients who were operated on during the past decade have described much more optimistic outcomes after SRP. In a recent systematic review of the literature, Chade et al. showed that SRP allowed 5-year and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47% to 82% and from 28% to 53%, respectively. The 10-year cancer-specific and OS rates ranged from 70% to 83% and from 54 to 89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS. The authors also highlighted that the associated surgical morbidities were acceptable in the hands of experienced surgeons (102).

In a multicentre series, at 10 years after SRP, Chade et al. reported a BCR-FS of 37%, a metastasis-free survival of 77%, and a CSS of 83%. In a preoperative multivariate analysis in the study, the pre-SRP PSA and the Gleason score at post-radiotherapy prostate biopsy were found to be predictive of biochemical recurrence (103).

In the series reported by Garzotto and Wajsman (97), 24 patients underwent radical cystoprostatectomy or RP with neoadjuvant ADT. Neoadjuvant ADT was associated with a lower rate of positive surgical margins (21%) in comparison with patients in whom ADT failed, who had a positive surgical margin rate of 80%. The authors showed that the disease-specific survival correlated strongly with surgical margin status. After a mean follow-up period of 5 years, the disease-specific survival rates were 95% and 44% for those with negative and positive surgical margins, respectively. Vaidya and Soloway reported a low rate of complications, good postoperative continence, and only one biochemical recurrence 36 months after SRP (98). Similar data have been described by Stephenson et al. (99).

In most contemporary series, organ-confined disease, negative SMs, and an absence of seminal vesicle and/or lymph node metastases were favorable prognostic indicators associated with a better disease-free survival of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa (100).

Heidenreich et al. (101) reported on the oncological and functional outcome in 55 patients who underwent radical salvage therapy for locally recurrent PCa after various types of modern state-of-the-art RT, performed in or after the year 2000. Forty (72.7%) and 15 (27.3%) patients demonstrated organ-confined and locally advanced PCa, respectively. Eleven patients (20%) and seven patients (14%) had lymph node metastases and
positive surgical margins, respectively. In the multivariate analysis, significant predictors of organ-confined PCa with negative surgical margins were:

- Biopsy Gleason score prior to SRP ($P = 0.02$)
- < 50% positive biopsy cores ($P = 0.001$)
- PSADT > 12 months ($P = 0.001$)
- Low-dose brachytherapy ($P = 0.001$)

Urinary continence was achieved after a mean of 8 months in virtually all men after low-dose brachytherapy, while UI persisted in about 20% of patients who underwent EBRT or high-dose brachytherapy.

More recently, salvage laparoscopic radical prostatectomy (SLRP) has been suggested by Ahallal et al. The authors analysed the data for 15 patients who underwent SLRP for biochemical recurrences after RT. Continence recovered in about 50% of the patients, and erectile dysfunction occurred in nearly all of them. The biochemical control was similar to that with the open technique (104).

The current status of salvage robotic RP is still under investigation (105).

19.6.1.1 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, an organ-confined PCa < T2, Gleason score < 7, and preoperative PSA < 10 ng/mL. In all other patients, accurate preoperative staging is not easily defined after RT, increasing the risk not only for anterior and total extirpation procedures, but also for associated complications and reduced long-term disease-specific survival.

19.6.2 Salvage cryoablation of the prostate

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year biochemical disease-free survival estimates ranged from 50% to 70%. With the use of third-generation technology, severe complications such as rectourethral fistulae have been significantly less common over the last decade than in the past (106).

According to Cespedes et al. (107), the risks of UI and erectile dysfunction at least 12 months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of the patients underwent surgical procedures for the management of treatment-associated complications.

With regard to the oncological outcome, studies have shown that a durable PSA response can be achieved in about 50% of patients with a pre-SCAP PSA < 10 ng/mL (108).

In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year BCR-free survival estimate according to the Phoenix criteria was $54.5 \pm 4.9%$. Positive biopsies were observed in 15 of the 46 patients (32.6%) who underwent prostate biopsy after SCAP. The UI rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients had to undergo transurethral resection of the prostate (TURP) for removal of sloughed tissue (109).

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 in the SRP group and 5.5 years in the SCAP group. The 5-year BCR-free survival was 61% following SRP, significantly better than the 21% detected after SCAP. The 5-year OS was also significantly higher in the SRP group (95% vs. 85%) (110).

19.6.3 Salvage brachytherapy for radiotherapy failure

Experience with salvage brachytherapy for patients in whom RT has failed is very limited. In a small study including 11 patients treated with high-dose brachytherapy after RT failure, Jo et al. reported that seven of the 11 patients were free of recurrent disease after a mean of 29 months of follow-up (111). Beyer (112) reported that 34-53% of patients remained free of biochemical relapse after 5 years, with local cancer control achieved in 98% of the patients. However, the complication rate was quite high:

- 27% of the patients became incontinent.
- 14% needed palliative TURP due to acute urinary retention.
• 4% developed rectal ulcers.
• 2% required a permanent colostomy.

A recent review of salvage brachytherapy for RT failure by Gomez-Veiga et al. reported 5-year BCR-free survival rates ranging from 20% to 87%. A single study reported a 10-year BCR-free survival rate of 54% (113).

Moman et al. (114) retrospectively evaluated the outcome and toxicity after salvage iodine-125 implantation in 31 patients with locally recurrent PCa after primary iodine-125 implantation and EBRT. The mean follow-up period was 9 years (SD ± 4). The rates of freedom from BCR were 51% and 20% after 1 and 5 years of follow-up, respectively. Grade 1, 2, or 3 toxicity of the genitourinary tract was reported in 29%, 58%, and 3% of the patients, respectively, in the acute phase, and in 16%, 39%, and 19%, respectively, in the late phase. Grade 1, 2, or 3 toxicity of the gastrointestinal tract was reported in 45%, 10%, and 0% of the patients, respectively, in the acute phase, and in 48%, 3%, and 6%, respectively, in the late phase.

In conclusion, freedom from BCR after salvage iodine-125 implantation for locally recurrent PCa following RT is limited, and both genitourinary and gastrointestinal toxicity occur frequently.

19.6.4 Observation
Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. watchful waiting in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSADT of > 12 months after RT. The 5-year metastasis-free survival rate was 88% with hormone therapy versus 92% with watchful waiting (P = 0.74) (115).

19.6.5 High-intensity focused ultrasound
Experience with high-intensity focused ultrasound (HIFU) for the treatment of locally recurrent PCa after RT is limited to a few retrospective studies. Zacharakis et al. (116) investigated the oncological and functional outcome of HIFU in a cohort of 31 men with biopsy-proven locally recurrent PCa following EBRT. The mean preoperative PSA level was 7.73 ng/mL (range 0.20-20.0 ng/mL). The patients were followed up for a mean of 7.4 months (range 3-24 months). Side effects included stricture or intervention for necrotic tissue in 11 patients (35%), urinary tract infection or dysuria syndrome in eight (26%), and UI in two (6%). Rectourethral fistulae occurred in two men (7%). Overall, 71% had no evidence of disease following salvage HIFU.

Murat et al. (117) evaluated the safety and efficacy of salvage HIFU in 167 patients with local PCA recurrence after EBRT and assessed prognostic factors for optimal patient selection. Local cancer control was achieved with negative biopsy results in 122 patients (73%). The median PSA nadir was 0.19 ng/mL. The mean follow-up period was 18.1 months (range 3-121 months). Seventy-four patients did not require HT. The actuarial 5-year OS rate was 84%. The actuarial 3-year progression-free survival was significantly lower in case of:
  • High pre-EBRT stage (with estimates as low as 53%, 42%, and 25% for low-risk, intermediate-risk, and high-risk patients, respectively).
  • High pre-HIFU PSA.
  • Use of ADT during PCa management.

Specifically, patients in the intermediate-risk and high-risk groups had a 1.32-fold and 1.96-fold higher risk, respectively, of any-cause mortality in comparison with the low-risk group. Moreover, patients treated with ADT had also a 2.8-fold higher risk of death in comparison with those who did not undergo ADT. No rectal complications were observed. Urinary incontinence accounted for 49.5% of the urinary sphincter implantations required in 11% of patients.

Urinary incontinence and the development of rectourethral fistulae are the most significant complications of salvage HiFU therapy (116-118). About 30% of men develop some form of incontinence, with significant UI treated with an artificial urinary sphincter in about 10% of patients. The oncological control rate after a short median follow-up period of about 2 years is 30-40%.
19.6.6 Guidelines for the management of PSA relapse after radiotherapy

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrences can be treated with salvage RP in carefully selected patients, who presumably have organ-confined disease - i.e., PSA &lt; 10 ng/mL, PSADT &gt; 12 months, low-dose brachytherapy, biopsy Gleason score &lt; 7.</td>
<td>B</td>
</tr>
<tr>
<td>Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery.</td>
<td>B</td>
</tr>
<tr>
<td>HIFU may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality, due to the short follow-up periods reported.</td>
<td></td>
</tr>
<tr>
<td>In patients with presumed systemic relapse, ADT may be offered.</td>
<td>B</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; HIFU = high-intensity focused ultrasound; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; RP = radical prostatectomy.

19.7 Guidelines for second-line therapy after treatment with curative intent

**Recommendations**

<table>
<thead>
<tr>
<th>Presumed local failure after radical prostatectomy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with presumed local failure only may be candidates for salvage RT. This should be given with at least 64 Gy and preferably before PSA has risen above 0.5 ng/mL.</td>
</tr>
<tr>
<td>Other patients are best offered a period of watchful waiting (active monitoring), with possible HT later on.</td>
</tr>
</tbody>
</table>

**Presumed local failure after radiotherapy:**

| Selected patients may be candidates for SRP, and patients should be informed about the higher risk of complications - e.g., urinary incontinence and erectile dysfunction. | C  |
| SRP should only be performed in experienced centres. |   |
| Other patients are best offered a period of watchful waiting (active monitoring), with possible HT later on. |   |

**Presumed distant failure:**

| There is some evidence that early HT may be of benefit with or without local failure, delaying progression and possibly achieving a survival benefit in comparison with delayed therapy. The results are not uncontroversial. | B  |
| Local therapy is not recommended except for palliative reasons. |   |

HT = hormone therapy; PSA = prostate-specific antigen; RT = radiotherapy; SRP = salvage radical prostatectomy.

19.8 References


http://www.mdconsult.com/das/citation/body/1206748702/jorg=journal&source=MI&sp=16362265&sid=0/N/16362265/1.html


20. CASTRATION-RESISTANT PCA (CRPC)

20.1 Background
Cancer of the prostate is a heterogeneous disease. Our knowledge of the mechanisms involved in androgen-independent prostate cancer, which is now known as castration-resistant prostate cancer (CRPC), remains incomplete, but is starting to become clearer (1,2). An alteration in normal androgen signalling is thought to be central to the pathogenesis of CRPC (3). It is mediated through two main, overlapping, mechanisms, which are androgen-receptor (AR)-independent and AR-dependent.

20.1.1 Androgen-receptor-independent mechanisms
Androgen-receptor-independent mechanisms may be associated with the deregulation of apoptosis through the deregulation of oncogenes. High levels of bcl-2 expression are seen with greater frequency as PCa progresses. The regulation of microtubule integrity may be a mechanism through which bcl-2 induces its anti-apoptotic effect (4,5). Indeed, most drugs that are active in CRPC work by inhibiting microtubule formation. The tumour suppressor gene p53 is more frequently mutated in CRPC. Overexpression of bcl-2 and p53 in prostatectomy specimens has been shown to predict an aggressive clinical course (6,7). Clinical trials are underway to target the bcl-2 pathway (8), and the MDM2 (mouse double minute 2) oncogene (9) and the PTEN
(phosphatase and tensin homolog) suppressor gene may also be involved (10).

20.1.2 Androgen-receptor-dependent mechanisms

Direct AR-dependent mechanisms comprise the main pathway. Ligand-independent androgen receptor (AR) activation has been suspected, such as the tyrosine-kinase-activated pathway [insulin-like growth factor-1, keratinocyte growth factor, and epidermal growth factor (EGF)]. EGF is a potent mitogen of prostate stromal and epithelial cells. It is produced in high levels locally and acts as a paracrine stimulator. In AR-independent tumours, autocrine stimulation may become more important, which could allow unregulated growth.

Androgen receptor amplification and overexpression are observed in one-third of CRPC tissues (11,12) and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in receptor function (13). At the same time, there is an intracellular increase in androgens from in-situ conversion (14,15). This increase may be secondary to an increase in the enzymes involved in intracellular androgen synthesis (16).

Androgen receptor mutations are found in only a subpopulation of tumour cells, therefore, they are unlikely to be responsible for the entire spectrum of the AR-independent state (17). The AR mutations might be related to the selective pressure of anti-androgens (17). The recent discovery of gene fusion between the androgen-driven TMPRSS2 and the EGR-ETS oncogene family (18) raises the question of oncogene regulation through androgen regulation pathways. In gene fusion, an androgen-responsive element from an androgen-regulated gene becomes associated with genes that are usually not androgen-regulated, so that they too become subject to androgen regulation. Currently, their implication in CRPC is hypothetical. Even in castrated patients, metastatic tissues have repeatedly shown high levels of androgens, suggesting a high level of intracrine synthesis (16,19). It is possible that a high intraprostatic cholesterol level can activate specific androgen pathways (20).

20.2 Definition of relapsing prostate cancer after castration

The precise definition of recurrent or relapsed PCa remains controversial and several groups have published practical recommendations for defining CRPC (19,20).

Various different terms have been used to describe PCa that relapses after initial hormonal ablation therapy, including hormone-refractory PCa, androgen-independent cancer and hormone-independent cancers. In recent years, the term CRPC has become more frequently used than hormone refractory or androgen-independent PCa. This is based predominantly on recent findings suggesting that advancing PCa is not uniformly refractory to further hormonal manipulation and that androgens and disease progression are frequently dependent on androgen receptor interactions. Castration-resistant prostate cancer, which is still hormone sensitive, has been clearly characterised, with new drugs targeting the AR, such as MDV3100 (Enzalutamide), or androgen synthesis, via CYP 17 inhibition, such as abiraterone acetate or TAK700 (21). Table 21 lists the key defining factors of CRPC.

Table 21: Definition of CRPC

| Castrate serum levels of testosterone < 50 ng/dL or < 1.7 nmol/L. |
| Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL. |
| Anti-androgen withdrawal for at least 4 weeks for flutamide and for at least 6 weeks for bicalutamide* |
| PSA progression, despite consecutive standard hormonal manipulations† |

* Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done to fulfill the criteria for CRPC if patients have been treated with anti-androgens in the context of maximum androgen blockade or step-up therapy following PSA progression after failure of LHRH treatment.

† Progression or appearance of two or more bone lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) with nodes ≥ 2 cm in diameter.

20.3 Assessing treatment outcome in CRPC

In general, the therapeutic outcome should be assessed using the guidelines for the evaluation of treatment response in solid tumours, recently published by the RECIST group (Response Evaluation Criteria In Solid Tumours) (22). However, 80-90% of patients do not have bi-dimensionally measurable disease. Patients with primarily soft tissue cancers often have a different prognosis to those with only bone metastases. Osteoblastic bone metastases remain difficult to quantify accurately. Magnetic resonance imaging (MRI) might be useful for assessing axial metastases (23). The cause of death in PCa patients is often unreliable, therefore a more valid end-point might be OS rather than a disease-specific one (24).
20.3.1 **PSA level as marker of response**

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a response marker. Trials of the vaccines sipuleucel-T (Provenge) (25) and TRICOM (PROSTVAC) (26) have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs (27).

In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effect of drugs on PSA expression should be considered when interpreting PSA response data, which should be viewed together with other clinical data (28-35).

Nevertheless, it has been shown reproducibly that ≥ 50% PSA decline in pre-treatment PSA following therapy carries a significant survival advantage (36,37).

An improved PSA response was also associated with prolonged survival in the TAX 327 study, with a median survival of 33 months when the PSA was normalised (< 4 ng/mL) vs. 15.8 months for an abnormal PSA. This study also showed that a PSA response was not a surrogate marker for survival. Even though the same PSA response rate was found in both docetaxel arms (45%), improved survival only occurred with the 3-weekly docetaxel regimen. According to the most recent evaluation of the TAX 327 and SWOG 99-16 studies, a PSA detection of ≥ 30% is associated with a significant survival benefit (38,39).

20.3.2 **Other parameters**

Evaluation of molecular markers is just beginning. The most frequently described and probably most interesting tool is the circulating tumour cell (CTC) count, which has been developed in parallel with abiraterone. The CTC count was related to survival in several trials (40-42) and might become a surrogate marker for survival. The Food and Drug Administration (FDA) has recently approved an assay for CTCs. In patients with symptomatic bone lesions, pain reduction or complete pain relief may be used as parameters to assess palliative therapeutic response (43). In a landmark analysis of TAX 327, PSA response and pain response, but not QoL response, were independently associated with survival (44).

20.3.3 **Recommendations for assessing therapeutic response**

In everyday practice, the evaluation of treatment response must be based on symptom improvement, prolonged survival, or other pre-defined targets. The Prostate Cancer Working Group 2 (PCWG2) recommends that investigators measure early outcomes by the changes in the individual disease manifestations present initially for both cytotoxic and non-cytotoxic drugs with the same methods used at enrolment (19). If a protocol defines a composite end-point for progression, the specified progression in any measure (with the exception of early changes in PSA or pain) overrides a change or improvement in other measures.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For PSA, recognise that a favourable effect may be delayed for ≥ 12 weeks, even for a cytotoxic drug. Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks, unless there is other evidence of progression. Ignore early rises ≤ 12 weeks when determining PSA response.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>For bone disease; record outcome as new lesions or no new lesions. • First scheduled reassessment: no new lesions: continue therapy. • New lesions: perform a confirmatory scan ≥ 6 weeks later; confirmatory scan: no new lesions: continue therapy. • Additional new lesions: progression; subsequent scheduled reassessments: no new lesions: continue; new lesions: progression.</td>
<td></td>
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<tr>
<td>In non-osseous metastases from CRPC, assessment should adhere to the RECIST criteria.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In patients with advanced symptomatic metastatic CRPC, the therapeutic response can be best assessed by improvement of symptoms. Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3-4 week intervals. Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, and additional anticancer therapy. Ignore early changes (12 weeks) in pain or HRQoL in absence of compelling evidence of disease progression. Confirm response or progression of pain or HRQoL end-points 3 weeks later.</td>
<td>1b</td>
<td>A</td>
</tr>
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</table>

CRPC = castration-resistant prostate cancer; HRQoL = health-related quality of life; PSA = prostate-specific antigen; RECIST = response evaluation criteria in solid tumours.
20.4 Androgen deprivation in castration-resistant PCa
The existence of androgen-resistant PCa shows that disease progression occurs despite castration. The castration levels of testosterone must therefore be documented and a serum testosterone level < 50 ng/dL (1.7 nmol/L) should be documented at initial relapse on hormonal therapy (45). Continued testicular androgen suppression in CRPC has a minimal overall effect. The recommendation to continue ADT with LHRH analogues, despite PSA progression, is based on the data of Manni et al. (46). They demonstrated significantly lower survival rates in patients without complete androgen blockade (CAB). However, these data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies (47,48). However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. Androgen suppression should therefore be continued indefinitely in these patients.

20.5 Secondary hormonal therapy
For the patient with progressive disease after ADT, there are many therapeutic options. They include anti-androgen withdrawal, addition of anti-androgens, anti-androgen replacement, oestrogenic compounds, adrenolytic agents, and novel approaches (49). Figure 1 summarises the treatment modalities and expected responses.

Figure 1: Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy

LHRH = luteinising hormone releasing hormone; Abiraterone A: abiraterone acetate
* Median cannot be compared because patients included in trials did not have the same characteristics

20.6 Anti-androgen withdrawal syndrome
Anti-androgen withdrawal syndrome is a critical discovery in understanding the biology of androgen independence, interpreting clinical trials, and treating patients (50-53). Approximately one-third of patients respond to anti-androgen withdrawal, as indicated by a ≥ 50% PSA decrease, for a median duration of approximately 4 months. Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (54-59). Recently, in the SWOG 9426 trial, PSA progression despite CAB was reported in a subgroup of 210 patients with an M0 or M1 stage tumour (60). A response was observed in 21% of patients, even though there was no radiographic response. Median PFS was 3 months, with 19% (all M0) having PFS ≥ 12 months*. Increased PFS and OS were associated with longer use of non-steroidal drugs, lower PSA at baseline and M0-stage. These results were obtained with patients on CAB.
following androgen withdrawal. No data were available on the withdrawal effect following second-line anti-
androgen treatment.

In conclusion, androgen withdrawal must be systematically considered as a first-line modality in relapsing patients, even if its efficacy is limited (LE: 2).

20.7  Classical hormonal treatment alternatives after CRPC occurrence
Simple old fashioned modalities have been reported, without any associated survival benefit ever reported.

20.7.1  Bicalutamide
Bicalutamide has a dose response, with higher doses producing a greater reduction in PSA level (61). The largest cohort so far is based on 52 CRPC patients treated with 150 mg bicalutamide (62). A palliative effect was clear and a 20% PSA response (at least 50% decrease) was observed, without any link to the palliative effect. Based on the affinity of dihydrotestosterone for the AR, a large randomised trial (TARP) is ongoing comparing the effectiveness of 50 mg bicalutamide combined with either dutasteride or placebo in non-metastatic CRPC (63). The addition of a non-steroidal anti-androgen to gonadal suppression at the time of PSA failure appears to result in declining PSA in only a few patients (64,65).

20.7.2  Switching to an alternative anti-androgen therapy
There has been recent interest in another simple modality, namely, the alternative anti-androgen therapy (66). After CAB was stopped in 232 patients with progressive disease (76% with stage M1b), a withdrawal effect was observed in 31 men (15.1%). Second-line hormonal treatment was performed by giving an alternative non-steroidal drug (i.e. initial flutamide was replaced by bicalutamide and vice versa). An overall > 50% decline in PSA was observed in 83 men (35.8%), irrespective of any previous withdrawal effect, which lasted > 6 months. The higher the PSA at the start of second-line therapy, the shorter was the FPS and the lower was the PSA response rate.

20.7.3  Anti-androgen withdrawal accompanied by simultaneous ketoconazole
The adrenal glands secrete approximately 10% of circulating androgen in humans. This can be inhibited using aminoglutethimide, ketoconazole and corticosteroids (67-71) resulting in a PSA response in ~ 25% of patients of ~ 4 months duration. The simultaneous addition of ketoconazole to anti-androgen withdrawal, produced a significantly increased PSA response (32% vs. 11%) and a longer time to PSA progression (8.6 vs. 5.9 months) compared to anti-androgen withdrawal alone (71).

20.7.4  Oestrogens
Prostate cancer usually expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. Diethylstilboestrol (DES) (72-74) achieved a positive PSA response in 24% and 80% of patients, with an overall estimated survival of 83% at 2 years. However, even at low doses of DES, about one-third (31%) of patients developed deep venous thrombosis and 7% experienced myocardial infarction.

20.8  Novel hormonal drugs targeting the endocrine pathways
In the past 2 years, following early phase II/III trials in patients with CRPC, new compounds appeared for treating CRPC (Section 19.4). Most have been developed post docetaxel, but abiraterone acetate and MDV 3100 have been used before chemotherapy. The initial results have been recently published from the large phase III trial COU-AA-302, in which 1088 chemonaive CRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone (75). Patients were diagnosed with CRPC according to the PCWG2 criteria, and were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and asymptomatic or mildly symptomatic. The study had two joint primary end-points: OS and radiographic PFS. The results reported are from the second preplanned interim analysis. After a median follow-up of 22 months, there was significant radiological PFS (median 16.5 vs. 8.3 months, HR: 0.53, P < 0.01 below the prespecified boundary). Regarding OS, there was a trend (median not reached vs. 27.2 months, HR: 0.75, P = 0.01). However, this value was above the prespecified P value for the second interim analysis (P < 0.001), leading to a non-significant difference. All the subgroup analyses and secondary end-points consistently favoured the abiraterone arm. Side effects related to mineralocorticoids and liver function were more frequent with abiraterone, but mostly grade 1/2. These positive results have led to European Medicines Agency (EMEA) drug approval but it must be emphasised that one of the primary end-points has not yet been reached, leading to an overall inconclusive result.

Regarding MDV3100, accrual for the phase III trial (PREVAIL) is complete but no results are available to date.

20.9  Non-hormonal therapy
Several chemotherapeutic options have been reported from phase III trials in CRPC (Table 22). Several trials
are underway, using different approaches through all the known pathways. A detailed review is far beyond the scope of these guidelines (1). Docetaxel is currently the standard of care.

20.9.1 Docetaxel regimen
A significant improvement in median survival of 2-2.5 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy (76,77). In the SWOG 99-16 trial, pain relief was similar in both groups, although side effects occurred significantly more often with docetaxel than with mitoxantrone.

The standard for first-line cytotoxic chemotherapy is docetaxel using the same regimen as in the TAX 327 trial, that is, 75 mg/m² 3 weekly combined with prednisone 5 mg BID, up to 10 cycles of survival, and palliation is the main target. The weekly regimen is not associated with improved survival and does not appear to be better tolerated.

The patients considered for docetaxel represent a heterogeneous population. Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, PSA doubling time (PSA-DT) < 55 days, or the presence of visceral metastases (78). A better risk group definition has been recently presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), leading to three different lengths of median OS: 25.7, 18.7 and 12.8 months, respectively (39). In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (HR, 2.96) (79,80). Age by itself is not a contraindication to docetaxel (81).

Table 22: PSA response rates, mean survival, time to progression, and pain reduction in the large, prospective, randomised phase III trials of chemotherapy in patients with CRPC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PSA decrease &gt; 50%</th>
<th>Decrease in pain</th>
<th>Survival (months)</th>
<th>Time to progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAX 327 (77)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mitoxantrone, 3 times weekly, 12 mg/m², Prednisone 5 mg BID</td>
<td>32%</td>
<td>22%</td>
<td>16.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Docetaxel, 3 times weekly, 75 mg/m² prednisone 5 mg BID</td>
<td>45%</td>
<td>35%</td>
<td>18.91</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Docetaxel, weekly, 30 mg/m² prednisone 5 mg BID</td>
<td>48%</td>
<td>31%</td>
<td>17.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>SWOG 99-16 (76)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone, 3 times weekly, 12 mg/m² prednisone 5 mg BID</td>
<td>336</td>
<td>50%</td>
<td>-</td>
<td>15.6</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Docetaxel/EMP, 3 times weekly, 60 mg/m², EMP 3 x 280mg/day</td>
<td>338</td>
<td>27%</td>
<td>-</td>
<td>17.52</td>
<td>6.3 months</td>
</tr>
<tr>
<td><strong>CALGB 9182 (82)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hydrocortisone</td>
<td>123</td>
<td>38%</td>
<td>-</td>
<td>12.3</td>
<td>2.3 months</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone/HC, 3 times times weekly, 12 mg/m²</td>
<td>119</td>
<td>22%</td>
<td>-</td>
<td>12.6</td>
<td>3.7 months</td>
</tr>
<tr>
<td><strong>Tannock et al. (83)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>81</td>
<td>22%</td>
<td>12%</td>
<td>-</td>
<td>18 weeks</td>
</tr>
<tr>
<td>Mitoxantrone/Pred, 3 times weekly, 12 mg/m²</td>
<td>80</td>
<td>33%</td>
<td>29%</td>
<td>-</td>
<td>43 weeks</td>
</tr>
</tbody>
</table>

EMP = estramustine; HC = hydrocortisone; 1p < 0.000 compared to mitoxantrone; 2p = 0.001 compared to mitoxantrone.

20.9.2 Other classical regimen
20.9.2.1 Mitoxantrone combined with corticosteroids
Mitoxantrone combined with corticosteroids (82,83) has been extensively studied; primarily in patients with symptomatic bone lesions due to CRPC. Palliation is effective with a clear PSA response and increased PFS, leading to a significant improvement in QoL, no survival benefit was ever observed.

20.9.2.2 Other chemotherapy regimen
The synergy observed for estramustine combined with other drugs that target microtubule action has generated promising results in prospective clinical trials. Combination with vinblastine is the most frequently studied
combination. Significant PSA and measurable responses have been reported, without any survival benefit (84). A recent meta-analysis (85) concluded that addition of estramustine to chemotherapy increased the time to PSA progression and OS. However, there was a significant increased risk (up to 7%) of thromboembolic events, (86), requiring systematic prevention with coumadin. Intravenous cyclophosphamide, or new oral formulations have been tested, without any clear survival benefit (87,88). Cisplatin and carboplatin have activity as single agents against PCa and have a synergistic effect, as with estramustine. Combination of estramustine, etoposide and cisplatin (or carboplatin) has significant activity against poorly differentiated CRPC. Combination of estramustine, etoposide and paclitaxel has high response rates (89,90). Preliminary results from phase II with alternative chemotherapy regimens have been reported (89,91-93), including pegylated doxorubicin, vinorelbine; a combination of paclitaxel, carboplatin and estramustine; combination of vinblastine, doxorubicin and radionuclides; and combination of docetaxel and mitoxantrone. The lack of large phase III trials and unknown long-term efficacy are major problems associated with all these studies. Therefore none of the above drugs are considered as clear valid options in CRPC.

20.9.3 Specific bone-targeted therapies
Bone is a primary target for prostatic metastatic cells, which forms a rationale for bone-protective drugs that prevent cancer cells from colonising and developing in bone. Besides zoledronic acid and denosumab (see Section 12.7.1), other drugs, that specifically target the endothelin-1 axis have been tested. The first of these (atarsentan) resulted in clear biological responses, but questionable clinical results (94), possibly secondary to an inappropriate trial design. Second-generation blockers (zibotentan) have been tried in large phase III trials in metastatic and non-metastatic CRPC but finally stopped due to negative results in relation to OS (95).

The only bone-specific drug that is associated with a survival benefit is alpharadin, a radium 223 α-emitter. In the large phase III trial (ALSYMPCA) 921 patients with symptomatic CRPC, who failed or were unfit for docetaxel therapy, were randomised to six injections of 50 kBq/kg alpharadin or placebo. The primary endpoint was OS. The results of this trial have been repeatedly presented but only partially published (96,97). Alpharadin significantly improved OS by 3.6 months. The associated toxicity was minimal, specially the hematologic one, and did not differ significantly from that in the placebo arm.

20.9.4 Vaccine
In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients (97). This was the first time that a PCA vaccine had shown a benefit and led to FDA approval and a submission to the EMEA. Sipuleucel T is an active cellular immunotherapy agent consisting of autologous peripheral blood mononuclear cells, activated in vitro by a recombinant fusion protein comprising prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor, which is an immune-cell activator. In the above trial, patients with metastatic CRPC, with PSA > 5 ng/mL, castrate testosterone level, and no visceral metastases, were randomised to three infusions 2 weeks apart with Sipuleucel T or placebo. Up to two previous chemotherapy regimens were allowed (effective in 19.6% Sipuleucel T treated patients and in 15.2% respectively). The main objective was OS. After a median follow-up of 34 months, the median survival was 25.8 months in the Sipuleucel T group compared to 21.7 months in the placebo group, leading to a significant point was OS. The results of this trial have been repeatedly presented but only partially published (96,97). Alpharadin significantly improved OS by 3.6 months. The associated toxicity was minimal, specially the hematologic one, and did not differ significantly from that in the placebo arm.

The COU-AA-302 trial raises the question of prechemotherapy use of this new compound, and the possible selection criteria between second-line chemotherapy or hormonotherapy. Also some very preliminary retrospective observations might be helpful, it is so far impossible to predict which subset of patients is most likely to respond to one specific second-line treatment modality. Finally, the only indication for chemotherapy in CRPC non-metastatic patients is inside clinical trials and patients should be advised to participate.
20.11 Salvage treatment after first-line docetaxel

All patients who receive docetaxel-based chemotherapy for CRPC will progress, thus, there have been many clinical trials investigating the role of salvage chemotherapy. Recently, there have been major improvements in this situation. Two treatment possibilities are now available: new hormonal treatment or new chemotherapy regimens. The results suggest that the most appropriate approaches are cabazitaxel, intermittent docetaxel chemotherapy, and potentially, molecular-targeted therapy.

Several groups have used second-line intermittent docetaxel in patients who had clearly responded to first-line docetaxel. In general, a PSA response can be achieved in about 60% of patients with a median time to progression of about 6 months, while treatment-associated toxicity is minimal and similar to that of first-line docetaxel. Another, recently identified approach is molecular-targeted therapy although more research is needed in larger groups of patients.

Platinum-based chemotherapeutic regimens have been investigated in patients with CRPC. Although more research is needed in larger groups of patients. First-line docetaxel chemotherapy (101), intermittent docetaxel chemotherapy (102), and potentially, molecular-targeted therapy (103, 104) have been tested in phase II/III trials without any positive impact on the primary end-point. The G-Vax trial was stopped prematurely because of a significantly higher mortality in the treatment arm as compared to the docetaxel control arm.

20.11.1 Cabazitaxel

Cabazitaxel is a taxane derivative with some significant differences compared to docetaxel. Positive results have been published from a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with CRPC, who had progressed after or during docetaxel-based chemotherapy (100). Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) plus prednisone (10 mg/day), respectively. Overall survival was the primary end-point, and PFS, treatment response and safety were secondary end-points. An OS benefit (15.1 vs. 12.7 months, P < 0.0001) was observed in the cabazitaxel arm. There was also a significant improvement in PFS (2.8 vs. 1.4 months, P < 0.0001), objective response rate according to RECIST criteria (14.4% vs. 4.4%, P < 0.005), and PSA response rate (39.2% vs. 17.8%, P < 0.0002). Treatment-associated WHO grade 3/4 side effects developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, P < 0.0002) and non-haematological (57.4% vs. 39.8%, P < 0.0002) toxicity (100). This drug should be administered by physicians with expertise in handling neutropenia and sepsis, possibly with granulocyte colony-stimulating factor.

20.11.2 Enzalutamide (MDV3100)

Enzalutamide (formerly known as MDV3100) is a novel anti-androgen that blocks AR transfer to the nucleus, in contrast to currently available drugs with which AR is able to transfer to the nucleus. Enzalutamide is used as a once-daily oral treatment. The planned preliminary analysis of the AFFIRM study was published in 2012 (109). This trial randomised 1,199 patients with metastatic CRPC in a 2/1 fashion between enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not requested but possible, and therefore received by 30% of the population. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, P < 0.001). This led to the recommendation that the study be halted and unblinded. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects were observed in the 2 groups, with a lower incidence of grade 3-4 side effects in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

20.11.3 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor. It is used once daily combined with prednisone twice daily (10 mg/day). Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months (110) and the final results have been reported more recently (111). A total of 1,195 patients with metastatic CRPC were randomised in a 1/1 fashion between abiraterone acetate or placebo. All patients had progressive disease based on the PCWG2 criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, P < 0.001). The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of abiraterone.
(PSA, radiologic tissue response, time to PSA or objective progression). With regard to previous docetaxel therapy, no benefit was observed in the abiraterone arm when docetaxel had been used for < 3 months, but the benefit remained independent of the delay since the last dose of docetaxel (less or more than 3 months). The incidence of the most common grade 3/4 side effects did not differ significantly between both arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly grade 1/2 (fluid retention, oedema or hypokalaemia). The longer follow-up did not lead to an unexpected increased in toxicity compared to the preliminary analysis.

However, the choice between third-line hormonal treatment (using enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) remains unclear with no clear decision-making findings published. They are urgently awaited because nothing is known regarding the optimal sequencing of drugs. The cost of each drug will be a major challenge to public health.

<table>
<thead>
<tr>
<th>Recommendations on salvage treatment after Docetaxel</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabazitaxel is a valid option for management of progressive CRPC following docetaxel therapy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Abiraterone and enzalutamide are both valid options for management of progressive CRPC following docetaxel therapy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>No definitive strategy regarding treatment choice (which drug/which drug family first) can be devised</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

CRPC = castration-resistant prostate cancer.

20.12 Palliative therapeutic options: bone targeted therapies in CRPC
CRPC is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is often required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers (112).

20.12.1 Painful bone metastases
Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective (113), even as single fraction (114). The two radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients, but should not be given too late when pain is intractable. Early use can give rise to myelosuppression, making subsequent chemotherapy more difficult (115), even though a recent phase I trial has demonstrated manageable haematological toxicity with repeated administration of docetaxel and samarium-153. The use of samarium-153 as consolidation therapy, following a clear docetaxel response, may also help with initially painful bone metastases (116). Apart from the OS benefit, the α-radioisotope emitter, radium-223, has also shown a significant palliative effect in patients with painful bone metastases (117). The full results of this study are urgently awaited.

20.12.2 Common complications due to bone metastases
Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Osteoporosis may also cause fractures and should be prevented (see above). Cementation is an effective treatment for painful fracture, clearly improving both pain and QoL (118). However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases (119,120). Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression (121). Otherwise, external beam radiotherapy, with or without systemic therapy, is the treatment of choice.

20.12.3 Bisphosphonates
Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in CRPC. In the largest single phase III trial to date (122), 643 patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44% vs. 33%, P = 0.021) and fewer pathological fractures (13.1% vs. 22.1%, P = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group, thus improving QoL. Patients were initially randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg because of toxicity. No survival benefit was seen in any trial with bisphosphonates, except in a post hoc analysis of an old compound without any significant impact on SREs (123).
Currently, bisphosphonates can be offered to patients with CRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear. At present, it is every 3 weeks or less. The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind (122). Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as intravenous long-term bisphosphonate administration (124).

Pain due to bone metastases is one of the most debilitating complications of CRPC. Bisphosphonates have proven to be highly effective in reducing bone pain, but so far this has been investigated only in small, open trials. Data from these trials suggest that bisphosphonates have a low side-effect profile (125-127).

Bisphosphonates should be considered early in the management of symptomatic CRPC. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur (i.e., palliative external beam radiation, cortisone, analgesics and antiemetics).

20.12.4 **RANK ligand inhibitors**

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85; P = 0.028) (128). However, this benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively). The practical impact of this finding remains under discussion. The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with metastatic CRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR 0.82; P = 0.008). Denosumab also extended time to first and subsequent on-study SRE (HR 0.82; P = 0.008). Both urinary NTX and BAP were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (P < 0.0001 for both). However, these positive findings were not associated with any survival benefit. Denosumab is FDA approved for preventing SREs in patients with bone metastases from solid tumours, and EMEA approval is pending.

**20.13 Summary of treatment after hormonal therapy (first second-line modality)**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended to stop anti-androgen therapy once PSA progression is documented.</td>
<td>B</td>
</tr>
<tr>
<td>No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormonotherapy or chemotherapy) as no clear predictive factors exist.</td>
<td>C</td>
</tr>
<tr>
<td>Second-line salvage hormonal treatment using abiraterone acetate is considered to be a valid option. It must be remembered that one of the 2 coprimary end-points of the pivotal trial has not yet been met.</td>
<td>A</td>
</tr>
<tr>
<td>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</td>
<td></td>
</tr>
</tbody>
</table>

*PSA = prostate-specific antigen.*

**20.14 Cytotoxic and pre/post-docetaxel therapy in CRPC**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CRPC should be counselled, managed and treated by a multidisciplinary team.</td>
<td></td>
</tr>
<tr>
<td>In non-metastatic CRPC, cytotoxic therapy should only be used in a clinical trial setting.</td>
<td>B</td>
</tr>
<tr>
<td>In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.</td>
<td>B</td>
</tr>
<tr>
<td>Patients should not be started on second-line therapy unless their testosterone serum levels are &lt; 50 ng/dL.</td>
<td>B</td>
</tr>
<tr>
<td>Patients should not be started on second-line therapy unless their PSA serum levels are &gt; 2 ng/mL to ensure correct interpretation of therapeutic efficacy.</td>
<td>B</td>
</tr>
<tr>
<td>Prior to treatment, the potential benefits of second-line therapy and expected side effects should be discussed with the patient.</td>
<td>C</td>
</tr>
<tr>
<td>In patients with metastatic CRPC who are candidates for cytotoxic therapy, docetaxel at 75 mg/m² every 3 weeks is the drug of choice because it has shown a significant survival benefit.</td>
<td>A</td>
</tr>
</tbody>
</table>
If chemotherapy is considered in patients with symptomatic bone metastases due to CRPC, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable options. If not contraindicated, docetaxel is the preferred agent based on the significant advantage in pain relief.

In patients with relapse following first-line docetaxel chemotherapy cabazitaxel, abiraterone and enzalutamide are regarded as first-choice options for second-line treatment.

Second-line docetaxel can be offered to previously responding docetaxel-treated patients. Otherwise, treatment should be tailored to the individual patient. In case patients are not eligible for cabazitaxel, abiraterone or enzalutamide, docetaxel re-challenge is an option.

In men with CRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel treatment with 223Ra (alpharadin) has shown a survival benefit.

CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen.

### 20.15 Recommendations for “non-specific” management of CRPC

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of patients with extended symptomatic bone metastases has to be directed at improvement of QoL and mainly pain reduction.</td>
<td>A</td>
</tr>
<tr>
<td>Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.</td>
<td>A</td>
</tr>
<tr>
<td>Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.</td>
<td>A</td>
</tr>
<tr>
<td>Calcium and vitamine D supplementation must be systematically considered when using either Denosumab or biphosphonates.</td>
<td>A</td>
</tr>
<tr>
<td>In the management of painful bone metastases, early use of palliative treatments such as radionuclides, external beam radiotherapy and adequate use of analgesics is recommended.</td>
<td>B</td>
</tr>
<tr>
<td>In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must be always initially considered.</td>
<td>A</td>
</tr>
</tbody>
</table>

### 20.16 References


21. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-US</td>
<td>three-dimensional ultrasound</td>
</tr>
<tr>
<td>ADT</td>
<td>androgen-deprivation therapy</td>
</tr>
<tr>
<td>AR</td>
<td>androgen-receptor</td>
</tr>
<tr>
<td>AS</td>
<td>active surveillance</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>ASTRO</td>
<td>American Society for Therapeutic Radiology and Oncology</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urological Association</td>
</tr>
<tr>
<td>BCF</td>
<td>biochemical failure</td>
</tr>
<tr>
<td>BCR</td>
<td>biochemical recurrence</td>
</tr>
<tr>
<td>BDFS</td>
<td>biochemical disease-free survival</td>
</tr>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>bNED</td>
<td>actuarial biochemical freedom from disease</td>
</tr>
<tr>
<td>CAB</td>
<td>complete (or maximal or total) androgen blockade</td>
</tr>
<tr>
<td>CAD</td>
<td>complete androgen deprivation</td>
</tr>
<tr>
<td>CPA</td>
<td>cyproterone acetate</td>
</tr>
<tr>
<td>CRT</td>
<td>conformal radiotherapy</td>
</tr>
<tr>
<td>CRPC</td>
<td>castration-resistant prostate cancer</td>
</tr>
<tr>
<td>CSAP</td>
<td>cryosurgical ablation of the prostate</td>
</tr>
<tr>
<td>CSS</td>
<td>cancer-specific survival</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTC</td>
<td>circulating tumour cells</td>
</tr>
<tr>
<td>DES</td>
<td>diethylstilboestrol</td>
</tr>
<tr>
<td>DRE</td>
<td>digital rectal anticipation</td>
</tr>
<tr>
<td>DHT</td>
<td>dihydrotestosterone</td>
</tr>
<tr>
<td>DSS</td>
<td>disease-specific survival</td>
</tr>
<tr>
<td>EBRT</td>
<td>external beam radiation therapy</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EGF</td>
<td>epidermal growth factor</td>
</tr>
<tr>
<td>eLND</td>
<td>extended lymph node dissection</td>
</tr>
<tr>
<td>ELND</td>
<td>elective lymph node dissection</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>e-MRI</td>
<td>endorectal MRI</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EPC</td>
<td>Early Prostate Cancer Trialists’ Group</td>
</tr>
<tr>
<td>EPCP</td>
<td>Early Prostate Cancer Programme</td>
</tr>
<tr>
<td>EPE</td>
<td>extraprostatic extension</td>
</tr>
<tr>
<td>ER-®</td>
<td>oestrogen receptor-®</td>
</tr>
<tr>
<td>ESRPC</td>
<td>European Randomized Screening for Prostate Cancer</td>
</tr>
<tr>
<td>FACT-P</td>
<td>Functional Assessment of Cancer Therapy-prostate</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FNAB</td>
<td>fine-needle aspiration biopsy</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
</tr>
<tr>
<td>GU</td>
<td>genitourinary</td>
</tr>
<tr>
<td>HD EBRT</td>
<td>high-dose EBRT</td>
</tr>
<tr>
<td>HDR</td>
<td>high-dose rate</td>
</tr>
<tr>
<td>HIFU</td>
<td>high-intensity focused ultrasound</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HRPC</td>
<td>hormone-refractory prostate cancer</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>HT</td>
<td>hormonal therapy</td>
</tr>
<tr>
<td>IAD</td>
<td>intermittent androgen deprivation</td>
</tr>
<tr>
<td>IGRT</td>
<td>image-guided radiotherapy</td>
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<tr>
<td>IMRT</td>
<td>intensity modulated radiotherapy</td>
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<tr>
<td>IPSS</td>
<td>International Prostatic Symptom Score</td>
</tr>
<tr>
<td>LDAT</td>
<td>long-term ADT</td>
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</tbody>
</table>
Conflict of interest
All members of the Prostate Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Renal Cell Carcinoma


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1. METHODOLOGY

1.1 Introduction
The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of renal cell cancer. The RCC panel is an international group consisting of 10 clinicians with particular expertise in this field of urological care.

The guideline update methodology is detailed below, but for a substantial portion of the text the evidence base has been upgraded. The aim is to progress this further in the years to come.

Without the inspiration and practical assistance provided by Prof. James N’Dow, this would have been unattainable. We owe him and his UCAN team (Urological Cancer Charity, Scotland) a debt of gratitude. In the course of 2012, Dr. Thomas Lam joined our efforts and his support of the review team at his home institution (Aberdeen University Hospital), and in particular of the three young urologists who joined the RCC panel last year (Dr. Saeed Dabestani, Dr. Fabian Hofmann and Dr. Lorenzo Marconi), has been invaluable. Drs. Dabestani, Hofmann and Marconi have taken on the data management of the systematic reviews underpinning this 2013 publication.

For this 2013 update, the Panel did not manage to complete all systematic reviews in a timely fashion. As a result, sections of the document have been updated following a structured literature assessment. The focus for 2014 is to proceed with the systematic review, aiming for the complete guidelines document to be based on a uniformly high level of data work-up.

1.2 Methodology
1.2.1 Data identification
All chapters of the 2013 RCC Guidelines publication have been updated. As mentioned above, the consistency of the data work-up will differ between sections. An overview is presented in Table 1.

Table 1: Description of update and summary of review methodology

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Brief description of review methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Epidemiology and etiology</td>
<td>The chapter has been updated using a structured data assessment</td>
</tr>
<tr>
<td>Diagnosis and staging</td>
<td>The chapter has been updated using a systematic review on tumour biopsy and a traditional narrative review for the other aspects of diagnosis and staging</td>
</tr>
<tr>
<td>Classification and prognostic factors</td>
<td>The chapter has been updated using a structured data assessment</td>
</tr>
<tr>
<td>Other renal tumours</td>
<td>The chapter has been updated using a traditional narrative review</td>
</tr>
<tr>
<td>Treatment of localised disease</td>
<td>The chapter has been updated using a systematic review</td>
</tr>
<tr>
<td>Systemic therapy for metastatic disease</td>
<td>The chapter has been updated using a mixed methods approach. Literature searching, study identification and data abstraction were carried out using systematic review methodology, with 54 studies being deemed eligible for inclusion. Ten of the most important and influential studies, as determined by consensus, were data-abstracted and the review was based on these 10 studies</td>
</tr>
<tr>
<td>Surveillance following radical or partial nephrectomy or ablative therapies</td>
<td>The chapter has been updated using a traditional narrative review</td>
</tr>
</tbody>
</table>

For the parts of the guideline that have been updated by way of a systematic review, the review methodology is outlined in detail elsewhere (1). In brief, a systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2). Important topics and questions were prioritised by the panel for the present update. Elements for inclusion and exclusion, including patient population, intervention, comparison, outcomes, study design, and search terms and restrictions were developed using an iterative process involving all members of the panel, to achieve consensus. Individual literature searches were conducted separately for each update question, and in most instances the search was conducted up to the end of September 2012. Two independent reviewers screened abstracts and full texts, carried out data abstraction and assessed risk of bias. The results were presented in
tables showing baseline characteristics and summaries of findings. A narrative synthesis of the evidence was produced.

The remaining parts of the guideline have been updated using a traditional narrative review strategy. Structured literature searches using an expert consultant were designed. Searches were carried out in the Cochrane Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials and Medline and Embase on the Dialog-Datastar platform. The controlled terminology of the respective databases was used, and both MeSH and Emtree were analysed for relevant entry terms. The search strategies covered the last 3 years. An update search was carried out before the publication of this document. Other data sources were also consulted, such as the Database of Abstracts of Reviews of Effectiveness (DARE), as well as relevant reference lists from other guideline producers such as the National Institute for Clinical Excellence (NICE) and the American Urological Association (AUA).

Most reviewed studies are retrospective analyses that include some larger multicentre studies and well-designed controlled studies. As only a few randomised controlled trials are available, there is a certain lack of data with a strong evidence base. Conversely, in the systemic treatment of metastasised RCC, a number of randomised studies have been performed, resulting in highly evidence-based recommendations.

1.3 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (Table 2), and guideline recommendations have been graded (Table 3) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 2: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

* Adapted from (3).

It should be noted that when recommendations are graded, the link between the level of evidence (LE) and the grade of recommendation (GR) is not directly linear. The availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation when there are methodological limitations or disparities in the published results.

Conversely, an absence of a high level of evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. There may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons, and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus.” The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (4-6).

The EAU Guidelines Office does not perform structured cost assessments, nor can it address local/ national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.
### Table 3: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

* Adapted from (3).

### 1.4 Publication history

The EAU Renal Cell Cancer Guidelines were first published in 2000, with subsequent updates in 2001 (limited update), 2002 (limited update), and 2006 (full update), and partial updates in 2007, 2008, 2009, and 2010. This current 2013 printing presents a full-text update.

A quick reference guide presenting the main findings of the Renal Cell Cancer Guidelines is also available (Pocket Guidelines), as well as a number of scientific publications in the EAU journal, European Urology (7-9). All of the texts can be viewed and downloaded for personal use at the society’s web site: [http://www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/).

The RCC panel recognises that there is a constant need to reevaluate the published evidence for this particular topic, but the next update, scheduled for 2014, will focus on covering sections with systematic reviews that could not be completed for the current printing.

### 1.5 Future goals

In addition to the systematic review, a number of other goals need to be taken into account. These include patient-derived needs, as well as recommendations requested by the ordinary urologist. We will be introducing such thoughts in the coming updates.

### 1.6 Potential conflict of interest statement

The members of the expert panel have submitted potential conflict of interest statements, which can be viewed on the EAU web site: [http://www.uroweb.org/guidelines/](http://www.uroweb.org/guidelines/).

### 1.5 References

2. EPIDEMIOLOGY AND ETIOLOGY

Renal cell carcinoma (RCC) represents 2-3% of all cancers with an age-standardised rate incidence of 5.8 and mortality of 1.4 per 100,000, respectively, in more developed areas (1). The highest incidence all over the world is in the Czech Republic, where in 2010 the incidence rate was 14.62 and mortality 5.17 (age-standardised rate/world per 100,000) (2).

Generally, during the last two decades and until recently, there has been an annual increase of about 2% in the incidence both worldwide and in Europe, although in Denmark and Sweden a continuing decrease has been observed (3). In 2008, it was estimated that there were 88,400 new cases of RCC and 39,300 kidney cancer-related deaths in the European Union (4). In Europe, the overall mortality rates for RCC increased up until the early 1990s, with rates generally stabilising in the following years, but increasing again in recent years (5). There has been a decrease in the mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), the mortality rates are still showing an upward trend, with increasing rates (5). The mortality rate in Europe is 14,500 in females and 24,800 in males (both sexes 39,300) (4).

Renal cell carcinoma is the commonest solid lesion in the kidney and accounts for approximately 90% of all kidney malignancies. It includes different types, with specific histopathological and genetic characteristics (6). There is a 1.5:1.0 predominance of men over women, with the peak incidence occurring between the ages of 60 and 70. Etiological factors include lifestyle factors such as smoking, obesity, and hypertension (7-11). Obesity is a controversial issue, as there have been reports showing a better prognosis for obese patients suffering from renal cell cancer (12) Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC (13,14). The most effective prophylaxis is to avoid cigarette smoking and obesity.

As tumours are detected more frequently using imaging techniques such as ultrasound and computed tomography (CT), the numbers of RCCs diagnosed incidentally has increased. These tumours are more often smaller and at a lower stage (15-17).

2.1 Conclusion

Several verified risk factors have been identified, including smoking, obesity, and hypertension. Cigarette smoking is a definite risk factor for RCC (LE: 2a).

2.2 Recommendation

| The most important methods for primary prevention of RCC are to eliminate cigarette smoking and avoid obesity. | B |

2.3 References

3. DIAGNOSIS AND STAGING

3.1 Symptoms

Many renal masses remain asymptomatic until the late stages of the disease. Currently, more than 50% of RCCs are detected incidentally when non-invasive imaging is used to investigate a variety of nonspecific symptoms and other abdominal diseases (1,2) (LE: 3). The classic triad of flank pain, gross haematuria, and palpable abdominal mass is now rare (6-10%) and correlates with aggressive histology and advanced disease (3,4) (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (Table 4) (LE: 4). A few symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough (5) (LE: 3).
Table 4. Most common paraneoplastic syndromes

- Hypertension
- Cachexia
- Weight loss
- Pyrexia
- Neuromyopathy
- Amyloidosis
- Elevated erythrocyte sedimentation rate
- Anemia
- Abnormal liver function
- Hypercalcemia
- Polycythemia

3.1.1 Physical examination
Physical examination has only a limited role in the diagnosis of RCC. However, the following findings should prompt radiological examinations:
- Palpable abdominal mass;
- Palpable cervical lymphadenopathy;
- Nonreducing varicocele and bilateral lower extremity edema, that suggest venous involvement.

3.1.2 Laboratory findings
The most commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium, coagulation study, and urinalysis.

If there are central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment of the upper urinary tract should be considered in order to rule out the presence of urothelial cancer.

Split renal function should be estimated using renal scintigraphy in the following situations:
- When renal function is compromised, as indicated by an increased concentration of serum creatinine or a significantly decreased GFR.
- When renal function is clinically important - e.g., in patients with a solitary kidney or multiple or bilateral tumours (as in the hereditary forms of RCC).

Renal scintigraphy is an additional diagnostic option in patients who are at risk of future renal impairment due to comorbid disorders - e.g., diabetes, severe hypertension, chronic pyelonephritis, renovascular disease, urinary stones, or renal polycystic disease.

3.2 Imaging investigations
Most renal tumours are diagnosed when abdominal ultrasonography (US) or computed tomography (CT) are carried out for other medical reasons. Renal masses can be classified as solid or cystic on the basis of the imaging findings.

3.2.1 Presence of enhancement
With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement. The traditional approach for detecting and characterising renal masses is to use US, CT, or magnetic resonance imaging (MRI). Most renal masses can be diagnosed accurately using imaging alone. Contrast-enhanced US can be helpful in specific cases (e.g., chronic renal failure with a relative contraindication for iodinated or gadolinium contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis).

3.2.2 CT or MRI
Computed tomography or MRI are used to characterise a renal mass. Imaging must be performed both before and after administration of intravenous contrast material in order to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield unit (HU) readings before and after contrast administration. A change of 15 Hounsfield units or more is evidence of enhancement. To maximise differential diagnosis and detection, the evaluation should include images from the nephrographic phase, as this phase provides the best depiction of renal masses, which typically do not enhance to the same degree as the renal parenchyma.
CT or MRI allow accurate diagnosis of RCC in most cases. However, CT and MRI features cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms (15-18) (LE: 3).

Abdominal CT provides information on:
- Function and morphology of the contralateral kidney (19) (LE: 3);
- Primary tumour extension (extrarenal spread);
- Venous involvement;
- Enlargement of locoregional lymph nodes;
- Condition of the adrenal glands and liver (LE: 3).

Abdominal contrast-enhanced biphasic CT angiography is a useful tool in selected cases to obtain detailed information about the renal vascular supply (e.g., for segmental renal artery clamping during partial nephrectomy) (20,21). If the patient is allergic to CT contrast medium, MRI biphasic angiography (MRA) may be indicated, but this is less sensitive and accurate than CT angiography for detecting supernumerary vessels (22). If the results of CT are indeterminate, MRI may provide additional information in order to:
- Demonstrate enhancement in renal masses (including solid enhancing nodular components in complex cystic masses) (23);
- Investigate locally advanced malignancy (24-26);
- Investigate venous involvement if the extent of an inferior vena cava tumour thrombus is poorly defined on CT scanning (24-27) (LE: 3). Doppler US is less accurate for identification of the extent of a venous tumour thrombus (26) (LE: 3).

MRI is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure (25,28) (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored in the assessment of renal masses (29).

3.2.3 Other investigations
Renal arteriography and inferior venacavography only have a limited role in the work-up of selected patients with RCC (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered in order to optimise treatment decision-making - e.g., the need to preserve renal function (8,9) (LE: 2a).

The true value of positron-emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined, and PET is not currently a standard investigation (30) (LE: 3).

3.2.4 Radiographic investigations for metastatic RCC
Chest CT is the most accurate investigation for chest staging (31-35) (LE: 3). However, at the very least, routine chest radiography must be performed for metastatic evaluation, as a less accurate alternative to chest CT (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis, so that routine bone or brain imaging is not generally indicated (31,36,37) (LE: 3). However, bone scan, brain CT, or MRI may be used in presence of specific clinical or laboratory signs and symptoms (37-39) (LE: 3).

3.2.5 Bosniak classification of renal cystic masses
For the evaluation of renal cystic masses, the Bosniak classification classifies renal cysts into five categories based on their CT imaging appearance, in an attempt to predict the risk of malignancy (40,41) (LE: 3). The Bosniak system also advocates treatment for each category (Table 5).
Table 5: The Bosniak classification of renal cysts (40)

<table>
<thead>
<tr>
<th>Bosniak category</th>
<th>Features</th>
<th>Work-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A simple benign cyst with a hairline-thin wall that does not contain septa, calcification, or solid components. It has the same density as water and does not enhance with contrast medium.</td>
<td>Benign</td>
</tr>
<tr>
<td>II</td>
<td>A benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions &lt; 3 cm in size, with sharp margins but without enhancement.</td>
<td>Benign</td>
</tr>
<tr>
<td>IIF</td>
<td>These cysts may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall can be seen. There may be minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, but there is no contrast enhancement. There are no enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high-attenuation renal lesions ≥ 3 cm in size. These lesions are generally well-marginated.</td>
<td>Follow-up. A small proportion are malignant.</td>
</tr>
<tr>
<td>III</td>
<td>These lesions are indeterminate cystic masses that have thickened irregular walls or septa in which enhancement can be seen.</td>
<td>Surgery or follow-up. Over 50% of the lesions are malignant.</td>
</tr>
<tr>
<td>IV</td>
<td>These lesions are clearly malignant cystic lesions that contain enhancing soft-tissue components.</td>
<td>Surgical therapy recommended. Mostly malignant tumour.</td>
</tr>
</tbody>
</table>

3.3 Renal tumour biopsy (42-111)

Percutaneous renal tumour biopsies are increasingly being used: 1, for histological diagnosis of radiologically indeterminate renal masses; 2, to select patients with small renal masses for surveillance approaches; 3, to obtain histology before ablative treatments; 4, to select the most suitable form of targeted pharmacologic therapy in the setting of metastatic disease (42-51) (LE: 3).

Percutaneous sampling of a renal mass can be carried out using needle core biopsy and/or fine-needle aspiration (FNA). The aim is to determine malignancy, histological type, and grade of the renal tumour evaluated.

Due to the high diagnostic accuracy of current abdominal imaging findings, renal tumour biopsy is not necessary before surgical treatment in fit patients with a long life expectancy and a clearly suspicious, contrast-enhancing renal mass at abdominal CT or MRI (LE: 4).

Percutaneous sampling of renal masses can be performed under local anesthesia in the majority of cases (42-51) (LE: 3). Depending on the tumour’s location, its echogenic features, and the patient’s physical characteristics, biopsies can be performed with either ultrasound or CT guidance, with a similar diagnostic yield (47,50) (LE: 2b).

There is currently agreement that 18-gauge needles are ideal for renal tumour core biopsies, as they are associated with low morbidity and provide sufficient tissue for diagnosis in the majority of cases (42-50,52) (LE: 2b). A coaxial technique that allows multiple biopsies to be performed through a coaxial guide or cannula should always be used, in order to avoid the potential risk of tumour seeding (42-50) (LE: 3). With the use of coaxial techniques, no cases of seeding of renal tumours have been reported in recent years (42-50).

Overall, percutaneous biopsies have low morbidity. Spontaneously resolving subcapsular/perinephric haematoma and haematuria are the most frequently reported complications, while clinically significant bleeding is unusual (0-1.4%) and generally self-limiting (42-111).

Needle core biopsies are preferable for solid renal masses, as they have a greater diagnostic yield and better accuracy for diagnosing malignancy and histological type in comparison with FNA (44,47,49,53-55) (LE: 2b). Larger tumour size and solid pattern are predictors of a diagnostic core biopsy (47,50) (LE: 2b).

The ideal number and location of core biopsies have not been defined. However, at least two good-
quality cores (nonfragmented, > 10 mm in length) should be obtained, and necrotic areas should be avoided in order to maximize the diagnostic yield (42,44,47,48,50) (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis (56) (LE: 2b).

In recent series from experienced centers, core biopsies of solid renal tumours have shown a diagnostic yield of 78-97%, high specificity (98-100%), and high sensitivity (86-100%) for the diagnosis of malignancy (42-50,54,55,57-75) (LE: 2b). However, it should be noted that 2.5-22% of core biopsies are nondiagnostic (42-50,54,55,57-75) (LE: 2b). If a biopsy is nondiagnostic, but there are radiologic findings suspicious for malignancy, a further biopsy or surgical exploration should always be considered (LE: 4).

Assessment of tumour grade on core biopsies is challenging. The accuracy of Fuhrman grading on biopsies is poor (43-75%), but it can be improved using a simplified two-tier system (high-grade vs. low grade) (42-50,54,55,57-75) (LE: 2b). Core biopsies have a low diagnostic yield for cystic renal masses and should not be recommended alone in these cases, unless areas with a solid pattern are present (Bosniak IV cysts) (47,50) (LE: 2b). Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions (49,55,57,58,76,77) (LE: 3).

### 3.4 Histological diagnosis

The histological diagnosis of RCC is established after surgical removal of renal tumours with radical or partial nephrectomy or after percutaneous biopsy. According to the World Health Organization (112), there are three major histological subtypes of RCC:

- **Clear cell** (cRCC, 80-90%)
- **Papillary** (pRCC, 10-15%)
- **Chromophobe** (chRCC, 4-5%)

These RCC types can be differentiated on the basis of histological and genetic features (110) (LE: 3) (Table 6). Papillary RCC can be further divided into two different subtypes, type 1 and type 2 (Table 6) (113,114) (LE: 3).

#### Table 6: Major histological subtypes of RCC

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Percentage of RCC</th>
<th>Histological description</th>
<th>Associated genetic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell (cRCC)</td>
<td>80-90%</td>
<td>Most cRCC are composed predominantly of cells containing clear cytoplasm, although eosinophilic cytoplasm predominates in some cells. The growth pattern may be solid, tubular, and cystic.</td>
<td>Identified by the specific deletion of chromosome 3p and mutation of the VHL gene. Other changes are duplication of the chromosome band 5q22, deletion of chromosome 6q, 8p, 9p, and 14q.</td>
</tr>
<tr>
<td>Papillary (pRCC)</td>
<td>10-15%</td>
<td>Most pRCCs have small cells with scanty cytoplasm, but also basophilic, eosinophilic, or pail-staining characteristics. A papillary growth pattern predominates, although there may be tubular papillary and solid architectures. Necrotic areas are common. Papillary RCC can be divided into two different subtypes: type 1 with small cells and pale cytoplasm and type 2 with large cells and eosinophilic cytoplasm, the latter having a worse prognosis.</td>
<td>The most consistent genetic alterations are trisomies of chromosomes 3q, 7, 8, 12, 16, 17, and loss of the y chromosome.</td>
</tr>
<tr>
<td>Chromophobe (chRCC)</td>
<td>4-5%</td>
<td>The cells of chRCC may have pall or eosinophilic granular cytoplasm. Growth usually occurs in solid sheets.</td>
<td>The genetic characteristic is a combination of loss of chromosomes 1, 2, 6, 10, 13, and 17.</td>
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</tbody>
</table>

### 3.5 Conclusions

- The incidence of small and incidental renal tumours has significantly increased in recent decades, but a proportion of patients with RCC still present with a palpable mass, haematuria, and paraneoplastic
and metastatic symptoms (LE: 3). Appropriate staging of RCC requires abdominal CT or MRI and chest imaging (LE: 3). Chest CT is the most sensitive approach for detecting lung metastases, but at least a chest radiograph should be performed for chest staging. There is no role for routine bone scanning or brain CT or MRI in the standard clinical work-up of asymptomatic patients.

- Percutaneous renal tumour biopsies are increasingly being used: 1, to establish the diagnosis of radiologically indeterminate renal masses; 2, to obtain histology of incidentally detected renal masses in patients who are candidates for nonsurgical treatment (active surveillance, ablative therapies); and 3, to select the most suitable targeted therapy for metastatic renal tumours.

### 3.6 Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a patient with one or more suspicious laboratory or physical findings, the possible presence of RCC should be suspected.</td>
<td>B</td>
</tr>
<tr>
<td>Contrast-enhanced abdominal CT and MRI are recommended for the work-up of patients with RCC. These are the most appropriate imaging modalities for renal tumour staging prior to surgery.</td>
<td>A</td>
</tr>
<tr>
<td>A chest CT is most sensitive for assessment of the lung, but at least a plain chest radiograph should be taken for clinical staging.</td>
<td>A</td>
</tr>
<tr>
<td>In patients at risk for bone metastases (raised alkaline phosphatase level or bone pain), further evaluation with a bone scan is needed.</td>
<td>A</td>
</tr>
<tr>
<td>Evaluation of renal function is recommended before treatment decision in any patient in whom renal impairment is suspected.</td>
<td>B</td>
</tr>
<tr>
<td>Percutaneous biopsy is always recommended before ablative therapy and systemic therapy without previous pathology.</td>
<td>A</td>
</tr>
<tr>
<td>Percutaneous biopsy is recommended in active surveillance strategies in order to stratify the follow-up according to tumour histology.</td>
<td>B</td>
</tr>
<tr>
<td>When biopsy is indicated, good-quality needle cores should be obtained with a coaxial technique in order to increase the safety of the procedure and maximise its diagnostic yield.</td>
<td>B</td>
</tr>
</tbody>
</table>

### 3.7 References

    875-85. 
16. Rosenkrantz AB, Hindman N, Fitzgerald EF, et al. MRI features of renal oncocytoma and 
17. Hindman N, Ngo L, Genega EM, et al. Angiomyolipoma with minimal fat: can it be differentiated from 
    source computed tomography angiography during laparoscopic partial nephrectomy. Eur Urol 2012 
    preoperative assessment of the vascular supply in renal tumours-a surgical perspective. World J Urol. 
    2012 Apr 19. [Epub ahead of print] 
23. Adey GS, Pedrosa I, Rofsky NM, et al. Lower limits of detection using magnetic resonance imaging for 
24. Janus CL, Mendelson DS. Comparison of MRI and CT for study of renal and perirenal masses. Crit 
25. Krestin GP, Gross-Fengels W, Marinecek B. [The importance of magnetic resonance tomography in the 
    diagnosis and staging of renal cell carcinoma.] Radiologe 1992;32(3):121-6. [Article in German] 
    Jun;28(3):253-61. 


4. CLASSIFICATION AND PROGNOSTIC FACTORS

4.1 Classification
The TNM classification system is generally recommended for clinical and scientific use (1). However, the system requires continuous improvements (2). The latest version of the TNM classification was published in 2010 (Table 7). The prognostic value of the 2010 TNM classification has been confirmed in both single and multi-institution studies (3,4). However, some uncertainties remain:
- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal with the widening of nephron-sparing surgery for localised cancer.
- The value of size stratification of T2 tumours has been questioned (5).
- Since the 2002 version of the TNM classification, tumours with renal sinus fat invasion have been classified as pT3a. However, accumulating data suggest that renal sinus fat invasion carries a worse prognosis than perinephric fat invasion and therefore should not be included in the same pT3a stage group (LE: 3) (6-8).
- Some substages of the classification (pT2b, pT3a, pT3c and pT4) may overlap (4).
- The accuracy of the N1-N2 sub-classification has been questioned (9) (LE: 3). For adequate M staging...
of patients with RCC, accurate preoperative imaging (currently, chest and abdominal CT) should be performed (10,11) (LE: 4).

4.2 Prognostic factors
Factors influencing prognosis can be classified into: anatomical, histological, clinical, and molecular.

4.2.1 Anatomical factors
Anatomical factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement, and lymph node and distant metastasis. These factors are commonly gathered together in the universally used TNM classification system (Table 7).

Table 7: 2009 TNM classification system (1)

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
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<td></td>
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<tr>
<td>T1</td>
<td>Tumour ≤ 7 cm in greatest dimension, limited to the kidney</td>
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</tr>
<tr>
<td>T1a</td>
<td>Tumour ≤ 4 cm in greatest dimension, limited to the kidney</td>
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<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour &gt; 4 cm but ≤ 7 cm in greatest dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 7 cm in greatest dimension, limited to the kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour &gt; 7 cm but ≤ 10 cm in greatest dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Tumours &gt; 10 cm limited to the kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota’s fascia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota’s fascia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour grossly extends into the vena cava below the diaphragm</td>
<td></td>
<td></td>
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<tr>
<td>T3c</td>
<td>Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava</td>
<td></td>
<td></td>
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<tr>
<td>T4</td>
<td>Tumour invades beyond Gerota’s fascia (including contiguous extension into the ipsilateral adrenal gland)</td>
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<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single regional lymph node</td>
<td></td>
<td></td>
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<tr>
<td>N2</td>
<td>Metastasis in more than 1 regional lymph node</td>
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<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TNM stage grouping</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.

4.2.2 Histological factors
Histological factors include Fuhrman grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system. Fuhrman nuclear grade is the most widely accepted histological grading system in RCC (12). Although affected by intra- and inter-observer discrepancies, it is an independent prognostic factor (13). It has been suggested that a simplified two- or three-strata Fuhrman grading system could be as accurate as the classical four-tiered grading scheme (14,15) (LE: 3).

According to the WHO classification (16), three major histological subtypes of RCC exist: conventional (clear cell) (80-90%); papillary (10-15%); and chromophobe (4-5%). In univariate analysis, there is a trend towards a better prognosis for patients with chromophobe versus papillary versus conventional (clear cell) RCC.
(17,18). However, the prognostic information provided by the RCC subtype is lost when stratified to tumour stage (18,19) (LE: 3).

Among papillary RCCs, two subgroups with different outcomes have been identified (20): Type 1 are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis. Type 2 are mostly high-grade tumours with an eosinophilic cytoplasm and a great propensity for developing metastases (LE: 3).

RCC with Xp 11.2 translocation has been associated with a poor prognosis (21). Its incidence is low but should be systematically addressed in young patients.

The RCC type classification has been confirmed at the molecular level by cytogenetic and genetic analyses (22-24) (LE: 2b).

4.2.3 Clinical factors
Clinical factors include patient performance status, localised symptoms, cachexia, anaemia, and platelet count (25-28) (LE: 3).

4.2.4 Molecular factors
Numerous molecular markers being investigated, including: carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, C-reactive protein (CRP), osteopontin (29) and CD44 (cell adhesion) (30,31) (LE: 3). To date, none of these markers has been shown to improve the predictive accuracy of current prognostic systems and their use is therefore not recommended in routine practice. Finally, even though gene expression profiling seems a promising method, it has not helped so far to identify new relevant prognostic factors (32).

4.2.5 Prognostic systems and nomograms
Postoperative prognostic systems and nomograms that combine independent prognostic factors have been developed and externally validated (33-39). These systems may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An important advantage of nomograms is their ability to measure predictive accuracy (PA), which enables all new predictive parameters to be objectively evaluated. Before being adopted, every new prognostic variable or system should be able to demonstrate that its PA is superior to conventional postoperative histo-prognostic schemes (40). Recently, new preoperative nomograms with excellent PAs have been designed (41,42). Table 8 summarises the current most relevant prognostic systems.

4.3 Conclusions

<table>
<thead>
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<th>LE</th>
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<td>2</td>
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In patients with RCC, TNM stage, nuclear grade according to Fuhrman, and RCC subtype (WHO, 2004; [21]), should be performed because they contribute important prognostic information.

Prognostic systems should currently be used in a metastatic setting and are still investigational in localised disease.

4.4 Recommendations

<table>
<thead>
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<td>B</td>
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The current TNM classification system is recommended because it has consequences for prognosis and therapy.

The Fuhrman grading system and classification of RCC subtype should be used.

A stratification system should be used in a metastatic setting for selecting the appropriate first-line treatment.

In localised disease, the use of integrated prognostic systems or nomograms is not routinely recommended, even though these systems can provide a rationale for enrolling patients into clinical trials.

No molecular prognostic marker is currently recommended for routine clinical use.
Table 8: Summary of the anatomical, histological, and clinical variables included in the most commonly used prognostic models for localised and metastatic RCC

<table>
<thead>
<tr>
<th>Prognostic Models</th>
<th>Variables</th>
<th>Localised RCC</th>
<th>Metastatic RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNM Stage</td>
<td>ECOG PS</td>
<td>Kamofsky PS</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>UISS</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>SSIGN</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Post operative Karakiewicz's nomogram</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSKCC prognostic system</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Heng’s model</td>
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<td>X</td>
</tr>
</tbody>
</table>

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; SSIGN = Stage Size Grade Necrosis; UISS = University of California Los Angeles integrated staging system.
4.5 References


5. OTHER RENAL TUMOURS

Detailed morphological studies, which use contemporary immunohistochemical and molecular techniques, have resulted in the current classification of renal epithelial neoplasms, as outlined in the 2004 WHO monograph (1). A revised histopathological classification is expected in 2013. The common clear cell renal carcinoma (cRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC) types account for 85-90% of renal malignancies. The remaining 10-15% of renal tumours includes a variety of uncommon, sporadic, and familial carcinomas, some of which have recently been described, and a group of unclassified carcinomas.

5.1 Bellini duct carcinoma (collecting-duct carcinoma)
Collecting-duct carcinoma is a very rare type of RCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation and most patients die within 1-3 years from the time of primary diagnosis. The hazard ratio in cancer specific survival is in comparison with cRCC 4.49 (2). To date, the largest case series (n = 81) to consider outcome showed that regional lymph node metastases were present in 44% of patients at diagnosis and distant metastases were present in 32%. The survival rate was 48% at 5 years and 14% at 10 years (3-5). Median survival was 30 months (6). Response to targeted therapies was poor (7).

5.2 Renal medullary carcinoma
Renal medullary carcinoma is a devastating malignancy that primarily affects young black men with sickle cell trait. However, case reports in white and Hispanic patients without sickle cell trait have emerged (3). Renal medullary carcinoma is considered to be a subtype of collecting duct carcinoma (8). It is extremely rare; comprising approximately 2% of all primary renal tumours in young people aged 10 to 20 years. Metastatic disease is seen at presentation in 95% of patients (3,9,10). Median survival is 5 months (6). Surgical intervention alone is inadequate (9), systemic therapy is not defined, different regimes of chemotherapy are used, and the tumour is radiosensitive. Due to the rarity of this tumour type, it is unlikely that a randomised trial can be carried out in a timely fashion (11).

5.3 Sarcomatoid RCC
Sarcomatoid RCC represents high-grade transformation in different RCC types, without being a distinct histological entity. Sarcomatoid changes in RCC carry a worse prognosis (12). The hazard ratio in cancer specific survival is in comparison with cRCC (2). Metastatic sarcomatoid RCC is associated with a poor response to systemic therapy. Sunitinib treatment resulted in a modest response rate (13). The combination of gemcitabine and doxorubicin could also be an option (14). (LE: 3) (GR: C).
5.4 Unclassified RCC
Unclassified RCC is a diagnostic category for RCC that cannot be assigned to any other category of RCC-type carcinoma (1).

5.5 Multilocular cystic RCC
There are no strict histopathological criteria for this subtype. In the WHO 2004 classification (1), multilocular cystic RCC is an independent entity, but it is essentially a well-differentiated clear cell RCC (15). This subtype accounts for up to approximately 3.5% of surgically treated kidney tumours (16). To date, metastases of this tumour have not been described (16,17). According to the Bosniak classification, which is based on imaging criteria, multilocular cystic RCC presents as a Bosniak type II or III cystic lesion (18-20). However, this type of Bosniak lesion can also be due to a mixed epithelial and stromal tumour of the kidney (MESTK), a cystic nephroma (both see section 5.11), or a multilocular cyst, all of which are benign lesions. In many cases, a pre-operative biopsy and intra-operative frozen-section analysis does not lead to a correct diagnosis. Fortunately, all these tumours are treated with the same operative strategy. For this reason, if technically feasible, a nephron-sparing procedure is the technique of choice for a complex multicystic renal mass when enhanced density is observed (LE: 3) (GR: B) (15-17,19,20).

5.6 Papillary adenoma
Papillary adenomas are tumours with papillary or tubular architecture of low nuclear grade and are 5 mm in diameter or smaller (1). Because they are so small, they are only found incidentally in a nephrectomy specimen.

5.7 Translocation carcinoma (MITF/TFE family translocation-associated carcinoma)
Renal translocation carcinomas are uncommon tumours, which usually occur in children and young adults. Most translocation carcinomas (about 90%) involve the transcription factor E3 (TFE3) located on Xp11.2 and seem to follow a relatively indolent course, despite often being at an advanced stage at presentation, however, the clinical course is most aggressive in adults (3). Basically, there are 2 well-defined subtypes (ASPL/TFE3 and PRCC/TFE3). VEGF-targeted agents appear to demonstrate some efficacy (21,22). Another rare group of RCCs that show a translocation [t(6; 11) (p21; q12)] has also been reported (3,23). A case report with a metastatic course and a partial response to sunitinib malate was described (24).

5.8 Mucinous tubular and spindle cell carcinoma
This tumour is associated with the loop of Henle. Most mucinous tubular and spindle-cell carcinomas behave in a low-grade fashion (1,3,25).

5.9 Carcinoma associated with end-stage renal disease
Acquired cystic disease-associated renal cell carcinoma, clear cell papillary RCC.
Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC are typical features of ESKD (end-stage kidney disease). The incidence of ACKD is about 50% in patients undergoing dialysis, but also depends on the duration of dialysis, gender (three times more common in men), and the diagnostic criteria of the method of evaluation. RCCs of native end-stage kidneys are found in about 4% of patients. The lifetime risk of developing RCCs is at least 10 times higher than that in the general population. Compared with sporadic RCCs, the RCCs associated with ESKD and ACKD are characterised by multicentricity and bilaterality, are found in younger patients (mostly male), and have a less aggressive behaviour (26, 27). A relatively indolent outcome of tumours in ESKD is due only to the mode of diagnosis and not to specific ESKD-related molecular pathways still to be determined (27). RCC arising in native kidneys of transplant patients seems to exhibit many favourable clinical, pathological and outcome features compared with those diagnosed in dialysis-only patients. Further research is needed to determine whether this is due to particular molecular pathways or to biases in relation to mode of diagnosis (28). Although the histological spectrum of tumours within ACKD is similar to that in sporadic RCC, the most predominant form is pRCC, being found in 41-71% of ACKD-associated RCC versus 10% in sporadic RCC. The remaining tumours are mostly cRCC (3,26,27). Tickoo et al. (29) described two new renal tumours associated with ESKD: ‘acquired cystic disease-associated RCC’ and ‘clear-cell pRCC’. To date, these two entities are under conscientious discussion. Clear cell (tubulo) pRCC has been reported in otherwise normal kidneys as well, and has low potential for malignancy (30,31). The existence of ACKD-associated RCC is in dispute (27). Patients with ESKD should undergo an annual ultrasound evaluation of the kidneys. Minimally invasive radical nephrectomy can be performed safely in these patients (32).

5.10 Metanephric tumours
Metanephric tumours are divided into metanephric adenoma, adenofibroma, and metanephric stromal tumour. These are very rare benign tumours and surgical excision is sufficient (1).
5.11 Renal epithelial and stromal tumours
Renal epithelial and stromal tumours (REST) is a new concept that brings together two benign mixed mesenchymal and epithelial tumours: cystic nephroma and mixed epithelial and stromal tumours (33). Imaging studies have revealed that most REST cystic lesions are Bosniak type III and less frequently Bosniak type II or IV (18,20). Although aggressive behaviour has been reported in very few cases, both neoplasms are generally considered to be benign and surgical excision is curative (33).

5.12 Oncocytoma
Renal oncocytomas are benign tumours (1) that comprise about 3-7% of all renal tumours (34). Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard (35,36). Although only a percutaneous biopsy can lead to a preoperative diagnosis, it has a low specificity for oncocytoma because oncocytotic cells are also found in cRCC, (the granular-cell variant of RCC), and in the eosinophilic variant of pRCC (type 2) and the oncocytic variant of pRCC. ‘Watchful waiting’ can be considered in selected cases of histologically verified oncocytoma. Alternative management includes partial nephrectomy and minimally invasive approaches. (LE: 3) (GR: C) (37,38).

5.13 Hereditary kidney tumours
Hereditary kidney tumours can be found as part of the following entities: Von Hippel-Lindau syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see Hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and renal cell cancer (HLRCC), tuberous sclerosis, and constitutional chromosome 3 translocation (1,39).

5.14 Mesenchymal tumours
Mesenchymal tumours include different types of benign tumours and sarcomas and are relatively rare, except for angiomyolipoma.

5.14.1 Angiomyolipoma
Angiomyolipoma (AML) is a benign mesenchymal tumour composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels. It can occur sporadically, and is four times more likely in women. It also occurs in tuberous sclerosis (TS), when it is multiple, bilateral, larger, and likely to cause spontaneous haemorrhage. It accounts for approximately 1% of surgically removed tumours. Ultrasound, CT, and MRI often lead to diagnosis due to the presence of adipose tissue. Biopsy is rarely useful. Pre-operatively, it may be difficult to differentiate between tumours composed predominantly of smooth muscle cells and epithelial tumours. AML can be found in TS in lymph nodes, but it is not metastatic disease, but disease with a multicentric genesis. AML can be due to angiotropic-type growth involved in the renal vein even the inferior vena cava. AML with involvement of lymph nodes and tumorous thrombus is benign. Only epithelioid AML is a potentially malignant variant of AML (1,40). AML is associated with a slow and consistent growth rate (0.088 cm/year), and typically has minimal morbidity (41). The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which may be life-threatening (42). The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels (42). The major risk factors for bleeding are tumour size, grade of the angiogenic component of the tumour, and the presence of tuberous sclerosis (42,43). Primary indications for intervention include symptoms such as pain, bleeding, or suspected malignancy.

Prophylactic intervention is justified for:
• large tumours (the recommended threshold of intervention does not exist, the formerly recommended size of > (3) 4 cm wide is disputed) (41,42,44);
• females of childbearing age;
• patients in whom follow-up or access to emergency care may be inadequate (43) (LE: 3) (GR: C).

Most cases of AML can be managed by conservative nephron-sparing approaches, although some cases of AML may require complete nephrectomy (43) (LE: 3). Of the standard surgical interventions, selective arterial embolisation (SAE) and radiofrequency ablation (RFA) can be used (41,42,44). Although SAE is effective at controlling haemorrhage in the acute setting, it has limited value in the longer-term management of AML (45). Clinical trials of medical management with m-TOR inhibitors are ongoing (46) and sirolimus can be combined with deferred surgery (47).

5.15 New histological entities
New histological entities have recently been described, for which there currently is very little clinical data. Some
of these entities are supposed to be included in a new ongoing histopathological classification. These entities include:

- **Hybrid oncocytoma-chromophobe RCC**
  Hybrid oncocytic/chromophobe tumours (HOCT) of the kidney have been described for the first time in patients with Birt-Hogg-Dubé syndrome (a rare autosomal dominant syndrome characterised by skin hamartomas and multiple renal tumours) in association with renal oncocytoysis. A sporadic variant also exists. The tumours seem to behave indolently as no evidence of malignant behaviour has been documented to date. However, these tumours could have a low malignant potential and patients should be followed-up as chromophobe RCC (48,49).

- **Oncocytic papillary renal cell carcinoma - type 3**
  This tumour could be termed a pRCC type 3. In comparison with pRCC type I and II, it has no pseudocapsule, no massive necroses, and extrarenal growth is relatively rare. The malignant potential is low (50).

- **Tubulocystic renal cell carcinoma (TCRCC)**
  This occurs predominantly in men over a wide age range. There is a possible relationship to pRCC. It frequently displays a cystic component which may result in a radiological classification of Bosniak III or IV. TCRCC has definite malignant potential (51).

- **Thyroid-like follicular carcinoma of the kidney**; rare tumour closely mimicking well-differentiated thyroid follicular neoplasms.

- **RCC associated with neuroblastoma**; extremely rare, morphologically heterogeneous entity.

- **Renal angiomyoadenomatous tumour**; the relation with clear cell pRCC (see above 5.9) is discussed (30,31,54).

### Table 9: Summary of other renal tumours with an indication of malignant potential and recommendation for treatment (GR: C)

<table>
<thead>
<tr>
<th>Entity</th>
<th>Malignant potential</th>
<th>Treatment of localised tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomatoid variants of RCC</td>
<td>High</td>
<td>Surgery</td>
</tr>
<tr>
<td>Multilocular clear cell RCC</td>
<td>Low, no metastasis</td>
<td>Surgery, NSS*</td>
</tr>
<tr>
<td>Carcinoma of the collecting ducts of Bellini</td>
<td>High, very aggressive</td>
<td>Surgery, in M+ discussable</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>High, very aggressive</td>
<td>Surgery</td>
</tr>
<tr>
<td>Translocation carcinoma</td>
<td>Intermediate</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>Intermediate</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Carcinoma associated with end-stage renal disease</td>
<td>Variable</td>
<td>Surgery</td>
</tr>
<tr>
<td>Metanephric tumours</td>
<td>Benign</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Renal epithelial and stromal tumours (REST)</td>
<td>Low</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Benign</td>
<td>Observation/surgery, NSS</td>
</tr>
<tr>
<td>Hereditary kidney tumours</td>
<td>High</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>Benign</td>
<td>Consider treatment only in very well selected patients</td>
</tr>
<tr>
<td>Unclassified RCC</td>
<td>Variable</td>
<td>Surgery, NSS</td>
</tr>
</tbody>
</table>

*NSS = nephron-sparing surgery.

### 5.16 Summary

A variety of renal tumours exists, of which about 15% are benign. All kidney lesions have to be examined (e.g. imaging, biopsy, etc.) and judged regarding the likelihood of malignant behaviour.
5.17 Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Except for angiomyolipomas, most of these less common renal tumours cannot be</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>differentiated from RCC on the basis of radiology and should therefore be treated in the same way as RCC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosniak cysts &gt; type III should be treated surgically. When possible, a nephron-sparing procedure should be performed in Bosniak type III.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>In oncocytomas verified on biopsy, follow-up is an option.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered in only very well selected cases. A nephron-sparing procedure is preferred.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

5.18 References


6. TREATMENT OF LOCALISED RCC AND LOCAL TREATMENT OF METASTATIC RCC

A systematic review underpins the findings of sections 6.1 – 6.2. This review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) (1,2). Randomised or quasi-randomised controlled trials (RCTs) were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from well-defined registries databases were also included. Studies with no comparator group (for example, case series), unmatched retrospective studies, and chart reviews were excluded due to their inherent risk of selection bias. The systematic review methodology has been reported in detail elsewhere (1,2).

For sections 6.3 – 6.5, a traditional narrative review was performed (see Chapter 1).
For sections 6.6 – 6.7, a systematic review and narrative synthesis of the evidence was performed (see Chapter 1).

6.1 Main comparisons
6.1.1 Surgery versus non-surgical treatment
One matched pair study (derived from the SEER database) compared surgery for small renal masses (≤ 4 cm) with non-surgical management (3). Included were pT1a patients who were assigned to either observation or active surveillance. The analysis showed that surgical therapy had a significant 5 year cancer-specific mortality benefit over non-surgical intervention. However, even though this study was matched, it is marked by allocation bias; the patients assigned to the surveillance arm were older and likely more frail and less suitable candidates for surgery. There was no comparative study addressing this comparison in terms of perioperative and QoL outcomes.

6.1.2 Nephron-sparing surgery versus radical nephrectomy
Based on the available oncological and QoL outcomes, the current evidence suggests that localised renal cancers are best managed by nephron-sparing surgery (partial nephrectomy) rather than by radical nephrectomy, irrespective of the surgical approach.

When open partial nephrectomy was compared to open radical nephrectomy the estimated cancer-specific survival rates (CSS) at 5 years were comparable. (4-7). A number of studies compared partial against radical nephrectomy, either performed by an open or laparoscopic approach for renal carcinoma (≤ 4 cm) (8-11). These studies showed that radical nephrectomy was associated with increased mortality from any cause after adjusting for patient characteristics. In studies analysing RCCs 4-7 cm no differences were shown...
for CSS between partial nephrectomy and radical nephrectomy (11-16). Also when laparoscopic partial nephrectomy and laparoscopic radical nephrectomy was compared in RCCs > 4 cm there was no difference in overall survival (OS), CSS and recurrence-free survival rates (RFS) (17).

In a number of studies various aspects of QoL and safety were compared for open partial and open radical nephrectomy (4-7,18-20). No difference in length of hospital stay (5,6,20), blood transfusions (5,18,20), or mean blood loss was found (5,20). In general, complication rates are inconsistently reported in NRS, and no clear conclusions in favour of one intervention over another can be drawn (21). The mean operative time was longer for the open partial group (20) but others found no such difference (22). Three studies consistently reported worse renal function after radical nephrectomy compared to partial nephrectomy (4,7,18). A greater proportion of patients had impaired postoperative renal function after radical nephrectomy after adjustment for diabetes, hypertension and age (7).

One database review compared open partial with laparoscopic radical nephrectomy in RCCs 4-7 cm (13). After partial nephrectomy, the mean increase of post-operative creatinine levels was significantly lower. When laparoscopic partial nephrectomy was compared to laparoscopic radical nephrectomy, the estimated GFR in the nephron-sparing group decreased less as compared to the radical nephrectomy group which showed a significantly greater proportion of patients with a 2-stage increase in the CKD stage (17). Another database review (23) compared laparoscopic partial with laparoscopic radical nephrectomy for RCCs > 4 cm in size. The laparoscopic radical nephrectomy group had a significantly greater decrease in estimated GFR and a greater proportion of patients with a CKD 2 stage.

Two studies reported QoL post-surgery for RCC. Patients who underwent partial nephrectomy reported better scores, in many aspects of quality of life (19). Those who underwent radical nephrectomy reported a higher degree of fear associated with living with only one kidney. Regardless of the intervention, patients with RCCs < 4 cm and a normal contralateral kidney showed the highest QoL scores after treatment, which matched their pre-diagnosis scores. Patients who had higher complications rates had lower QoL scores (5).

No comparative studies were identified reporting on oncological outcomes for minimally invasive ablative procedures compared with radical nephrectomy.

Patient and tumour characteristics permitting, the current oncological outcomes evidence base suggests that localised RCCs are best managed by NSS rather than by radical nephrectomy irrespective of surgical approach. Where open surgery is deemed necessary, the oncological outcomes following open NSS are at least as good as open radical nephrectomy and should be the preferred option when technically feasible. However, in some patients with localised RCC, NSS is not suitable because of:

- locally advanced tumour growth;
- partial resection is not technically feasible because the tumour is in an unfavourable location;
- significant deterioration of a patient’s general health.

In these situations, the curative therapy remains radical nephrectomy, which includes removal of the tumour-bearing kidney. Complete resection of the primary tumour by either open or laparoscopic surgery offers a reasonable chance of curing the disease.

6.1.3 Associated procedures

6.1.3.1 Adrenalectomy

One prospective NRS compared the outcomes of radical or partial nephrectomy with, or without, ipsilateral adrenalectomy (24). On multivariate analysis, upper pole location was not predictive of adrenal involvement but tumour size proved significant. There was no difference in overall survival (OS) at 5 or 10 years, with, or without, adrenalectomy. Adrenalectomy was justified using criteria, based on radiographic and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 were for benign lesions.

6.1.3.2 Lymph node dissection

An extended or radical lymph node dissection does not appear to improve long-term survival following tumour nephrectomy (25). Thus, for staging purposes, lymph node dissection can be limited to the hilar region. In patients with palpable or CT-detected enlarged lymph nodes, resection of the affected lymph nodes should be performed to obtain adequate staging information.

6.1.3.3 Embolisation

Before a routine nephrectomy, there is no benefit in performing tumour embolisation (26,27). In patients who are unfit for surgery, or who present with non-resectable disease, embolisation can control symptoms such as gross haematuria or flank pain (28-30). Embolisation prior to the resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss (31). In selected patients with painful bone or paravertebral
metastases, embolisation can help to relieve symptoms (32).

**Conclusions**

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical nephrectomy is no longer the standard treatment for low-stage RCC (T1).</td>
<td>3</td>
</tr>
<tr>
<td>There is an increased risk of intrarenal recurrences in larger-size (&gt; 7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin.</td>
<td>3</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical therapy remains the mainstay of therapy to achieve a cure in the management of RCC.</td>
<td>LE</td>
<td>C</td>
</tr>
<tr>
<td>Patients with low-stage RCC (T1) should undergo nephron-sparing surgery rather than radical nephrectomy whenever possible.</td>
<td>LE</td>
<td>B</td>
</tr>
<tr>
<td>Adrenalectomy is not recommended, provided a pre-operative CT scan shows the adrenal gland is normal and the intra-operative findings do not suggest intra-adrenal metastatic spread or a direct invasion of the adrenal gland.</td>
<td>LE</td>
<td>C</td>
</tr>
<tr>
<td>Extended lymphadenectomy is not recommended since it does not appear to improve survival. It should be restricted to staging purposes with dissection of palpable and/or enlarged lymph nodes.</td>
<td>LE</td>
<td>A</td>
</tr>
<tr>
<td>In patients unfit for surgery and suffering from massive haematuria or flank pain, embolisation can be a beneficial palliative approach.</td>
<td>LE</td>
<td>C</td>
</tr>
<tr>
<td>For solitary renal tumours up to a diameter of 7 cm, nephron-sparing surgery is the standard procedure, whenever technically feasible.</td>
<td>LE</td>
<td>C</td>
</tr>
<tr>
<td>A minimal tumour-free surgical margin following partial resection of RCC is sufficient to avoid local recurrence.</td>
<td>LE</td>
<td>B</td>
</tr>
</tbody>
</table>

### 6.2 Techniques of radical and partial nephrectomy

#### 6.2.1 Techniques of radical nephrectomy

There are no randomised studies assessing oncological outcomes of laparoscopic versus open radical nephrectomy. A prospective cohort study (33) and a retrospective database review (5), both of low methodological quality, found similar oncological outcomes for laparoscopic versus open radical nephrectomy. Data from one RCT (34) and two NRSs (5,33) showed significantly shorter hospital stay and lower analgesic requirement for the laparoscopic radical nephrectomy group compared with the open group. Convalescence time was also significantly shorter (33). There was no difference in number of patients receiving a blood transfusion between the approaches but the perioperative blood loss was significantly less in the laparoscopic arm in all three studies (5,33,34). Surgical complications were marked by low event rates and very wide confidence intervals. There was no difference in complications but the operation time was significantly shorter in the open arm. Post-operative QoL scores were similar between the two groups (5).

In regard to the approach of performing radical nephrectomy, both retroperitoneal or transperitoneal approaches had similar oncologic outcomes in two RTCs (35,36) and one quasi-randomised study (37). There was no significant difference in quality of life variables between the two approaches.

Hand-assisted laparoscopic radical nephrectomy and standard laparoscopic radical nephrectomy was compared in one RCT (37) and one database review (21). Estimated 5-year overall survival, cancer-specific survival, and recurrence free survival rates were comparable between the approaches. Duration of operation was significantly shorter in the hand-assisted compared to the laparoscopic approach but length of hospital stay and time to non-strenuous activities were shorter for standard laparoscopic radical nephrectomy (21,37). However, the sample size was small.

Robot-assisted laparoscopic radical nephrectomy versus laparoscopic radical nephrectomy was compared in one small prospective cohort study (38). There were no local recurrences, port-site or distant metastases, but sample size was small and follow-up was less than 1 year. Similar results were presented in observational cohort studies comparing ‘portless’ (n = 14) and 3-port (n = 15) laparoscopic radical nephrectomy (39,40). There was no difference in perioperative outcomes.

#### 6.2.2 Techniques of partial nephrectomy and minimally invasive ablative procedures

Laparoscopic partial nephrectomy compared to open partial nephrectomy showed no difference in overall survival (41-44). Regarding the number of deaths during the study period, a lower risk of all cause death was shown in the laparoscopic group in one study (42) while in other studies no difference in the recurrence patterns between laparoscopic and open partial nephrectomy was reported (41,44). In a matched pair analysis (43) the length of hospital stay was significantly shorter and there was less mean blood loss in the laparoscopic
partial group. In one database review more blood transfusion events occurred in the laparoscopic group (41). There were no differences between the groups in postoperative mortality events (41,43), DVT events (43), or pulmonary embolism events but the operative time was significantly longer in the laparoscopic partial group (22,43,44). Decline in GFR was greater in the laparoscopic partial nephrectomy group in the immediate postoperative period (44), but not after a follow-up of 3.6 years.

There is no comparative study that reported on oncological outcomes between robotic assisted partial nephrectomy and laparoscopic partial nephrectomy. One study based on a matched-pair analysis (45) showed no difference in perioperative outcomes (10) or in the estimated GFR.

In regard to partial nephrectomy versus minimally invasive ablative procedures, several studies were identified. For radiofrequency-assisted robotic partial nephrectomy versus laparoscopic partial nephrectomy, a database review (46) found no differences between the groups in terms of positive surgical margins and recurrence rates, but the study was marked by very low event rates, a high number of benign tumours, and short-term survival data.

Data on laparoscopic cryoablation versus laparoscopic partial nephrectomy obtained from one database review (47) reported 3 deaths out of 78 patients treated, compared with none out of 153 patients treated with laparoscopic partial nephrectomy. In another matched pair study no recurrences were reported in either treatment but with a follow-up of less than 12 months (48). It should be noted that the studies also included benign tumours and the data should be treated with caution. In a database review (47) and a matched-pair study (48) there were no differences in perioperative outcomes, recovery times, complication rates or postoperative serum creatinine levels between laparoscopic cryoablation and laparoscopic partial nephrectomy. Blood loss was less and surgical time was quicker in the cryoablation group than the laparoscopic partial nephrectomy group (47,48). In one matched comparison between laparoscopic cryoablation and open partial nephrectomy (49) no local recurrences or metastasis was found in either group. The length of hospital stay was shorter and the mean blood loss was significantly less in the laparoscopic cryoablation group, but there was no difference in number of patients requiring blood transfusions or duration of operation. However, there were only 20 patients in each arm and the follow-up time was short.

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic radical nephrectomy appears to have a lower morbidity compared to open surgery.</td>
<td>1a</td>
</tr>
<tr>
<td>Tumour control rates appear equivalent for T1-T2 tumours between laparoscopic and open radical nephrectomy.</td>
<td>3</td>
</tr>
<tr>
<td>Long-term outcome data indicate that laparoscopic radical nephrectomy has equivalent cancer-free survival rates to those of open radical nephrectomy.</td>
<td>3</td>
</tr>
<tr>
<td>Partial nephrectomy by laparoscopic surgery is technically feasible.</td>
<td>3</td>
</tr>
<tr>
<td>The data regarding quality of life and perioperative outcomes for laparoscopic nephron-sparing surgery compared with open nephron-sparing surgery remains.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic radical nephrectomy is recommended in T2 renal cell cancer.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic radical nephrectomy is the standard of care for patients with T2 tumours and those renal masses not treatable by nephron-sparing surgery.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Extended lymphadenectomy is not recommended since it does not appear to improve survival. It should be restricted to staging purposes with dissection of palpable and/or enlarged lymph nodes.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Laparoscopic and robot assisted partial nephrectomy is an alternative to open nephron-sparing surgery.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Open partial nephrectomy currently remains as a standard of care for partial nephrectomy.</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

6.3 Therapeutic approaches as alternatives to surgery

6.3.1 Surveillance

Elderly and co-morbid patients with incidentally detected small renal masses have a relatively low RCC-specific mortality and a significant competing-cause mortality (50,51).

Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (ultrasound, CT, or MRI) with delayed intervention reserved for those tumours that show clinical progression during follow-up (52).

In the largest reported series of active surveillance the growth of renal tumours is low in the majority of
cases and progression to metastatic disease is reported in a limited number of patients (1-2%) (53,54). Both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, active surveillance is an appropriate strategy to initially monitor small renal masses, followed if required by treatment for progression (52-58).

6.4 Adjuvant therapy
Current evidence that adjuvant tumour vaccination might improve the duration of the progression-free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas needs further confirmation regarding the impact on overall survival (LE: 1b) (59-63). Prognostic algorithms might identify patients likely to derive the largest clinical benefit from adjuvant vaccination therapy.

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (ultrasound, CT, or MRI) with delayed intervention reserved for those tumours that show clinical progression during follow-up.</td>
<td>3</td>
</tr>
<tr>
<td>Adjuvant therapy with cytokines does not improve survival after nephrectomy.</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance is a reasonable option for elderly and/or comorbid patients with small renal masses and limited life expectancy.</td>
<td>C</td>
</tr>
<tr>
<td>Patients with small renal tumours and/or significant co-morbidity who are unfit for surgery should be considered for an ablative approach, e.g. cryotherapy and radiofrequency ablation.</td>
<td>C</td>
</tr>
<tr>
<td>Pre-treatment biopsy has to be carried out as a standard before ablative therapy and is useful when active surveillance is considered in order to stratify follow-up based on tumour histology.</td>
<td>C</td>
</tr>
<tr>
<td>Other image-guided percutaneous and minimally invasive techniques, such as microwave ablation, laser ablation, and high-intensity focused ultrasound ablation are experimental and are recommended only in studies.</td>
<td>C</td>
</tr>
<tr>
<td>Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.</td>
<td>A</td>
</tr>
</tbody>
</table>

6.5 Surgical treatment of metastatic RCC (tumour nephrectomy or cytoreductive nephrectomy)
Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For the majority of patients with metastatic disease, cytoreductive nephrectomy is palliative and systemic treatments are necessary. In a meta-analysis of two randomized studies, comparing cytoreductive nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to cytoreductive nephrectomy (64). At present, only limited data are available addressing the value of cytoreductive nephrectomy combined with targeting agents such as sunitinib, sorafenib and others. Randomised studies are ongoing.

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour nephrectomy in combination with interferon-alpha (IFN-α) improves the survival of patients with metastatic RCC (mRCC) and good performance status.</td>
<td>1a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour nephrectomy is recommended for metastatic RCC patients with good performance status when combined with IFN-α.</td>
<td>A</td>
</tr>
</tbody>
</table>

6.6 Surgical resection of metastases in metastatic RCC
A systematic review was undertaken (65). No randomised trials were identified comparing metastasectomy with other treatments, but 12 non-randomised comparative studies involving metastasectomy were identified. A number of studies compared complete metastasectomy with partial metastasectomy in patients with metastatic RCC involving multiple organ sites (66-68). The results showed an overall survival advantage for complete resection. When complete metastasectomy was compared with no surgical resection (69-71), complete metastasectomy offered a slight overall survival advantage.

In the treatment of bone metastases, metastasectomy in combination with local stabilization provided a significant survival advantage over that of non-surgical treatment (72).
In visceral metastases affecting the liver and pancreas, metastasectomy showed a significantly prolonged overall survival compared with non-surgical treatment (73,74). For patients with liver metastases, radical resection was associated with significantly better overall survival compared with either partial resection or ablation (75).

For the treatment of brain lesions, one study compared metastasectomy followed by whole brain radiotherapy, against fractionated stereotactic radiotherapy or conventional radiotherapy alone (76). There was no difference in cancer specific survival, although surgery appeared to offer some benefits regarding local tumour control.

### 6.7 Radiotherapy for metastases in metastatic RCC

A systematic review was undertaken (65). Three non-randomised comparative studies involving different radiotherapy modalities were identified. The results showed there was no significant survival benefit using radiotherapy. However, there was evidence of improved local tumour control with radiotherapy. Two studies (77,78) involving bone metastases showed an improvement in bone pain using different radiotherapy modalities. In a study on brain metastases (79) whole brain radiotherapy alone, stereotactic radiosurgery alone or a combination of the two were compared. The study showed a good local tumour control using either individual modality in patients with 1-3 metastases to the brain.

### Conclusions

There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis. Its role has to be continuously re-evaluated, especially in combination with targeted systemic therapy.

### Recommendations

- In patients with metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status. **C**
- Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or other systemic treatment. **C**
- In individual cases, stereotactic radiotherapy for the treatment of bone and brain metastases can induce symptom relief. **C**

### References


http://www.uroweb.org/?id=217&tid=1&oid=4


7. SYSTEMIC THERAPY FOR METASTATIC RCC

7.1 Chemotherapy

Since RCCs develop from the proximal tubules, they have high levels of expression of the multiple-drug resistance protein, P-glycoprotein, and are therefore resistant to most forms of chemotherapy. Chemotherapy appears to be moderately effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents (1). However, in a prospective randomised study, interferon-alpha (IFN-\(\alpha\)) showed equivalent efficacy to a combination of IFN-\(\alpha\) + interleukin-2 (IL-2) + 5-FU (2).

7.1.1 Conclusion and recommendation

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU in combination with immunotherapy is equivalent in efficacy to monotherapy with IFN-(\alpha) in patients with mRCC.</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with clear-cell mRCC, chemotherapy as monotherapy should not be considered effective in patients with mRCC.</td>
<td>B</td>
</tr>
</tbody>
</table>

7.2 Immunotherapy

7.2.1 Interferon alpha as monotherapy and combined with bevacizumab

Interferon alpha has been shown in randomised studies to be superior in relation to survival to hormonal therapy in patients with mRCC (3). IFN-\(\alpha\) provided a response rate of 6-15\%, together with a 25% decrease in the risk for tumour progression and a modest survival benefit of 3-5 months in comparison with a placebo equivalent (4,5).

The positive effect of IFN-\(\alpha\) is particularly apparent in mRCC patients with clear cell histology, good-risk Motzer criteria, and lung metastases only (5). In a prospective randomised study, IFN-\(\alpha\) showed equivalent efficacy to a combination of IFN-\(\alpha\) + IL2 + 5-FU (2). The moderate efficacy of immunotherapy was also confirmed in a Cochrane meta-analysis including 42 eligible studies (6).

A combination of bevacizumab + IFN-\(\alpha\) was recently shown to be associated with increased response rates and better progression-free survival in first-line therapy in comparison with IFN-\(\alpha\) monotherapy (7). All recent randomized studies comparing anti-angiogenic drugs in a first-line setting to IFN-\(\alpha\) monotherapy have shown superiority for either sunitinib, bevacizumab + IFN-\(\alpha\), or temsirolimus (7-10).

<table>
<thead>
<tr>
<th>Table 10: Memorial Sloan-Kettering Cancer Center (Motzer) criteria for predicting survival in patients with advanced RCC treated with interferon alpha, depending on the presence or absence of five distinct risk factors (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors*</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
</tr>
<tr>
<td>Time from diagnosis to treatment with IFN-(\alpha)</td>
</tr>
<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
</tr>
</tbody>
</table>

* Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three or more risk factors.

7.2.2 Interleukin-2

Interleukin-2 (IL-2) has been used to treat mRCC since 1985, with response rates ranging from 7\% to 27\% (10-12). The optimal IL-2 regimen is not clear, but long-term (> 10 years) complete responses have been achieved.
with high-dose bolus IL-2 in a randomised phase III study (13). The toxicity of IL-2 is substantially greater than that of IFN-α. Only clear cell-type RCC responds to immunotherapy. Interleukin-2 has not been validated in controlled randomised studies in comparison with best supportive care (5).

7.2.3 Vaccines and targeted immunotherapy

No recommendations can be made. An earlier phase III trial of vaccine therapy with tumour antigen 5T4 in combination with the first-line standard of care (either sunitinib, interleukin-2, or interferon alpha) failed to demonstrate any survival benefit in comparison with placebo and the first-line standard of care (14). Several phase III vaccination studies are ongoing. Targeted immunotherapy with programmed death-1 ligand (PD-1L), which has shown efficacy and acceptable toxicity in patients with RCC (15), is currently under investigation in a phase II trial in comparison with everolimus in patients in whom anti-angiogenic therapy previously failed.

7.2.4 Conclusions

<table>
<thead>
<tr>
<th>LE</th>
<th>Interferon-alpha monotherapy is no longer recommended as first-line therapy for mRCC. 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE</td>
<td>Interferon alpha monotherapy still has a role only in selected cases (good performance status, clear cell type, lung metastases only). 2</td>
</tr>
<tr>
<td>LE</td>
<td>Interleukin-2 has more side effects than IFN-α. 2-3</td>
</tr>
<tr>
<td>LE</td>
<td>High-dose IL-2 is associated with durable complete responses in a limited number of patients. 1b</td>
</tr>
<tr>
<td>LE</td>
<td>Interleukin-2 can be considered as monotherapy in selected patients with a good prognosis profile. 1b</td>
</tr>
<tr>
<td>LE</td>
<td>A combination of bevacizumab and IFN-α is more effective than IFN-α in treatment-naïve, low-risk and intermediate-risk tumours. 1b</td>
</tr>
<tr>
<td>LE</td>
<td>Vaccination therapy with tumour antigen 5T4 showed no survival benefit over the first-line standard of care. 1b</td>
</tr>
</tbody>
</table>

7.2.5 Recommendations

| GR       | Monotherapy with IFN-α or high-dose bolus IL-2 can only be recommended as a first-line treatment for mRCC in selected patients with clear cell histology and good prognostic factors. A |
| GR       | Bevacizumab + IFN-α is recommended as first-line therapy in low-risk and intermediate-risk patients. B |
| GR       | Only selected patients with mRCC who have a good risk profile and clear cell subtype histology show clinical benefit from immunotherapy with IL-2. |
| GR       | Cytokine combinations, with or without additional chemotherapy, do not improve the overall survival in comparison with monotherapy. A |

7.3 Drugs targeting VEGF, including other receptor kinases and mammalian target of rapamycin (mTOR)

Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC (Table 11).

In sporadic clear cell RCC, hypoxia-inducible factor (HIF) accumulation due to von Hippel-Lindau (VHL) inactivation results in overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which promote neoangiogenesis (16-18). This process substantially contributes to the development and progression of RCC. At present, several targeting drugs have been approved both in the USA and in Europe for the treatment of mRCC:

- Sorafenib (Nexavar®)
- Sunitinib (Sutent®)
- Bevacizumab (Avastin®) combined with IFN-α
- Pazopanib (Votrient®)
- Temsirolimus (Torisel®)
- Everolimus (Afinitor®)
- Axitinib (Inlyta®)

New agents targeting angiogenesis are under investigation, as well as combinations of these new agents with each other or with cytokines. One of the new agents targeting angiogenesis, tivozanib, has been investigated in a phase III trial and is currently not approved. Evidence-based data for this drug are presented below. Most published trials have selected for clear cell carcinoma subtypes, and consequently no evidence-based
recommendations can be given for non-clear cell subtypes.

In the major phase III trials leading to registration of the approved targeted agents, patients were stratified according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk model, as published in 2002 (3) (Table 10). Since the MSKCC criteria were established in the era of cytokines, an international database consortium has established and validated a risk model (the Database Consortium Model, DCM) which may yield a more accurate prognosis for patients treated in the era of targeted therapy. In the DCM, neutrophilia and thrombocytosis are added to the MSKCC risk factors. By contrast, lactate dehydrogenase (LDH) is omitted from the factors associated with the prognosis (19). The DCM has recently been used to establish data on conditional survival that can be used to counsel patients (20). The DCM has been validated and compared with the risk model of the Cleveland Clinic Foundation (CCF), the French model, MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The DCM showed a concordance level of 0.66, which did not differ from the other models, indicating that a ceiling has been reached for clinical risk models for predicting the prognosis based solely on clinical factors. However, the reported versus predicted number of deaths at 2 years was most similar in the DCM in comparison with the other models (21). The DCM has been externally validated for use in the era of targeted therapy (21).

Table 11: Median overall survival and percentage of patients surviving 2 years treated in the era of targeted therapy per DCM risk group, based on the publications by Heng et al. (19,21)

<table>
<thead>
<tr>
<th>Database Consortium Model ***</th>
<th>Patients**</th>
<th>Median OS* (months)</th>
<th>2-y OS (95% CI) **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>157</td>
<td>43.2</td>
<td>75% (65-82%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>440</td>
<td>22.5</td>
<td>53% (46-59%)</td>
</tr>
<tr>
<td>Poor</td>
<td>252</td>
<td>7.8</td>
<td>7% (2-16%)</td>
</tr>
</tbody>
</table>

* Based on (21); ** based on (19); CI = confidence intervals; OS = overall survival.

7.3.1 Tyrosine kinase inhibitors

7.3.1.1 Sorafenib

Sorafenib is an oral multikinase inhibitor with activity against Raf-1 serine/threonine kinase, B-Raf, vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase 3 (FLT-3), and c-KIT. A phase III trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. The trial reported a 3-month improvement in progression-free survival in favor of sorafenib (22). Survival appears to improve in patients crossed over from placebo to sorafenib treatment (23).

7.3.1.2 Sunitinib

Sunitinib is an oxindol tyrosine kinase (TK) inhibitor. It selectively inhibits PDGFR, VEGFR, c-KIT, and FLT-3 and has antitumour and anti-angiogenic activity. Phase II trials with sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response in 34-40% of patients and stable disease > 3 months in 27-29% of patients (24).

In a pivotal phase III trial of first-line monotherapy comparing treatment with sunitinib versus IFN-α, sunitinib achieved a longer progression-free survival than IFN-α (11 versus 5 months; P = 0.000001). The results suggested that monotherapy with IFN-α was inferior to sunitinib in low-risk and intermediate-risk patients with mRCC (25). The overall survival was 26.4 and 21.8 months in the sunitinib and IFN-α arms, respectively (P = 0.05) (25). In patients crossed over from IFN-α to sunitinib (n = 25), median survival times were 26.4 versus 20.0 months for sunitinib and IFN-α, respectively (P = 0.03). In patients who did not receive any post-study treatment, the median overall survival reached 28.1 months in the sunitinib group versus 14.1 months in the IFN-α group (P = 0.003).

In a recent randomised phase II trial including 292 patients, sunitinib 50 mg/day (4 weeks on / 2 weeks off) was compared with a continuous uninterrupted dosage of sunitinib 37.5 mg/day in patients with metastatic clear cell renal carcinoma (26). The median time to progression with sunitinib 50 mg (4/2) (n = 146) was 9.9 months, compared with 7.1 months with 37.5 mg/day continuous dosing (n = 146). The overall response rate was 32% for 50 mg (4/2) versus 28% for 37.5 mg continuous dosing. No significant differences were observed with regard to overall survival (23.1 vs. 23.5 months; P = 0.615), commonly reported adverse events, or patient-reported kidney cancer symptoms. Because of the statistically nonsignificant but numerically longer time to progression with the standard 50 mg (4/2) dosage, the authors recommended adherence to this regimen.
7.3.1.3 Pazopanib
Pazopanib is an oral angiogenesis inhibitor that targets VEGFR, PDGFR, and c-KIT. In a prospective randomized trial of pazopanib versus placebo in treatment-naive mRCC patients and cytokine-treated patients, there was a significant improvement in the progression-free survival and tumour response (9.2 vs 4.2 months) (27). The trial showed significant results that established pazopanib as a first-line option. Since the initial phase III study involved a substantially smaller number of patients than in phase III studies of other targeted agents, the recommendation was to use pazopanib as second option in first-line treatment. Recently, the results of a randomized phase III non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) showed no significant differences in the outcome parameters, with different toxicity profiles for the two drugs. With a very short follow-up period, these data are not yet mature, particularly with regard to remission. One major shortcoming of the COMPARZ trial is the fact that the study recruited almost one-third of its patients in Asia. Given the fact that there are ethnic differences in side effect profiles, the overall assessment of this trial remains unstable and further interpretation of any subgroups is almost impossible. Full publication is expected, but COMPARZ has established pazopanib as a first-line treatment option.

7.3.1.4 Axitinib
Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3 that blocks VEGFR receptors at subnanomolar drug concentrations with minimal inhibition of other targets. It has a short half-life. In the AXIS trial (a randomized phase III trial of axitinib versus sorafenib in patients in whom previous cytokine treatment or targeted agents had failed), the sample size calculation was based on a 40% improvement in the median progression-free survival PFS from 5 months to 7 months in patients randomly assigned to receive axitinib (28). Sorafenib was chosen as the comparator because at the time the trial was designed there was no standard for second-line treatment after failure of a previous VEGF targeted therapy. With 723 patients included, the overall median progression-free survival was 6.7 months for patients in the axitinib group in comparison with 4.7 months for those in the sorafenib group (hazard ratio [HR] 0.67; 95% CI, 0.54 to 0.81). However, the difference in PFS was greatest in the patients in whom cytokine treatment had failed. For those in whom sunitinib had failed (n = 194 axitinib and n = 195 sorafenib), axitinib led to a PFS of 4.8 months (95% CI, 4.5 to 6.4) versus 3.4 months (95% CI, 2.6 to 4.7) for sorafenib.

In the AXIS trial, axitinib showed greater than or equal to grade 3 toxicity for diarrhea in 11%, hypertension in 16%, and fatigue in 11%. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21%. Overall survival (OS) was a secondary end point of the trial, but these data were not mature at the time of publication. However, since crossover was not allowed in this trial comparing two active VEGFR inhibitors, the data have in the meantime been analyzed and showed no significant differences between axitinib and sorafenib in second-line treatment (29).

7.3.1.5 Tivozanib
Tivozanib is an oral selective tyrosine kinase inhibitor targeting all three VEGF receptors. It has a long half-life. Tivozanib showed activity and tolerability in a phase II discontinuation trial. The overall response rate was 24% (95% CI, 19% to 30%), and the median PFS was 11.7 months (95% CI, 8.3 to 14.3 months) in the trial population. The most common grade 3 and 4 treatment-related adverse event was hypertension (12%) (30). The results of a phase III trial of tivozanib versus sorafenib in treatment-naive mRCC patients or those having received one prior systemic treatment excluding VEGF targeted therapy or mTOR inhibitors were reported at the American Society of Clinical Oncology (ASCO) meeting in 2012, and full publication is pending. For the 70% treatment-naive patients enrolled, the median PFS was 12.7 months for tivozanib versus 9.1 months for sorafenib (HR 0.756; 95% CI, 0.580 to 0.985). For all patients, the objective response rates were 33% for tivozanib versus 23% for sorafenib. The most common adverse events (AEs) for tivozanib (all grades / ≥ grade 3) were hypertension (46%/26%), diarrhea (22%/2%), fatigue (18%/5%), and neutropenia (10%/2%) (31). Full publication of this study is pending. If approved, tivozanib might be a tyrosine kinase inhibitor with effectiveness not inferior to that of sorafenib, as apparent in the groups of patients tested.

7.3.2 Monoclonal antibody against circulating VEGF
7.3.2.1 Bevacizumab monotherapy and combined with interferon alpha
Bevacizumab is a humanized monoclonal antibody that binds isoforms of VEGF-A. Bevacizumab 10 mg/kg every 2 weeks in patients refractory to immunotherapy was associated with an increase in the overall response (10%) and in the progression-free survival in comparison with placebo (27). A double-blind phase III trial (AVOREN) (n = 649) in patients with mRCC compared bevacizumab + IFN-α with IFN-α monotherapy (7). The median overall response was 31% in the bevacizumab + IFN-α group versus 13% in the group receiving only IFN-α (P < 0.0001). The median progression-free survival increased significantly from 5.4 months with IFN-α to 10.2 months with bevacizumab + IFN-α (P < 0.0001), but only in low-risk and intermediate-risk patients. No benefit was seen in high-risk patients. In a recent update, the median OS in the AVOREN trial, which allowed
crossover after progression, was 23.3 months for bevacizumab-IFN-α versus 21.3 months for IFN-α alone (P < 0.336) (32).

A similarly designed trial (CALGB 90206), including 732 patients (33,34), of bevacizumab (10 mg/kg intravenously every 2 weeks) plus IFN (9 million units subcutaneously three times weekly) versus IFN (9 million units subcutaneously three times weekly) showed a median PFS of 8.5 months for the combination versus 5.2 months for IFN-α alone. The median OS with a crossover design was 18.3 months for the combination versus 17.4 months for IFN-α alone. Bevacizumab plus IFN-α had a higher objective response rate (ORR) in comparison with IFN (25.5%: 95% CI, 20.9% to 30.6%; vs. 13.1%: 95% CI, 9.5% to 17.3%; P < 0.0001). The overall toxicity was greater for bevacizumab plus IFN-α, with significantly more grade 3 hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%), and proteinuria (13% vs. 0%).

7.3.3 Mammalian target of rapamycin (mTOR) inhibitors

7.3.3.1 Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR) (35). Patients with high-risk mRCC were randomly assigned in a phase III trial (NCT00065468) to receive first-line treatment with temsirolimus or IFN-α monotherapy, or a combination. In the temsirolimus group, the overall survival was 10.9 months versus 7.3 months in the IFN-α group (P < 0.0069). However, the overall survival in the temsirolimus + IFN-α group was not significantly improved (9).

7.3.3.2 Everolimus

Everolimus is an oral mTOR inhibitor. A phase III study (RECORD-1) compared everolimus plus best supportive care (BSC) versus placebo plus BSC in patients in whom previous anti-VEGFR treatment had failed. The median progression-free survival was 4 months with everolimus versus 1.9 months with placebo (P < 0.001). In the RECORD-1 trial, 124 patients (46%) had received sunitinib as the only previous systemic treatment, with a PFS of 4.0 months (95% CI, 3.7 to 5.5 months). Comparison with the AXIS data is complicated by the fact that in the RECORD-1 trial, 53% of the patients with progression after previous targeted therapy had at least more than one previous treatment, often cytokines prior to tyrosine kinase inhibitors (TKIs). In addition, the PFS analysis in this trial was not specifically carried out for previous sunitinib treatment (16,36).

7.3.4 Sequencing targeted therapy

Currently, no recommendations can be given as to the best sequence of targeted therapy. The AXIS trial is the only recent randomized phase III superiority trial comparing two TKIs after failure of a prior TKI. The results and interpretation are described under 7.3.1.3 above. For the subgroup of patients treated previously with sunitinib, the difference in PFS did not reach statistical significance for axitinib versus sorafenib, and no difference in the OS was observed. Randomized phase III trials investigating the safety and efficacy of sorafenib followed by sunitinib versus sunitinib followed by sorafenib (SWITCH-I) and sequential pazopanib and sorafenib versus sorafenib and pazopanib (SWITCH-II) are ongoing.

7.3.5 Combination of targeted agents

No recommendations can be made. At present, there have been no phase III trials reporting on a combination of two targeted agents versus monotherapy with a targeted agent. A previous randomised phase II study reported unacceptable toxicity (37). The TORAVA trial showed that the toxicity of a combination of temsirolimus and bevacizumab was much greater than anticipated and that it limited treatment continuation over time in comparison with either standard treatment with sunitinib or bevacizumab and IFN-α. In addition, clinical activity was low in comparison with the benefit expected from sequential use of each targeted therapy. This combination has not been further recommended or investigated. In a nonrandomized phase II trial, the combination of everolimus with bevacizumab was found to be effective with acceptable toxicity, except for grade 3/4 proteinuria in 25% of the patients (38). A randomised phase II trial of everolimus in combination with bevacizumab and IFN-α versus IFN-α alone is ongoing.

7.3.6 Non-clear cell renal cancer

No recommendations can be made at present. No phase III trials on systemic treatment of patients with non-clear cell carcinoma have been reported. A nonrandomized phase II trial in patients with papillary renal cancer who were treated with foretinib, a dual MET/VEGFR2 inhibitor, reported activity and acceptable toxicity with high response rates in patients with germline MET mutations (39). Patients should be treated in the framework of clinical trials. If a trial is not available, a decision can be made in consultation with the patient to perform treatment in line with clear cell renal cell carcinoma.
<table>
<thead>
<tr>
<th>RCC type</th>
<th>MSKCC risk group (3)</th>
<th>1st-line therapy*</th>
<th>2nd-line therapy†</th>
<th>3rd-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>Favourable or intermediate</td>
<td>• Sunitinib [1b]</td>
<td>After prior TKI:</td>
<td>• Temsirolimus [1b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IFN-α + bevacizumab [1b]</td>
<td></td>
<td>• Everolimus after prior TKI(s) [1b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib ‡ [1b]</td>
<td></td>
<td>• Sorafenib [1b]</td>
</tr>
<tr>
<td></td>
<td>In selected patients:</td>
<td>• IFN-α [1b]</td>
<td></td>
<td>• Axitinib [1b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High-dose IL-2 [1b]</td>
<td></td>
<td>• Pazopanib [1b]</td>
</tr>
<tr>
<td></td>
<td>Poor ¶</td>
<td>• Temsirolimus [1b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-clear cell</td>
<td>Favourable Intermediate §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor §</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IFN-α = interferon alpha; MSKCC = Memorial Sloan-Kettering Cancer Center; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

* Doses: IFN-α 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for a period of 4 weeks, followed by 2 weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication.

† Listed in the order of data quality.
‡ Initial phase III study; involved a substantially smaller number of patients than in phase III studies of other targeted agents.
§ No standard treatment available. Patients should be treated in the framework of clinical trials. If a trial is not available, a decision can be made in consultation with the patient to perform treatment in line with clear cell renal cell carcinoma.
¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC (3) risk plus metastases in multiple organs.

7.3.7 Conclusions

| LE |
|-----------------------------|---|
| Tyrosine kinase inhibitors (TKIs) increase the progression-free survival and/or overall survival as both first-line and second-line treatments for mRCC. | 1b |
| Sorafenib has proven efficacy as a second-line treatment after failure of cytokine therapy or in patients unfit for cytokines. | 1b |
| Axitinib has proven efficacy and superiority as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib. | 1b |
| Sunitinib is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk tumours. | 1b |
| Sunitinib at 50 mg (4/2) or 37.5 mg continuous dosing did not show significant differences in relation to overall survival, time to progression, response rate, or safety. | 1b |
| A combination of bevacizumab and IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk tumours. | 1b |
| Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients. | 1b |
| Pazopanib is not inferior to sunitinib in good-risk and intermediate-risk clear cell mRCC patients. | 1b |
| Temsirolimus monotherapy in poor-risk mRCC patients is more effective than IFN-α or temsirolimus + IFN-α. | 1b |
| Everolimus prolongs the progression-free survival in patients in whom treatment with one or two TKIs has failed in second-line or later treatments. | 1b |
The role of the new drugs is still under development and combination studies are ongoing. To date, no data are available indicating whether the new agents have a curative effect. These agents appear promising for stabilizing mRCC for a prolonged period of time. However, this promise has to be balanced against their toxicity profile and the patient’s quality of life. Anti-angiogenic monotherapy and its sequences have become the standard of care in mRCC treatment.

7.3.8 Recommendations for systemic therapy for mRCC

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib is recommended as first-line therapy in favourable-risk and intermediate-risk patients.</td>
<td>A</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α is recommended as first-line therapy in favourable-risk and intermediate-risk patients.</td>
<td>A</td>
</tr>
<tr>
<td>Sorafenib is recommended as a second-line treatment for mRCC after cytokine failure.</td>
<td>A</td>
</tr>
<tr>
<td>Pazopanib is recommended as first-line or after cytokine failure in favourable-risk and intermediate-risk patients.</td>
<td>A</td>
</tr>
<tr>
<td>Temsirolimus is recommended as first-line treatment in poor-risk patients.</td>
<td>A</td>
</tr>
<tr>
<td>Everolimus is recommended as second-line treatment after failure of tyrosine kinase inhibitors.</td>
<td>A</td>
</tr>
<tr>
<td>Axitinib is recommended as second-line treatment after failure of cytokines or tyrosine kinase inhibitors.</td>
<td>A</td>
</tr>
</tbody>
</table>

7.4 References


8. FOLLOW-UP AFTER RADICAL OR PARTIAL NEPHRECTOMY OR ABLATIVE THERAPIES FOR RCC

8.1 Introduction
Surveillance after treatment for renal cell carcinoma (RCC) allows the urologist to monitor or identify:
• Postoperative complications
• Renal function
• Local recurrence after partial nephrectomy or ablative treatment
• Recurrence in the contralateral or ipsilateral (after partial nephrectomy) kidney
• Development of metastases

The method and timing of examinations have been the subject of many publications. There is no consensus on surveillance after treatment for RCC, and in fact there is no evidence that early versus later diagnosis of recurrences improves survival. However, follow-up is important in order to increase the information about RCC available, and it should be performed by the urologist, who should record the time that has elapsed up to a recurrence or the development of metastases.

Postoperative complications and renal function are readily assessed by the patient’s history, physical examination, and measurement of serum creatinine and estimated glomerular filtration rate (eGFR). Repeated long-term monitoring of eGFR is indicated if there is impaired renal function before surgery, or postoperative deterioration. Renal function (1,2) and non-cancer survival (3-5) can be optimized by carrying out nephron-sparing surgery whenever possible for T1 and T2 tumours (6) (LE: 3). Tumour-bed recurrence is rare (2.9%), but early diagnosis is useful, since the most effective treatment is cytoreductive surgery (7,8). Recurrence in the contralateral kidney is also rare (1.2%) and is related to positive margins, multifocality, and grade (9) (LE: 3).

The reason for carrying out surveillance is to identify local recurrences or metastases at an early stage. This is particularly important with ablative therapies such as cryotherapy and radiofrequency ablation (RFA). Although the local recurrence rate is higher than after conventional surgery, the patient may still be cured using repeat ablative therapy or radical nephrectomy (10) (LE: 3). In metastatic disease, more extended tumour growth can limit the opportunity for surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, in clinical trials, an early diagnosis of tumour recurrence may enhance the efficacy of a systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?
Intensive radiological surveillance for all patients is unnecessary. For example, the outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify the follow-up, taking into account the risk of a recurrence or metastases developing. Although there is no randomized evidence, there have been large studies examining prognostic factors with long follow-up periods, from which some conclusions can be drawn (11-13) (LE: 4):

- The sensitivity of chest radiography for small metastases is poor and ultrasound has limitations. Surveillance should therefore not be based on these imaging modalities. With low-risk tumours, the surveillance intervals should be adapted relative to radiation exposure and benefit. Magnetic resonance imaging (MRI) can be used to reduce radiation exposure.
- When the risk of relapse is intermediate or high, computed tomography (CT) of the chest and abdomen is the investigation of choice, although the significant morbidity associated with the radiation exposure involved in repeated CT scans should be taken into account (14).
- Surveillance should also include clinical evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography (PET) and PET-CT as well as bone scintigraphy are not the standard of care in RCC surveillance, due to their limited specificity and sensitivity.

Depending on the availability of effective new treatments, more strict follow-up schedules may be required, particularly as there is a higher local recurrence rate after cryotherapy and RFA. There is controversy over the optimal duration of follow-up. Some argue that follow-up with imaging is not cost-effective after 5 years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with nephron-sparing surgery if the tumours are detected when small. In addition, for tumours < 4 cm in size, there is no difference between partial and radical nephrectomy with regard to recurrences during the follow-up (15) (LE: 3).

Several authors - notably Kattan, Liebovich, UCLA, and Karakiewicz (16-19) - have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death. These systems have been compared and validated (20) (LE: 2). Using prognostic variables,
several stage-based surveillance regimens have been proposed (21,22), but these do not include ablative therapies. A postoperative nomogram is available for estimating the likelihood of freedom from recurrence at 5 years (23). Most recently, a preoperative prognostic model based on age, symptoms, and TNM staging has been published and validated (24) (LE: 3). There is therefore a need for a surveillance algorithm for monitoring patients after treatment for RCC, recognizing not only the patient risk profile, but also the efficacy of the treatment given (Table 13).

Table 13: Proposed algorithm for surveillance following treatment for RCC, taking into account patient risk profile and treatment efficacy

<table>
<thead>
<tr>
<th>Risk profile</th>
<th>Treatment</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>RN/PN only</td>
<td>US CT US CT US CT Discharge</td>
</tr>
<tr>
<td>Intermediate</td>
<td>RN/PN/ cryo/RFA</td>
<td>CT US CT US CT CT CT once every 2 years</td>
</tr>
<tr>
<td>High</td>
<td>RN/PN/ cryo/RFA</td>
<td>CT CT CT CT CT CT CT once every 2 years</td>
</tr>
</tbody>
</table>

Cryo = cryotherapy; CT = computed tomography of chest and abdomen, or MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; US = ultrasound of abdomen, kidneys and renal bed.

8.3 Conclusions and recommendations for surveillance following radical or partial nephrectomy or ablative therapies for RCC

**Conclusion**
The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable.

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance after treatment for RCC should be based on a patient’s risk factors and the type of treatment delivered.</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>For low-risk disease, CT/MRI can be used infrequently.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>In the intermediate-risk group, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>In high-risk patients, the follow-up examinations should include routine CT/MRI scans.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>There is an increased risk of intrarenal recurrences in larger-size (&gt; 7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin. Follow-up should be intensified in these patients.</td>
<td></td>
<td>C</td>
</tr>
</tbody>
</table>

8.4 References


9. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ACKD  acquired cystic kidney disease
AML   Angiomyolipoma
5FU   5-fluorouracil
BSC   best supportive care
CaIX  carbonic anhydrase IX
cRCC  clear cell renal carcinoma
chRCC chromophobe renal cell carcinoma
CT    computed tomography
ESKD  end-stage kidney disease
FLT-3 FMS-like tyrosine kinase 3
GR    grade of recommendation
HIF   hypoxia inducible factor
HIFU  high-intensity focused ultrasound
HU    Hounsfield unit
IFN-alpha interferon-alpha
IL-2   interleukin-2
LE    level of evidence
MESTK mixed epithelial and stromal tumour of the kidney
mRCC  metastatic renal cell carcinoma
MRI   magnetic resonance imaging
mTOR  mammalian target of rapamycin
NSS   nephron-sparing surgery
PA    predictive accuracy
pRCC  papillary renal cell carcinoma
RCC   renal cell carcinoma
PDGF  platelet-derived growth factor
PDGFR platelet-derived growth factor receptor
PET   positron emission tomography
PTEN  phosphatase and tensin homolog
REST  Renal epithelial and stromal tumours
RF    radiofrequency
RFA   radiofrequency ablation
SAE   selective arterial embolisation
TFE3 transcription factor E3
TK    tyrosine kinase
TKI   Tyrosine kinase inhibitors
TNM   Tumour Node Metastasis
US    abdominal ultrasound
VEGF  vascular endothelial growth factor
VEGFR vascular endothelial growth factor receptor
VHL   von Hippel-Lindau
WHO   World Health Organization

Conflict of interest
All members of the Renal Cell Cancer working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Testicular Cancer

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11. ABBREVIATIONS USED IN THE TEXT
1. BACKGROUND

Testicular cancer represents between 1% and 1.5% of male neoplasms and 5% of urological tumours in general, with 3-10 new cases occurring per 100,000 males per year in Western society (1-3). An increase in the incidence of testicular cancer was detected during the 1970s and 1980s, particularly in Northern European countries, and there is a clear trend towards an increased testicular cancer incidence in the last 30 years in the majority of the industrialised countries in North America, Europe and Oceania, although surprising differences in incidence rates are seen between neighbouring countries (4,5). Data from the Surveillance Epidemiology and End Results (SEER) Program during the years 1973 to 1998 show a continuing increased risk among Caucasian men in the USA only for seminoma (6).

Only 1-2% of cases are bilateral at diagnosis. The histological type varies, although there is a clear predominance (90-95%) of germ cell tumours (1). Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma. Familial clustering has been observed, particularly among siblings (7).

Genetic changes have been described in patients with testicular cancer. A specific genetic marker (an isochromosome of the short arm of chromosome 12 – i(12p) – has been described in all histological types of germ cell tumours (7)). Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, TIN) shows the same chromosomal changes, and alterations in the p53 locus have been found in 66% of cases of testicular TIN (8).

A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers such as M2A, C-KIT and OCT4/NANOG) is probably responsible for the development of TIN and germ cell neoplasia. There is overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma (9,10). Continued genome-wide screening studies and gene expression analysis data suggest testis cancer specific gene mutations on chromosomes 4, 5, 6 and 12 (namely expressing SPRY4, kit-Ligand and Synaptopodin) (11-13).

Epidemiological risk factors for the development of testicular tumours are: a history of cryptorchidism or undescended testis (testicular dysgenesis syndrome), Klinefelter’s syndrome, familial history of testicular tumours among first-grade relatives (father/brothers), the presence of a contralateral tumour or TIN, and infertility (14-20). Tallness was associated with a risk of germ cell cancer, although further confirmation is needed (21,22).

Testicular tumours show excellent cure rates. The main factors contributing to this are: careful staging at the time of diagnosis; adequate early treatment based on chemotherapeutic combinations, with or without radiotherapy and surgery; and very strict follow-up and salvage therapies. In the past decades, a decrease in the mean time delay to diagnosis and treatment has been observed (23). In the treatment of testicular cancer, the choice of centre where this treatment is going to be administered is of utmost importance. Although early stages can be successfully treated in a non-reference centre, the relapse rate is higher (24). In poor prognosis non-seminomatous germ cell tumours, it has been shown that overall survival within a clinical trial depended on the number of patients treated at the participating centre (worse < 5 patients enrolled) (25). In the same context, the frequency of post-chemotherapy residual tumour resection is associated with perioperative mortality and overall survival (26,27).

1.1 Methodology

A multidisciplinary team of urologists, medical oncologists, radiotherapists and a pathologist were involved in producing this text, which is based on a structured review of the literature from January 2008 until December 2010 for both the germ cell tumour and non-germ cell sections. Also, data from meta-analyses, Cochrane evidence, and the recommendations of the European Germ Cell Cancer Collaborative Group (EGCCCG) Meeting in Amsterdam in November 2006 have been included (28-31). A validation scoping search with a focus on the available level 1 (systematic reviews and meta-analyses of randomised controlled trials [RCTs]) data was carried out in Medline and Embase on the Dialog-Datastar platform, covering a time frame of 2009 through September 2010. The searches used the controlled terminology of the respective databases. Both MesH and EMTREE were analysed for relevant terms.

References used in the text have been assessed according to their level of scientific evidence (LE) (Table 1), and guideline recommendations have been graded (GR) (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (32). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.
Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (32).

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence – although a very important factor – has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (33-35).

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (32).

1.2 Publication history

The content of these guidelines has not changed with respect to the previous version, but for assessing the currency of the references used; replacing old references by more recent publications. This resulted in the inclusion of 5 new references. No changes in the recommendations were made. The European Association of Urology (EAU) published a first guideline on Testicular Cancer in 2001 with limited updates achieved in 2002, 2004, a major update in 2005, followed by limited updates in 2008, 2009 and 2010. Review papers have been published in the society scientific journal European Urology, the latest version dating to 2011 (36). Since 2008, the Testicular Guidelines contain a separate chapter on testicular stromal tumours.

A quick reference document presenting the main findings of the Testicular Cancer guidelines is also available, following the large text updates. All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.3 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/.
2. PATHOLOGICAL CLASSIFICATION

The recommended pathological classification (modified from the 2004 version of the World Health Organization [WHO] guidance) is shown below (37).

1. Germ cell tumours
   - Intratubular germ cell neoplasia, unclassified type (IGCNU)
   - Seminoma (including cases with syncytiotrophoblastic cells)
   - Spermatocytic seminoma (mention if there is sarcomatous component)
   - Embryonal carcinoma
   - Yolk sac tumour
   - Choriocarcinoma
   - Teratoma (mature, immature, with malignant component)
   - Tumours with more than one histological type (specify percentage of individual components).

2. Sex cord/gonadal stromal tumours
   - Leydig cell tumour
   - Malignant Leydig cell tumour
   - Sertoli cell tumour
     - lipid-rich variant
     - sclerosing
     - large cell calcifying
   - Malignant Sertoli cell tumour
   - Granulosa cell tumour
     - adult type
     - juvenile type
   - Thecoma/fibroma group of tumours
   - Other sex cord/gonadal stromal tumours
     - incompletely differentiated
     - mixed
   - Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma).

3. Miscellaneous non-specific stromal tumours
   - Ovarian epithelial tumours
   - Tumours of the collecting ducts and rete testis
   - Tumours (benign and malignant) of non-specific stroma.

3. DIAGNOSIS

3.1 Clinical examination
Testicular cancer generally affects young men in their third or fourth decade of life. It normally appears as a painless, unilateral mass in the scrotum or the casual finding of an intrascrotal mass (38). In approximately 20% of cases, the first symptom is scrotal pain, and up to 27% of patients with testicular cancer may have local pain (1).

Occasionally, trauma to the scrotum may reveal the presence of a testicular mass. Gynaecomastia appears in 7% of cases and is more common in non-seminomatous tumours. Back and flank pain are present in about 11% of cases (1).

In about 10% of cases, a testicular tumour can mimic an orchiepididymitis, with consequent delay of the correct diagnosis (1,2). Ultrasound (US) must be performed in any doubtful case. Physical examination reveals the features of the mass and must always be carried out in conjunction with a general examination in order to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. A correct diagnosis must be established in all patients with an intrascrotal mass (39).

3.2 Imaging of the testis
Currently, diagnostic US serves to confirm the presence of a testicular mass and to explore the contralateral testis. Its sensitivity in detecting a testicular tumour is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular (40). Ultrasound is an inexpensive test and should be performed even
in the presence of a testicular tumour that is clinically evident (41).

Ultrasound of the testis has to be performed in young men without a palpable testicular mass who have retroperitoneal or visceral masses or elevated serum chorionic gonadotrophin (hCG) or AFP or in men consulting for fertility problems (42-44).

Ultrasound may be recommended in the follow up of patients at risk (45), when other risk factors than microlithiasis are present (e.g. size < 12 ml or atrophy, inhomogeneous parenchyma). Solely, the presence of microlithiasis is not an indication for a regular scrotal US (46).

In the absence of other risk factors (< 12 ml (atrophy), maldescent testis), testicular microlithiasis is not an indication for biopsy or further US screening (45,47).

Magnetic resonance imaging (MRI) offers higher sensitivity and specificity than US for diagnosing tumours (40,48). MRI of the scrotum offers a sensitivity of 100% and a specificity of 95-100% (49), but its high cost does not justify its use for diagnosis.

3.3 Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging (50). The following markers should be determined:

- **AFP** (produced by yolk sac cells);
- **hCG** (expression of trophoblasts);
- **LDH** (lactate dehydrogenase).

In all tumours, there is an increase in these markers in 51% of cases of testicular cancer (23,38). Alphafetoprotein increases in 50-70% of patients with non-seminomatous germ cell tumour (NSGCT), and a rise in hCG is seen in 40-60% of patients with NSGCT. About 90% of non-seminomatous tumours present with a rise in one or two of the markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease (51,52).

Lactate dehydrogenase is a less specific marker, and its concentration is proportional to tumour volume. Its level may be elevated in 80% of patients with advanced testicular cancer (51). It should be noted that negative marker levels do not exclude the diagnosis of a germ cell tumour. Other markers studied include placental alkaline phosphatase (PLAP), which may be of value in monitoring patients with pure seminoma. Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research studies. Measurement of serum AFP, hCG and LDH is mandatory, while that of PLAP is optional.

3.4 Inguinal exploration and orchidectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorisation of the testis within its tunics. Orchidectomy with division of the spermatic cord at the internal inguinal ring must be performed if a malignant tumour is found. If the diagnosis is not clear, a testicular biopsy (an enucleation of the intraparenchymal tumour) is taken for frozen (fresh tissue) section histological examination.

In cases of disseminated disease and life-threatening metastases, it is current practice to start with up-front chemotherapy, and orchidectomy may be delayed until clinical stabilisation has occurred.

3.5 Organ-sparing surgery

Although organ-sparing surgery is not indicated in the presence of non-tumoural contralateral testis, it can be attempted in special cases with all the necessary precautions.

In synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed when the tumour volume is less than 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated TIN is high (at least up to 82%), and all patients must be treated with adjuvant radiotherapy (16-20 Gy) at some point (53).

Infertility will result after radiotherapy and the risk of long-term Leydig cell insufficiency after radiotherapy of a solitary testis is increased (54). Radiation treatment may be delayed in fertile patients who wish to father children. The option must be carefully discussed with the patient and surgery performed in a centre with experience (55,56).
3.6 Pathological examination of the testis

Mandatory pathological requirements:

- Macroscopic features: side, testis size, maximum tumour size, and macroscopic features of epididymis, spermatic cord, and tunica vaginalis.
- Sampling: a 1 cm² section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area.
- Microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2004 (37):
  - presence or absence of peri-tumoural venous and/or lymphatic invasion;
  - presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion;
  - presence or absence of intratubular germ cell neoplasia (TIN) in non-tumour parenchyma intratubular germ cell neoplasia.
- pT category according to Tumour Node Metastasis (TNM) 2009 (57).
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Advisable immunohistochemical markers, in cases of doubt, are:

- in seminoma: cytokeratins (CAM 5.2), PLAP, c-kit;
- in intratubular germ cell neoplasia: PLAP, c-kit;
- other advisable markers: chromogranine A (Cg A), Ki-1 (MIB-1).

3.7 Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

Contralateral biopsy has been advocated to rule out the presence of TIN (58). Although this is routine policy in some countries, the low incidence of TIN and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) (59,60), the morbidity of TIN treatment, and the fact that most of these metachronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients (61-63). It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be offered to high-risk patients for contralateral TIN with a testicular volume of less than 12 mL, a history of cryptorchidism, or poor spermatogenesis (Johnson Score 1-3). A contralateral biopsy is not necessary in patients older than 40 years (64-69). A double biopsy is preferred to increase sensitivity (66).

Once TIN is diagnosed, local radiotherapy (16-20 Gy in fractions of 2 Gy) is the treatment of choice in solitary tests. Because this may produce infertility, the patient must be carefully counselled before treatment commences (61,70). In addition to infertility, Leydig cell function and testosterone production may be impaired long-term following radiotherapy for TIN (55). Radiation treatment may be delayed in fertile patients who wish to father children (66). Patients have to be informed that a testicular tumour may arise in spite of a negative biopsy (71).

If TIN is diagnosed and the contralateral testis is healthy, the options for management are orchidectomy or close observation (with a risk of 50% in 5 years to develop a testicular cancer) (72).

3.8 Screening

Although there are no surveys proving the advantages of screening programmes, it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, self physical examination by the affected individual is advisable.

4. STAGING

4.1 Diagnostic tools

To determine the presence of metastatic or occult disease, the half-life kinetics of serum tumour markers must be assessed, the nodal pathway must be screened, and the presence of visceral metastases ruled out. Consequently, it is mandatory to assess:

- the post-orchidectomy half-life kinetics of serum tumour markers;
- the status of retroperitoneal and supraclavicular lymph nodes, and the liver;
- the presence or absence of mediastinal nodal involvement and lung metastases;
- the status of brain and bone, if any suspicious symptoms are present.
The mandatory tests are:
- serial blood sampling;
- abdominopelvic and chest computed tomography (CT).

### 4.2 Serum tumour markers: post-orchidectomy half-life kinetics

The mean serum half-life of AFP and hCG is 5-7 days and 2-3 days, respectively (51). Tumour markers have to be re-evaluated after orchidectomy to determine half-life kinetics. Marker decline in patients with clinical stage I disease should be assessed until normalisation has occurred. Markers before start of chemotherapy are important to classify the patient according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification. The persistence of elevated serum tumour markers after orchidectomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchidectomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value.

### 4.3 Retroperitoneal, mediastinal and supraclavicular lymph nodes and viscera

Retroperitoneal and mediastinal lymph nodes are best assessed by means of a CT. The supraclavicular nodes are best assessed by physical examination.

Abdominopelvic CT offers a sensitivity of 70-80% in determining the state of the retroperitoneal nodes. Its accuracy depends on the size of the nodes; sensitivity and the negative predictive value increase using a 3 mm threshold to define metastatic nodes in the landing zones (69). Those figures decrease slightly in stages I and II (70,73), with a rate of understaging of 25-30% (74). New generations of CT devices do not seem to improve the sensitivity.

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement (75,76). Again, the main objections to its routine use are its high cost and limited availability. Nevertheless, MRI can be helpful when abdominopelvic CT or ultrasound are inconclusive (75), when CT is contraindicated because of allergy to contrast media, or when the physician or the patient are concerned about radiation dose. MRI is an optional test, and there are currently no indications for its systematic use in the staging of testicular cancer.

A chest CT is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration has to be recommended in all patients with testicular cancer because up to 10% of cases can present with small subpleural nodes that are not visible radiologically (77). A CT has high sensitivity but low specificity (75).

There is no evidence to support the use of the fluorodeoxyglucose-PET (FDG-PET) in the staging of testis cancer (78,79). It is recommended in the follow-up of patients with seminoma with any residual mass at least 6 weeks after chemotherapy in order to decide on watchful waiting or active treatment (80-83). Fluorodeoxyglucose-PET, however, is not recommended in the re-staging of patients with non-seminomatous tumours after chemotherapy (84,85).

Other examinations, such as brain or spinal CT, bone scan or liver ultrasound, should be performed if there is suspicion of metastases to these organs. A CT or MRI of the skull is advisable in patients with NSGCT and multiple lung metastases and poor prognosis IGCCG risk group. Table 3 shows the recommended tests at staging.

**Table 3: Recommended tests for staging at diagnosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
<th>GR</th>
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<tbody>
<tr>
<td>Serum tumour markers</td>
<td>Alpha-fetoprotein</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>hCG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>Abdominopelvic CT</td>
<td>All patients</td>
<td>A</td>
</tr>
<tr>
<td>Chest CT</td>
<td>All patients</td>
<td>A</td>
</tr>
<tr>
<td>Testis ultrasound (bilateral)</td>
<td>All patients</td>
<td>A</td>
</tr>
<tr>
<td>Bone scan</td>
<td>In case of symptoms</td>
<td></td>
</tr>
<tr>
<td>Brain scan (CT/MRI)</td>
<td>In case of symptoms and patients with metastatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disease with multiple lung metastases and high beta-hHG values</td>
<td></td>
</tr>
</tbody>
</table>
Further investigations

<table>
<thead>
<tr>
<th>Fertility investigations:</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone</td>
<td></td>
</tr>
<tr>
<td>LH</td>
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</tr>
<tr>
<td>FSH</td>
<td></td>
</tr>
<tr>
<td>Semen analysis</td>
<td></td>
</tr>
<tr>
<td>Sperm banking should be offered</td>
<td>A</td>
</tr>
</tbody>
</table>

hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; CT = computed tomography; LH = luteinising hormone; FSH = follicle-stimulating hormone.

4.4 Staging and prognostic classifications

The staging system recommended in these guidelines is the 2009 TNM of the International Union Against Cancer (UICC) (Table 4) (57). This includes:

- determination of the anatomical extent of disease;
- assessment of serum tumour markers, including nadir values of hCG, AFP and LDH after orchidectomy (S category);
- clear definition of regional nodes;
- some N-category modifications related to node size.

Table 4: TNM classification for testicular cancer (UICC, 2009, 7th edn [57])

<table>
<thead>
<tr>
<th></th>
<th>pT</th>
<th>Primary tumour¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pTX</td>
<td>Primary tumour cannot be assessed (see note 1)</td>
</tr>
<tr>
<td></td>
<td>pT0</td>
<td>No evidence of primary tumour (e.g. histological scar in testis)</td>
</tr>
<tr>
<td></td>
<td>pTis</td>
<td>Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)</td>
</tr>
<tr>
<td></td>
<td>pT1</td>
<td>Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis</td>
</tr>
<tr>
<td></td>
<td>pT3</td>
<td>Tumour invades spermatic cord with or without vascular/lymphatic invasion</td>
</tr>
<tr>
<td></td>
<td>pT4</td>
<td>Tumour invades scrotum with or without vascular/lymphatic invasion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Regional lymph nodes clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>N3</td>
<td>Metastasis with a lymph node mass more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>pN</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>pN1</td>
<td>Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>pN2</td>
<td>Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour</td>
</tr>
<tr>
<td></td>
<td>pN3</td>
<td>Metastasis with a lymph node mass more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1a</td>
<td>Non-regional lymph node(s) or lung</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>Other sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>S</th>
<th>Serum tumour markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sx</td>
<td>Serum marker studies not available or not performed</td>
</tr>
<tr>
<td></td>
<td>S0</td>
<td>Serum marker study levels within normal limits</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>hCG (mIU/mL)</td>
<td>AFP (ng/mL)</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>S1</td>
<td>&lt; 1.5 x N and</td>
<td>&lt; 5,000 and</td>
</tr>
<tr>
<td>S2</td>
<td>1.5-10 x N or</td>
<td>5,000-50,000 or</td>
</tr>
<tr>
<td>S3</td>
<td>&gt; 10 x N or</td>
<td>&gt; 50,000 or</td>
</tr>
</tbody>
</table>

N indicates the upper limit of normal for the LDH assay.

LDH, lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

According to the 2009 TNM classification, stage I testicular cancer includes the following substages:

**Stage grouping**

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>pTis</th>
<th>N0</th>
<th>M0</th>
<th>S0,SX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>pT1-T4</td>
<td>N0</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IA</td>
<td>pT1</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>pT2 - pT4</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IS</td>
<td>Any patient/TX</td>
<td>N0</td>
<td>M0</td>
<td>S1-3</td>
</tr>
<tr>
<td>Stage II</td>
<td>Any patient/TX</td>
<td>N1-N3</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Any patient/TX</td>
<td>N1</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>N1</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Any patient/TX</td>
<td>N2</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>N2</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any patient/TX</td>
<td>N3</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>N3</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any patient/TX</td>
<td>N1-N3</td>
<td>M0</td>
<td>S2</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S2</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Any patient/TX</td>
<td>N1-N3</td>
<td>M0</td>
<td>S3</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S3</td>
</tr>
<tr>
<td></td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1b</td>
<td>Any S</td>
</tr>
</tbody>
</table>

Stage IA patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchidectomy serum tumour marker levels within normal limits. Marker decline in patients with clinical stage I disease should be assessed until normalisation. Stage IB patients have a more locally invasive primary tumour, but no sign of metastatic disease. Stage IS patients have persistently elevated (and usually increasing) serum tumour marker levels after orchidectomy, which is evidence of subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis). If serum tumour marker levels are declining according to the expected half-life decay after orchidectomy, the patient is usually followed up until normalisation.

In large population-based patient series, 75-80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis (86,87). True stage IS (persistently elevated or increasing serum marker levels after orchidectomy) is found in about 5% of non-seminoma patients. If a staging retroperitoneal lymph node dissection (RPLND) was to be performed in stage IS patients, nearly all patients would be found to have pathological stage II disease (pN+) (1,7,86,88).

In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testis tumour based on identification of some clinical independent adverse factors. This staging system has been incorporated...
into the TNM Classification and uses histology, location of the primary tumour, location, of metastases and prechemotherapy marker levels in serum as prognostic factors to categorise patients into ‘good’, ‘intermediate’ or ‘poor’ prognosis (Table 5) (89).

Table 5: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)*

<table>
<thead>
<tr>
<th>Good-prognosis group</th>
<th>All of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-seminoma (56% of cases)</td>
<td>Testis/retroperitoneal primary</td>
</tr>
<tr>
<td>5-year PFS 89%</td>
<td>No non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>5-year survival 92%</td>
<td>AFP &lt; 1,000 ng/mL</td>
</tr>
<tr>
<td></td>
<td>hCG &lt; 5,000 IU/L (1,000 ng/mL)</td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 1.5 x ULN</td>
</tr>
<tr>
<td>Seminoma (90% of cases)</td>
<td>Any primary site</td>
</tr>
<tr>
<td>5-year PFS 82%</td>
<td>No non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>5-year survival 86%</td>
<td>Normal AFP</td>
</tr>
<tr>
<td></td>
<td>Any hCG</td>
</tr>
<tr>
<td></td>
<td>Any LDH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate prognosis group</th>
<th>Any of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-seminoma (28% of cases)</td>
<td>Testis/retroperitoneal primary</td>
</tr>
<tr>
<td>5 years PFS 75%</td>
<td>No non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>5-year survival 80%</td>
<td>AFP 1,000 - 10,000 ng/mL or</td>
</tr>
<tr>
<td></td>
<td>hCG 5,000 - 50,000 IU/L or</td>
</tr>
<tr>
<td></td>
<td>LDH 1.5 - 10 x ULN</td>
</tr>
<tr>
<td>Seminoma (10% of cases)</td>
<td>Any primary site</td>
</tr>
<tr>
<td>5-year PFS 67%</td>
<td>Non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>5-year survival 72%</td>
<td>Normal AFP</td>
</tr>
<tr>
<td></td>
<td>Any hCG</td>
</tr>
<tr>
<td></td>
<td>Any LDH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poor prognosis group</th>
<th>Any of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-seminoma (16% of cases)</td>
<td>Mediastinal primary</td>
</tr>
<tr>
<td>5-year PFS 41%</td>
<td>Non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>5-year survival 48%</td>
<td>AFP &gt; 10,000 ng/mL or</td>
</tr>
<tr>
<td></td>
<td>hCG &gt; 50,000 IU/L (10,000 ng/mL) or</td>
</tr>
<tr>
<td></td>
<td>LDH &gt; 10 x ULN</td>
</tr>
<tr>
<td>Seminoma</td>
<td>No patients classified as poor prognosis</td>
</tr>
</tbody>
</table>

*Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).
PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

4.5 Prognostic risk factors

Retrospectively, for seminoma stage I, tumour size (≥ 4 cm) and invasion of the rete testis have been identified as predictors for relapse in a pooled analysis (29). However, these risk factors have not been validated in a prospective setting except that the absence of both factors indicated a low recurrence rate (6%) (90).

For non-seminoma stage I, vascular invasion of the primary tumour in blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate, as well as the percentage of embryonal carcinoma, are additional predictors that improve upon the positive and negative predictive value of vascular invasion (91,92).

The significant prognostic pathological risk factors for stage I and clinical risk factors for metastatic disease are listed in Table 6.
Table 6: Prognostic factors for occult metastatic disease in testicular cancer

<table>
<thead>
<tr>
<th></th>
<th>For seminoma</th>
<th>For non-seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological (for stage I)</strong></td>
<td>• Tumour size (&gt; 4 cm)</td>
<td>• Vascular/lymphatic in or peri-tumoural invasion</td>
</tr>
<tr>
<td></td>
<td>• Invasion of the rete testis</td>
<td>• Proliferation rate &gt; 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Percentage of embryonal carcinoma &gt; 50%</td>
</tr>
<tr>
<td><strong>Clinical (for metastatic disease)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Primary location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Elevation of tumour marker levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Presence of non-pulmonary visceral metastasis</td>
<td></td>
</tr>
</tbody>
</table>

4.6 Impact on fertility and fertility-associated issues
Sperm abnormalities are frequently found in patients with testis tumours. Furthermore, chemotherapy and radiation treatment can also impair fertility. In patients in the reproductive age group, pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and FSH levels) should be performed, and semen analysis and cryopreservation should be offered. If cryopreservation is desired, it should preferably be performed before orchidectomy, but in any case prior to chemotherapy treatment (54,93-99).

In cases of bilateral orchidectomy or low testosterone levels after treatment of TIN, life-long testosterone supplementation is necessary (100). Patients with unilateral or bilateral orchidectomy should be offered a testicular prosthesis (101). For more detailed information, the reader is referred to the EAU Male Infertility Guidelines (102).

5. GUIDELINES FOR THE DIAGNOSIS AND STAGING OF TESTICULAR CANCER

<table>
<thead>
<tr>
<th>Testicular US is a mandatory assessment</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

| Orchidectomy and pathological examination of the testis are necessary to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, chemotherapy must be started before orchidectomy. | A |
| Serum determination of tumour markers (AFP, hCG, and LDH) must be performed both before and 5-7 days after orchidectomy for staging and prognostic reasons | A |
| The state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera must be assessed in testicular cancer. | A |

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

6. TREATMENT: STAGE I GERM CELL TUMOURS

6.1 Stage I seminoma
After modern staging procedures, about 15-20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone.

6.1.1 Surveillance
Several prospective non-randomised surveillance studies have been conducted during the past decade, the largest study from Canada with > 1,500 patients (103). Previous analysis from four studies showed an actuarial 5 years’ relapse-free rate of 82.3%. The Princess Margaret Hospital series (n = 1559) showed an overall relapse rate in unselected patients of 16.8%. The actuarial relapse rate is in the order of 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes (104).
In patients with low risk (tumour size ≤ 4 cm and no rete testis invasion) the recurrence under surveillance is as low as 6% (105).

Chemotherapy, according to the IGCCCG classification, is a possible treatment for seminoma relapse under surveillance. However, 70% of patients with relapse are suitable for treatment with radiotherapy alone because of small volume disease at the time of recurrence. Patients who relapse again can be effectively treated with chemotherapy (106).

The overall cancer-specific survival rate reported under surveillance performed by experienced centres is 97-100% for seminoma stage I (104,106). The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchidectomy. This compares with the very low risk of subdiaphragmatic relapse after adjuvant radiotherapy.

There is a small but clinically significant risk of relapse more than 5 years after orchidectomy for stage I seminoma, which supports the need for long term surveillance.

6.1.2 Adjuvant chemotherapy
A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC) (MRC TE 19 trial), which compared one cycle of carboplatin (area under curve [AUC] 7) with adjuvant radiotherapy, did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow-up of 4 years (107-109). Therefore, adjuvant carboplatin therapy using a dosage of one course AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma (104,107-109). Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% (110,111), but further experience and long-term observation are needed.

6.1.3 Adjuvant radiotherapy
Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field or to a hockeystick field (para-aortic and ipsilateral iliac nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to 1-3% (112-115). After modern radiotherapy, nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs) (112-115). Based on the results of a large randomised MRC trial, Fossa et al. (112,113) recommended radiotherapy to a PA field as standard treatment for patients with testicular seminoma stage I, T1-T3 and with undisturbed lymphatic drainage. Acute toxicity was reduced and the sperm count within the first 18 months was significantly higher after PA irradiation than after irradiation of the traditional dog-leg field. On the other hand, the relapse rate in the iliac lymph nodes was about 2% (all of them on the right side) after PA and 0% after dog-leg irradiation. Another possible site of failure is in the left renal hilum. PA irradiation should be tailored according to the site of the primary tumour. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

With regard to the irradiation dose, the MRC recently finished a large randomised trial of 20 Gy versus 30 Gy PA radiation in stage I seminoma that showed equivalence for both doses in terms of recurrence rates (113). The rate of severe radiation-induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects are seen in about 5% of patients, and moderate acute GI toxicity in about 60% (112). The main concern surrounding adjuvant radiotherapy is the increased risk of radiation-induced second non-germ cell malignancies (116-120).

A scrotal shield can be of benefit during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis (119).

6.1.4 Retroperitoneal lymph node dissection (RPLND)
In a prospective, non-randomised study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. Therefore, this policy should not be recommended in stage I seminoma (121).

6.1.5 Risk-adapted treatment
Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided into a low-and high-risk group of occult metastatic disease. Patients with and without both risk factors have a risk of occult disease of 32% and 12%, respectively. These risk factors were introduced by an analysis of retrospective trials (29). A prospective trial based on these risk factors (no risk factors: surveillance; both risk factors: two courses of carboplatin AUC 7) showed the feasibility of a risk-adapted approach. Early data with limited follow-up indicate that patients without either risk factor have a 6.0% risk of relapse at 5 years. Patients
in the high risk group treated with carboplatin experienced a 1.4% relapse rate at mean follow up of 34 months (122).

However, given the fact that cure is achieved in ~100% in patients with stage I seminoma whatever therapy used (adjuvant radiotherapy, adjuvant chemotherapy, or surveillance) and that the relapse rate in large surveillance series not using risk factors is about 15-20%, indicates a risk of over-treatment.

Therefore, the therapeutic decision should be shared with an informed patient.

### 6.2 Guidelines for the treatment of seminoma stage I

| GR | Surveillance is the recommended management option (if facilities available and patient compliant) |
|----|-------------------------------------------------------------------------------------------------
|    | Carboplatin-based chemotherapy (one course at AUC 7) is recommended.                             |
|    | Adjuvant treatment is not recommended for patients at very low risk.                            |
|    | Radiotherapy is not recommended as adjuvant treatment.                                         |

*Upgraded following panel consensus.

### 6.3 NSGCT stage I

Up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchidectomy.

#### 6.3.1 Surveillance

Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of only close surveillance after orchidectomy in CS1 NSGCT patients. The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of relapses occurring during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later (123-127). About 35% of relapsing patients have normal levels of serum tumour markers at relapse. About 60% of relapses are in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

The somewhat lower relapse rates reported from surveillance studies compared with some series of patients staged by RPLND (128) can be explained by the fact that some patients (presumably at risk) are excluded once surveillance is advised. Based on the overall cancer-specific survival data, surveillance within an experienced surveillance programme may be offered to patients with non-risk stratified clinical stage I non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment (129,130).

#### 6.3.2 Primary chemotherapy

Several studies involving two courses of chemotherapy with cisplatin, etoposide and bleomycin (PEB) as primary treatment for high-risk patients (having about 50% risk of relapse) have been reported (131-136). In these series, involving more than 200 patients, some with a median follow-up of nearly 8 years (131), a relapse rate of only 2.7% was reported, with very little long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity (137). However, the very-long term (> 20 years) side effects of adjuvant chemotherapy in this setting are currently unknown, and this should be taken in consideration for decision-making; especially the long-term cardio-vascular effects of chemotherapy in GCT survivors (138).

It is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy (139).

The results of cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up procedures (140). With a low frequency of follow-up CTs (a surveillance strategy which has been proven to be effective in non-seminoma CS1), the costs of follow-up can be considerably reduced (141).

#### 6.3.3 Risk-adapted treatment

Risk-adapted treatment is based on the risk factor vascular invasion. Stratifying patients with CS1 NSGCT
according to their presumed risk of relapse is a rational option, as several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach (131-136,142-145). Risk-adapted treatment is therefore an equally effective alternative treatment of choice in CS1 NSGCT.

If the risk-adapted policy is applied, patients with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of PEB, and patients without vascular invasion are recommended to undergo surveillance. Only if patients or doctors are not willing to accept the consequent risk-adapted treatment, or if there are circumstances that militate against the risk-adapted treatment option, should the remaining treatments be considered.

Thus, the decision about treatment should be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient and/or the treatment centre. The Swedish-Norwegian Testicular Cancer Project (SWENOTECA) recently showed that in a large population-based study with a risk-adapted approach within a management programme and a median follow-up of 4.7 years, the relapse rate was 3.2% for patients with vascular invasion treated with only one adjuvant PEB (146). Taken together, about 300 patients with high risk CS I have been adjuvantly treated with 1 x PEB with a follow-up of more than 5 yrs. As long as 1 x PEB has not been proven superior or at least equivalent to 2 courses PEB, this adjuvant treatment cannot be recommended outside of a clinical trial or a prospective registry.

6.3.4 **Retroperitoneal lymph node dissection**

If RPLND is performed, about 30% of patients are found to have retroperitoneal lymph node metastases, which corresponds to pathological stage II (PS2) disease (147-149). If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites (92,129,150-152).

The main predictor of relapse in CS1 NSGCT managed by surveillance, for having PS2 disease and for relapse in PS1 after RPLND, is histopathological evidence of vascular invasion by tumour cells in, or near, the primary tumour in the testis (92,124,129,152,153). The presence of vascular invasion seems to be a very robust parameter, and is clinically usable even without centralised review by an expert panel (143,152). Vascular invasion was the most predictive of stage in a multifactorial analysis. The absence of vascular invasion has a negative predictive value of 77%, thus allowing for surveillance in low-risk compliant patients (92).

Patients without vascular invasion constitute about 50-70% of the CS1 population, and these patients have only a 15-20% risk of relapse on surveillance, compared with a 50% relapse rate in patients with vascular invasion. The risk of relapse for PS1 patients is less than 10% for those without vascular invasion and about 30% for those with vascular invasion (143,152,154,155).

If CS1 patients with PS2 are followed up only after RPLND, about 30% relapse, mainly at sites outside the abdomen and pelvis. The risk of relapse depends upon the amount of retroperitoneal disease resected (156-158). If two (or more) courses of cisplatin-based chemotherapy are given adjuvant to RPLND in PS2 cases, the relapse rate is reduced to less than 2%, including teratoma relapse (129,153,159). The risk of retroperitoneal relapse after a properly performed nerve-sparing RPLND is very low (less than 2%), as is the risk of ejaculatory disturbance or other significant side-effects (153,156,157).

The follow-up after RPLND is much simpler and less costly than that carried out during post-orchidectomy surveillance because of the reduced need for abdominal CT scans (153). If there is a rare indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as standard approach outside of a specialised laparoscopic centre (160-163). In a randomised comparison of RPLND with one course of PEB chemotherapy, adjuvant chemotherapy significantly increased the 2-year recurrence-free survival to 99.41% (confidence interval [CI] 95.87%, 99.92%) as opposed to surgery, which had a 2-year recurrence-free survival of 92.37% (CI 87.21%, 95.50%). The difference was 7.04%, CI 2.52%, 11.56%. The hazard ratio to experience a tumour recurrence with surgery as opposed to chemotherapy was 7.937, CI 1.808, 34.48. Therefore, one course of adjuvant PEB is superior to RPLND with regard to recurrence rates in patients unstratified for risk factors (164). In the SWENOTECA data mentioned in section 7.3.3 it was also found that one adjuvant PEB reduced the number of recurrences to 3.2% of the high risk and to 1.4% of the low risk patients (146).

6.4 **CS1S with (persistently) elevated serum tumour markers**

Serum tumour markers should be followed closely until levels fall into the reference values according to the expected half-life values for AFP and hCG. If the marker level increases after orchidectomy, the patient has
residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum (165). An US examination of the contralateral testicle must be performed, if this was not done initially.

The treatment of true CS1S patients is still controversial. They may be treated with three courses of primary PEB chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy (166), or by RPLND (141). The presence of vascular invasion may strengthen the indication for primary chemotherapy as most CS1S with vascular invasion will need chemotherapy sooner or later anyway.

6.5 Guidelines for the treatment of NSGCT stage I

Table 7: Risk-adapted treatments for CS1 based on vascular invasion

<table>
<thead>
<tr>
<th>NSGCT stage 1</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS1 risk-adapted treatments based on vascular invasion or surveillance without using risk factors are recommended treatment options.</td>
<td>A</td>
</tr>
</tbody>
</table>

Risk-adapted treatments for CS1 based on vascular invasion

<table>
<thead>
<tr>
<th>CS1A (pT1, no vascular invasion): low risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If the patient is willing and able to comply with a surveillance policy, long-term (at least 5 years) close follow-up should be recommended.</td>
<td>A*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CS1B (pT2-pT4): high risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary chemotherapy with two courses of PEB should be recommended (one course of PEB within a clinical trial or registry).</td>
<td>A*</td>
</tr>
</tbody>
</table>

| Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to undergo adjuvant chemotherapy. | A |
| If pathological stage II is revealed at RPLND, further chemotherapy should be considered. | |

*Upgraded following panel consensus.

PEB = cisplatin, eposide, bleomycin; RPLND = retroperitoneal lymph node dissection.
Figure 1 provides a treatment algorithm for patients with NSGCT stage I.

**Figure 1: Treatment algorithm after orchidectomy according to individual risk factors in patients with non-seminoma NSGCT CS1 (31)**

**Non-seminoma CS I**

- **Low risk** no vascular invasion
  - Standard option
  - Surveillance
  - Adjuvant chemotherapy 2 cycles PEB
  - Nerve-sparing (NS) RPLND

- **High risk** Vascular invasion present
  - Standard option
  - Option if conditions against surveillance and chemotherapy
  - Adjuvant chemotherapy 2 cycles PEB
  - NS RPLND

**Relapse**

Treatment according to the IGCCCG classification (3-4 cycles PEB [or VIP] followed by resection in case of residual tumour)

**PEB = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RPLND = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.**
7. TREATMENT: METASTATIC GERM CELL TUMOURS

The treatment of metastatic germ cell tumours depends on:
- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG based on 5,202 non-seminoma and 660 seminoma cases (Table 5) (167).

7.1 Low-volume metastatic disease (stage IIA/B)

7.1.1 Stage IIA/B seminoma

So far, the standard treatment for stage IIA/B seminoma has been radiotherapy. The radiation dose delivered in stage IIA and IIB is approximately 30 Gy and 36 Gy, respectively. The standard radiation field compared with stage I will be extended from the PA region to the ipsilateral iliac field (the hockey-stick field). In stage IIB, the lateral borders should include the metastatic lymph nodes with a safety margin of 1.0-1.5 cm. This technique yields a relapse-free survival in stage IIA and IIB of 92% and 90%, respectively. Overall survival is almost 100% (168,169). Conversely, dose reduction to 27 Gy has been associated with 11% of relapses (106).

In stage IIB chemotherapy (4 x etoposide and cisplatin [EP] or 3 x PEB in good prognosis) is an alternative to radiotherapy. Although more toxic in the short term, 4 x EP or 3 x PEB achieve a similar level of disease control (170). Single-agent carboplatin is not an alternative to standard EP or PEB chemotherapy (171).

7.1.2 Stage IIA/B non-seminoma

There is a general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage II NSGCT disease without elevated tumour markers, which alternatively can be managed by primary RPLND or surveillance to clarify stage (172,173).

If surveillance is chosen, one follow-up after 6 weeks is indicated to document whether the lesion is growing, remaining stable or shrinking. A shrinking lesion is likely to be of non-malignant origin and should be observed further. A stable or growing lesion indicates either teratoma or an undifferentiated malignant tumour. If the lesion is growing without a corresponding increase in the tumour markers AFP or beta-hCG, RPLND should be performed by an experienced surgeon because of suspected teratoma. Patients with a growing lesion and a concomitant increase in the tumour markers AFP or beta-hCG should not undergo surgery; they require chemotherapy with PEB according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations (174-176) (Figure 2). An alternative to the surveillance strategy in marker-negative II A/B non-seminoma with suspicion of an undifferentiated malignant tumour is a (computer tomography-guided) biopsy, if technically possible. There is insufficient published data on PET scans in this situation.

Patients not willing to undergo primary chemotherapy have the option of primary nerve-sparing RPLND with adjuvant chemotherapy (two cycles of PEB) in case of metastatic disease (pII A/B). Primary chemotherapy and primary RPLND are comparable options in terms of outcome but side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice (177). The cure rate with either approach will be close to 98% (159,178-183).
7.2 Advanced metastatic disease

7.2.1 Primary chemotherapy

The primary treatment of choice for advanced disease is three or four cycles of PEB combination chemotherapy (Table 8), depending on the IGCCCG risk classification (see Table 3). This regimen has proven superiority to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease (184-186). Data support a 3-day regimen of administering combination chemotherapy to be equally effective as a 5-day regimen, but associated with increased toxicity when four cycles are used (187).

Table 8: PEB regimen (interval 21 days)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Duration of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1-5*</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>30 mg</td>
<td>Days 1, 8, 15</td>
</tr>
</tbody>
</table>

*Plus hydration.

PEB = cisplatin, etoposide, bleomycin.

For patients with a ‘good prognosis’, according to the IGCCCG Classification (167), standard treatment consists of three cycles of PEB, and only in very selected cases where bleomycin is contraindicated, four cycles of EP (167,186-190). A randomised trial from the GETUG suggested that when the PEB regimen is being used in this setting the mortality was half that of EP, although the difference did not reached statistical significance (190,191). Therapy should be given without reduction of the doses at 21-day intervals; delaying the following chemotherapy cycle is justified only in cases of fever with granulocytopenia < 1000/mm³ or thrombocytopenia < 100,000/IU. There is no indication for prophylactic application of haematopoietic growth factors such as, for example, granulocyte colony-stimulating factor (G-CSF). However, if infectious complications have occurred during chemotherapy, prophylactic administration of G-CSF is recommended for the following cycles (188,192).

The ‘intermediate prognosis’ group in the IGCCCG has been defined as patients with a 5-year survival rate of about 80%. The available data support four cycles of PEB as standard treatment (167,193).

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**Figure 2: Treatment options in patients with non-seminoma clinical stage IIA (32)**

PEB = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.
For patients with a ‘poor prognosis’, standard treatment consists of four cycles of PEB. Four cycles of cisplatin, etoposide and ifosfamide (PEI) have the same effect, but are more myelotoxic (194,195). The 5-year progression-free survival is between 45% and 50%. Three randomised trials have shown no advantage in high-dose chemotherapy for the overall group of ‘poor prognosis’ patients (196-198). However, patients with a slow marker decline after the first or second cycle may represent a prognostically inferior subgroup with a potential role for dose-intensified chemotherapy after detection of inadequate marker decline (196). More aggressive chemotherapy may also be investigated in a very poor prognostic group (e.g. primary mediastinal germ cell tumours or synchronous brain metastasis).

Since a matched-pair analysis resulted in a better survival rate (199-201), poor prognosis patients should still be treated in ongoing prospective trials, investigating the value of dose intensified or high-dose chemotherapy (e.g. the international GETUG 13 trial [EU-20502, NCT00104676]). Patients meeting ‘poor-prognosis’ criteria should therefore be transferred to a reference centre because a better outcome was reported for intermediate and poor prognosis patients who had been treated within a clinical trial in a high volume centre (25). There are no general recommendations for treatment modifications for patients with a poor general condition (Karnofsky < 50%) or extended liver infiltration (> 50%). Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome: adapting the doses of the PEB regimen in the first cycle of chemotherapy (only 3 days of EP without bleomycin) was suggested to reduce the risk of early death in this setting (202).

7.3 Restaging and further treatment

7.3.1 Restaging

Restaging is performed by imaging investigations and re-evaluation of tumour markers. At marker decline and stable or regressive tumour manifestation, chemotherapy will be completed (three or four cycles, depending on the initial stage) (167,203,204). In the case of marker decline but growing metastases, resection of the tumour is obligatory after termination of induction therapy, other than in an emergency, according to local tumour growth (205).

Only with documented marker increase after two courses of chemotherapy is an early crossover of therapy indicated. These patients are usually candidates for new drugs trials (199,206). Patients with a low-level hCG marker plateau post-treatment should be observed to see whether complete normalisation occurs. Patients with a low plateau serum AFP level after chemotherapy, surgery of residual masses should be performed, with post-surgery AFP monitoring. Salvage chemotherapy is indicated for documented marker rise only (207,208).

7.3.2 Residual tumour resection

A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers (209-215).

FDG-PET has a high negative predictive value in patients with residual masses after treatment of seminoma but false positive results can be a problem and scans should not be performed less than 2 months after chemotherapy. In patients with residuals of > 3 cm, FDG-PET should be performed in order to gain more information on the viability of these residuals. In patients with residuals of < 3 cm, the use of FDG-PET is optional (216).

On progression, salvage therapy is indicated (chemotherapy, salvage surgery, radiotherapy) (217-221). In patients with concurrent hCG elevation, progressing seminoma after first-line chemotherapy should be treated by salvage chemotherapy (or radiotherapy if only small volume recurrence is present). Progressing patients without hCG progression should undergo histological verification (e.g. by biopsy or open surgery) before salvage chemotherapy is given.

In the case of non-seminoma and complete remission after chemotherapy (no tumour visible), residual tumour resection is not indicated (222-229). The long-term relapse rate in this patient group is 6-9%, however, one third of the late relapsing patients will not survive (229).

In the case of any visible residual mass and marker normalisation, surgical resection is indicated. In patients with lesions < 1 cm, there is still an increased risk of residual cancer or teratoma (230) although the role of surgery in this setting is debated. In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within 4-6 weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed (222,229-238).
Overall, following PEB induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue. As yet, no imaging investigations, including PET or a prognosis model, are able to predict histological differentiation of the non-seminomatous residual tumour. Thus, residual tumour resection is mandatory in all patients with residual disease > 1 cm (223-225,237-247).

The extent of surgery should be based on the risk of relapse of an individual patient and quality of life issues (232). If possible, all the masses should be resected, because a complete resection, in the setting of viable malignant cells, is more critical than recourse to post-operative chemotherapy (248). There is growing evidence that "template" resections in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients (249,250). However, the mere resection of the residual tumour (so called "lumpectomy") should not be performed.

The histology may diverge in different organ sites (240). Resection of contralateral pulmonary lesions is not mandatory in case pathologic examination of the lesions from the first lung shows complete necrosis (251).

7.3.3 Quality of surgery
Post-chemotherapy surgery is demanding and frequently needs ad hoc vascular interventions (like vena cava or aortic prosthesis). Therefore, patients should be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Patients treated within such centres benefit from a significant reduction in perioperative mortality from 6% to 0.8% (26,252). In addition, specialised urologic surgeons are capable to reduce the local recurrence rate from 16% to 3% (253) with a higher rate of complete resections.

7.3.4 Consolidation chemotherapy after secondary surgery
After resection of necrosis or mature/immature teratoma, no further treatment is required. In the case of incomplete resection of other germ cell tumour pathologies, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g. ‘poor prognosis’ patients) (248,254) (caution: cumulative doses of bleomycin). After complete resection of ‘vital’ tumour < 10% of the total volume, especially in patients with an initially good prognosis group according to IGCCCG, the relapse rate is very low and adjuvant chemotherapy is not beneficial for preventing further relapse. The prognosis will definitely deteriorate if vital malignant neoplasm is found in resection specimens after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated and is unable to improve the prognosis (236,241).

7.4 Systemic salvage treatment for relapse or refractory disease
Cisplatin-based combination salvage chemotherapy will result in long-term remissions for about 50% of the patients who relapse after first-line chemotherapy (255). The regimens of choice are four cycles of PEI/VIP (etoposide, ifosfamide, cisplatin), four cycles of TIP (paclitaxel, ifosfamide, cisplatin) or four cycles of VeIP (vinblastine, ifosfamide, cisplatin) (Table 9).

A randomised trial showed no benefit in progression-free survival nor overall survival in patients treated with 3 cycles of VeIP plus 1 cycle of high-dose chemotherapy, compared with 4 cycles of VeIP (256). At present, it is impossible to determine whether conventionally dosed cisplatin-based combination chemotherapy is sufficient as first-salvage treatment or whether early intensification of first-salvage treatment with high-dose chemotherapy should be attempted. However, there is evidence from large retrospective analyses that there are different prognostic groups in case of relapse after first line chemotherapy (257-259). An international randomised trial of high-dose versus conventional dose chemotherapy in patients with first-line relapse is planned. It is therefore of the utmost importance that these rare patients are treated within clinical trials and at experienced centres.
Table 9: Standard PEI/VIP, TIP and VelP chemotherapy (interval 21 days)

<table>
<thead>
<tr>
<th>Chemotherapy agents</th>
<th>Dosage</th>
<th>Duration of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEI/VIP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin*</td>
<td>20 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>75-100 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>Ifosfamide†</td>
<td>1.2 g/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td><strong>TIP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>250 mg/m² xx</td>
<td>24 hour continuous infusion day 1</td>
</tr>
<tr>
<td>Ifosfamide†</td>
<td>1.5 g/m²</td>
<td>Days 2-5</td>
</tr>
<tr>
<td>Cisplatin*</td>
<td>25 mg/m²</td>
<td>Days 2-5</td>
</tr>
<tr>
<td><strong>VelP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinblastin</td>
<td>0.11 mg/kg</td>
<td>Days 1 + 2</td>
</tr>
<tr>
<td>Ifosfamide†</td>
<td>1.2 g/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>Cisplatin*</td>
<td>20 mg/m²</td>
<td>Days 1-5</td>
</tr>
</tbody>
</table>

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; VelP = vinblastine, ifosfamide, cisplatin.
*Plus hydration.
†Plus mesna protection.
xx An MRC schedule uses paclitaxel at 175mg/m² in a 3 hour infusion (260).

Conventionally dosed salvage chemotherapy may achieve long-term remissions in 15-40% of patients, depending on individual risk factors (208,261-263).

The IGCCCG-2 prognostic score comprised of 7 important factors as listed in Table 10 (seminoma vs. non-seminoma histology, primary tumour site, response to initial chemotherapy, duration of progression-free interval, AFP marker level at salvage, HCG marker level at salvage, and the presence of liver, bone, or brain metastases at salvage). Using these factors, 5 risk groups (very low risk = -1 points; low risk = 0 points; intermediate-risk = 1-2 points, high risk = 3-4 points; and very high risk > 5 points) were identified with significant differences in PFS and OS. Table 9 illustrates the 5 risk groups and the corresponding 2-year PFS and 3-year OS rates (264).

Table 10: IGCCCG-2 (Lorch-Beyer) Score Construction (258)

<table>
<thead>
<tr>
<th>Points</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td></td>
<td>Seminoma</td>
<td>Non-seminoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>Gonadal</td>
<td>Retroperitoneal</td>
<td>Mediastinal</td>
<td></td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td>CR/PRm-</td>
<td>PRm+/SD</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td>&gt; 3 months</td>
<td>3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFI</td>
<td></td>
<td>Normal</td>
<td>&lt; 1000</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>AFP salvage</td>
<td></td>
<td>&lt; 1000</td>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCG salvage</td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; IGCCCG = International Germ Cell Cancer Collaborative Group; LBB = alkaline extract of L. barbarum; PFI = platinum-free interval.
Table 11: PFS and OS estimates for all patients according to IGCCCG-2 prognostic score (258)

<table>
<thead>
<tr>
<th>Score (n=1435)</th>
<th>n</th>
<th>%</th>
<th>HR</th>
<th>2-years PFS</th>
<th>3-years OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>76</td>
<td>5.30</td>
<td>1</td>
<td>75.1</td>
<td>77.0</td>
</tr>
<tr>
<td>Low</td>
<td>257</td>
<td>17.9</td>
<td>2.07</td>
<td>52.6</td>
<td>69.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>646</td>
<td>45.0</td>
<td>2.88</td>
<td>42.8</td>
<td>57.3</td>
</tr>
<tr>
<td>High</td>
<td>351</td>
<td>24.5</td>
<td>4.81</td>
<td>26.4</td>
<td>31.7</td>
</tr>
<tr>
<td>Very High</td>
<td>105</td>
<td>7.3</td>
<td>8.95</td>
<td>11.5</td>
<td>14.7</td>
</tr>
<tr>
<td>Missing</td>
<td>159</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IGCCCG = International Germ Cell Cancer Collaborative Group; OS = overall survival; PFS = progression-free survival.

Salvage therapy with VeIP is probably not superior to other conventionally dosed cisplatin-based combination regimens (251,254,255). Recently, paclitaxel and gemcitabine have proved to be active in the treatment of refractory germ cell tumours; both drugs are synergistic with cisplatin (265-267).

Depending on the presence of adverse prognostic factors, the results of salvage therapy after first-line cisplatin-based treatment are unsatisfactory (208,268). Although some phase II trials indicate a 10% improvement in survival with early intensification of first-salvage treatment using high-dose chemotherapy, others fail to demonstrate such improvement (260,269-272).

High dose chemotherapy offered no advantage as first salvage treatment according to the results of the randomised IT 94 trial in good prognosis patients (256). Patients with good prognostic features should therefore be offered conventional-dose first salvage treatment. However, several phase II trials, as well as one retrospectively matched-pair analysis, have shown an improvement in survival in poor-prognosis patients with early intensification of first-salvage treatment using high-dose chemotherapy (257,262,273,274). All of these patients should, if possible, be entered into ongoing studies to define the optimal approach to salvage treatment, and should be referred to centres experienced in caring for relapse and/or refractory patients (275,276).

7.4.1 Late relapse (> 2 years after end of first-line treatment)

Late relapse is defined as any patient relapsing more than 2 years following chemotherapy for metastatic non-seminoma. If technically feasible, all non-seminoma patients with late relapse should undergo immediate radical surgery of all lesions, irrespective of the level of their tumour markers to resect completely all undifferentiated germ-cell tumour, mature teratoma or secondary non-germ cell cancer (140,277). Patients with rapidly rising HCG may present an exception for immediate surgery and may benefit from induction salvage chemotherapy before complete resection. If the lesions are not completely resectable, biopsies should be obtained for histological assessment, and salvage chemotherapy should be initiated according to the histological results. In these cases consultation of an experienced pathologist is required to avoid misinterpretation of the therapeutic morphological changes in the germ cell neoplasms (278). If the patient responds to salvage chemotherapy, secondary surgery should be conducted whenever possible. In the case of unresectable, but localised, refractory disease, radiotherapy can be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients (279).

7.5 Salvage surgery

Residual tumours after salvage chemotherapy should be resected if possible. In the case of marker progression after salvage treatment and a lack of other chemotherapeutic options, resection of residual tumours (“desperation surgery”) should be considered if complete resection of all tumour seems feasible (about 25% long-term survival may be achieved) (207,233,241,244,280-289).

7.6 Treatment of brain metastases

Brain metastases occur in the frame of a systemic relapse and rarely as an isolated relapse. The long-term survival of patients presenting with brain metastases at initial diagnosis is poor (30-40%), but even poorer is the development of a brain metastasis as a recurrent disease (the 5-year survival-rate is 2-5%) (290,291). Chemotherapy is the initial treatment in this case, and some data support the use of consolidation radiotherapy, even in the case of a total response after chemotherapy (292). Surgery can be considered in the case of a persistent solitary metastasis, depending on the systemic state, the histology of the primary tumour and the location of the metastasis.
7.7 Guidelines for the treatment of metastatic germ cell tumours

<table>
<thead>
<tr>
<th>GR</th>
<th>Low volume NSGCT stage IIA/B with elevated markers should be treated like ‘good or intermediate prognosis’ advanced NSGCT, with three or four cycles of PEB.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>In stage IIA/B without marker elevation, histology can be gained by RPLND or biopsy. A repeat staging can be performed after six weeks of surveillance before final decision on further treatment.</td>
</tr>
<tr>
<td>A</td>
<td>In metastatic NSGCT (&gt; stage IIC) with a good prognosis, three courses of PEB is the primary treatment of choice.</td>
</tr>
<tr>
<td>A</td>
<td>In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard PEB and inclusion in clinical trials is strongly recommended.</td>
</tr>
<tr>
<td>A</td>
<td>Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.</td>
</tr>
<tr>
<td>A</td>
<td>Seminoma CSII A/B can initially be treated with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.</td>
</tr>
<tr>
<td>B</td>
<td>In seminoma stage CS IIB, chemotherapy (4 x EP or 3 x PEB, in good prognosis) is an alternative to radiotherapy. It appears that 4 x EP or 3 x PEB achieve a similar level of disease control.</td>
</tr>
<tr>
<td>A</td>
<td>Seminoma stage IIC and higher should be treated with primary chemotherapy according to the same principles used for NSGCT.</td>
</tr>
</tbody>
</table>

EP = epoide, cisplatin; GR = grade of recommendation; NSGCT = non-seminomatous germ cell tumour; PEB = cisplatin, epoide, bleomycin; RPLND = retroperitoneal lymph node dissection.

8. FOLLOW-UP AFTER CURATIVE THERAPY

8.1 General considerations

The selection of the test to be performed in follow-up should adhere to the following principles (293):
- the interval between examination and duration of testing should be consistent with the time of maximal risk of recurrence and the natural history of the tumour;
- the tests should be directed at the most likely sites of recurrence and should have a high predictive value, both positive and negative;
- therapy should be available that will result in cure of the recurrence, significant prolongation of life or palliation of symptoms. The initiation of earlier therapy should improve the outcome compared with therapy given when the patient becomes symptomatic from the tumour recurrence;
- the increased risk of second malignancy, both in the primary site and in other tissues that may have been exposed to the same carcinogens, or in which there is epidemiological evidence of increased risk, should also guide the ordering of tests. Malignant- and non-malignant complications of therapy must also be considered. Such testing should also be performed with a frequency and duration consistent with the nature of the risk, and include only tests with high positive- and negative-predictive values.

The following considerations apply in a general manner for the selection of an appropriate schedule and testing in the follow-up of all stages of testis tumour.
- Most recurrences after curative therapy will occur in the first 2 years; surveillance should therefore be most frequent and intensive during this time.
- Late relapses can occur beyond 5 years, and therefore yearly follow-up for life may be advocated.
- After RPLND, relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.
- The value of a plain radiography chest has been recently questioned in the follow-up of patients with disseminated disease after complete remission (294,295).
- CT of the chest has a higher predictive value than plain radiography chest (295).
- The results of therapy are dependent on the bulk of disease; thus an intensive strategy to detect asymptomatic disease may be justifiable.
- After chemotherapy or radiotherapy, there is a long-term risk of the development of secondary malignancies.
• Exposure to diagnostic X-rays causes second malignancies (296). Thus, the frequency of CT scans should generally be reduced and any exposure to X-rays should be well justified in a patient cohort with a very long life-expectancy after successful treatment.
• In specialised centres, CT can be substituted by MRI. However, MRI is a protocol-dependent method and, thus, should be performed in the same institution with a standardised protocol.
• With special expertise, US may be used as a method to screen the retroperitoneum during follow-up. However, the method is very much dependent on the investigator and cannot be recommended as general method during follow-up.
• Longer follow-up in patients after radiotherapy and chemotherapy is justified to detect late toxicities (e.g. cardio-vascular, endocrine).

A number of interdisciplinary organisations have presented recommendations for follow-up of testicular cancer patients (297-299). The follow-up tables presented below (tables 12 through 15) present the minimum follow-up criteria and should therefore be considered as a GRA.

8.2 Follow-up: stage I non-seminoma

Approximately 5% of patients with CS1 NSGCT present with elevated levels of tumour markers after orchidectomy, and up to 25-30% relapse during the first 2 years (5,132,152,155,178,300-303). The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen:
• surveillance;
• nerve-sparing RPLND;
• adjuvant chemotherapy.

8.2.1 Follow-up investigations during surveillance

The results of a surveillance policy depend upon a careful pre-operative staging procedure and follow-up management. In a ‘wait and see’ policy, relapses will occur in 30% of cases. Of these relapses, 80% will occur in the first 12 months after orchidectomy, and approximately 12% during the second year. The median time to relapse is 6 months (range 1-62 months), but relapses after 3-5 years, and even later, can still occur, with an annual rate of 4% (113,114). Relapse occurs mainly in the retroperitoneum: approximately 70% of patients have evident metastases in the retroperitoneum, and 10% in the mediastinum and lungs (304). Sometimes the only indication is an elevated level of tumour markers.

A randomised trial of two versus five CTs has been published by the MRC recommending the reduction of imaging during surveillance in this stage to one CT scan at 3 months after orchidectomy, and another at 12 months. The trial, with a cohort of 414 patients, was powered to exclude a 3% probability of detecting a patient during surveillance only, with a relapse presenting already-metastatic disease with ‘intermediate’ or ‘poor’ prognosis features. Relapses were detected in 15% with two CTs, and 20% with five CTs; 1.6% of these patients had ‘intermediate’ or ‘poor’ prognosis features. Only 10% of patients had high-risk features (vascular invasion). In summary, this first randomised trial yielded level 1 evidence for a minimum follow-up in patients with CS1 non-seminoma (142). The recommended follow-up schedule (Table 12) includes the minimum requirements for imaging, and adds recommendations for other surveillance tests.

Table 12: Recommended follow-up schedule in a surveillance policy: stage I non-seminoma

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td>4 times</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>4 times</td>
</tr>
<tr>
<td>Plain radiography chest</td>
<td>Twice</td>
</tr>
<tr>
<td>Abdominopelvic CT</td>
<td>Twice (at 3 and 12 months)</td>
</tr>
</tbody>
</table>

CT= computed tomography.

During the initial post-treatment phase, follow-up consists of regular clinical examinations, the monitoring of serum tumour markers, and imaging investigations. The frequency and type of the examinations depend on the estimated risk of relapse, the chosen treatment strategy, and the time that has elapsed since completion of therapy, and should be modified according to these risks. However, only limited information about the optimal follow-up strategy exists, and currently recommendations can only be given for seminoma (305).
For low-risk stage I non-seminoma, two abdominopelvic CTs during the first year seem sufficient to detect relapses at an early stage (142). The significance of additional CTs remains uncertain. No studies are available that address the optimal monitoring of such patients by serum tumour markers (AFP, beta-hCG).

8.2.2  **Follow-up after nerve-sparing RPLND**
Retroperitoneal relapse after a properly performed nerve-sparing RPLND is rare. RPLND should eliminate the retroperitoneal nodes as a site of relapse and thus the need for repeated abdominal CTs. The US Testicular Cancer Intergroup study data show retroperitoneal relapse in 7/264 patients with pathological stage I disease (and 20 pulmonary relapses); four of these seven had no marker elevation (306). In the Indiana series, only one relapse in 559 cases was reported (307). If a relapse occurs, it is generally in the chest, neck or at the margins of the surgical field.

Pulmonary relapses occur in 10-12% of patients, and more than 90% of those relapses occur within 2 years of RPLND (87,308). However, the low rate of retroperitoneal relapse after RPLND can only be achieved by surgery in specialised centres, as shown by the high in-field relapse rate (7/13 relapses) in the German randomised trial of RPLND versus one course of PEB (164). The recommended minimum follow-up schedule is shown in Table 13.

**Table 13: Recommended follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3-5</th>
<th>6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td></td>
<td>4 times</td>
<td>4 times</td>
<td>Once/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td></td>
<td>4 times</td>
<td>4 times</td>
<td>Once/year</td>
<td>Once/year</td>
</tr>
<tr>
<td>Plain radiography chest</td>
<td></td>
<td>Twice</td>
<td>Twice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominopelvic CT</td>
<td></td>
<td>Once</td>
<td>Twice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT = computed tomography.

8.2.3  **Follow-up after adjuvant chemotherapy**
Prospective reports with long-term follow-up after adjuvant chemotherapy have shown a low relapse rate of about 3% (132,133,300,301). In a randomised trial with one course of PEB versus RPLND, the relapse rate with adjuvant chemotherapy was 1% (2/174 patients, one with marker relapse, one with mature teratoma in the retroperitoneum) (164). The need for repeated and long-term assessment of the retroperitoneum is still not clear. Owing to the risk of developing a late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy, an abdominal CT should still be performed (see Table 13).

8.3  **Follow-up: stage I seminoma**
The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis. In 15-20% of cases, there is nodal radiological involvement at the level of the retroperitoneum, and only 5% of patients present with distant metastasis.

The relapse rate varies between 1% and 20%, depending on the post-orchiectomy therapy chosen. Only up to 30% of seminomas present with elevation of hCG at diagnosis or in the course of the disease. Consequently, in most cases, measurement of blood markers will not be a reliable test for follow-up (309). The treatment options post-orchiectomy in stage I seminoma are retroperitoneal radiotherapy, surveillance and adjuvant chemotherapy. Due to extreme radio- and chemosensitivity, high cure rates of almost 100% are reached with each of the approaches, even in cases of relapse. The costs of the different therapies vary, as do the expected side-effects (310-312).

8.3.1  **Follow-up after radiotherapy**
Low doses of radiotherapy (20-24 Gy) limited to the retroperitoneal or the hockey-stick field achieve an overall survival rate of approximately 99% at 5-10 years (113-115,313,315). The rate of relapse is 1-2% and the most common time of presentation is within 18 months of treatment (113,116,312,315,316), although late relapses have also been described (317). The site of relapse is mainly at the supradiaphragmatic lymph nodes, mediastinum, lungs or bones. In a small proportion of cases, the tumour will relapse in the inguinal or external iliac nodes. After para-aortic field RT there is also a pelvic node relapse pattern.
The side-effects of radiotherapy include temporary impaired spermatogenesis, GI symptoms (peptic ulceration), and induction of second malignancies (312,318,319). Up to 50% of patients can develop moderate toxicity grade I-II (309). The schedule of follow-up is described in Table 14.

Table 14: Recommended follow-up schedule for post-orchidectomy surveillance, radiotherapy or chemotherapy: stage I seminoma

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td>3 times</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>3 times</td>
</tr>
<tr>
<td>Plain radiography chest</td>
<td>Twice</td>
</tr>
<tr>
<td>Abdominopelvic CT</td>
<td>Twice</td>
</tr>
<tr>
<td>CT = computed tomography.</td>
<td></td>
</tr>
</tbody>
</table>

8.3.2 Follow-up during surveillance
The actuarial risk of relapse at 5 years ranges between 6% (low risk) and 20% (119,330-334). There is no increased risk of death. The median time to relapse ranges from 12-18 months, but up to 29% of relapses can develop later than this (103,325). The sites of relapse are the PA lymph nodes in up to 82% of cases; the pelvic lymph nodes, inguinal nodes and lungs can also be affected (103,138,326-329). Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years (330) (see Table 14).

8.3.3 Follow-up after adjuvant chemotherapy
One or two courses of carboplatin-based chemotherapy is an effective alternative treatment in stage I seminoma. The relapse rate is 1.9-4.5%. In general, this treatment is well tolerated, with only mild, acute and intermediate-term toxicity (330,331). Long-term data on late relapses and survival are missing (see Table 14).

8.4 Follow-up: stage II and advanced (metastatic) disease
The more advanced the nodal stage of the disease, the higher the likelihood of recurrence (159). In general, the primary tumour bulk governs the outcome for patients with NSGCT (332). In stage II NSGCT, regardless of the treatment policy adopted, excellent survival rates of 97% are reached provided that relapse is identified as soon as possible (172,173,179).

In advanced metastatic germ cell tumours, the extent of the disease correlates with the response to therapy and with survival. The combination of cisplatin-based chemotherapy and surgery (aggressive multimodality) achieves cure rates of between 65% and 85%, depending on the initial extent of disease (333,334). Complete response rates to chemotherapy are in the order of 50-60% (333); another 20-30% of patients could be rendered disease-free with post-chemotherapy surgery (335). The main reasons for failure of therapy in advanced NSGCT are (332,336,337):
- the presence of bulky disease not responding completely to chemotherapy;
- unresectable residual teratoma after chemotherapy;
- the presence or development of chemoresistant non-germ elements, which account for 8.2% of cases.

Table 15 presents the recommended minimum follow-up schedule in advanced NSGCT and seminoma.

Table 15: Recommended minimum follow-up schedule in advanced NSGCT and seminoma

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td>4 times</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>4 times</td>
</tr>
<tr>
<td>Plain radiography</td>
<td>4 times</td>
</tr>
<tr>
<td>Abdominopelvic CT†</td>
<td>Twice</td>
</tr>
<tr>
<td>Abdominopelvic CT‡</td>
<td>As indicated</td>
</tr>
</tbody>
</table>
Brain CT§ As indicated As indicated As indicated As indicated

CT = computed tomography.

*An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.
†If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.
‡A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.
§In patients with headaches, focal neurological findings, or any central nervous system symptoms.

9. TESTICULAR STROMAL TUMOURS

9.1 Background
Testicular stromal tumours are rare and account for only 2-4% of adult testicular tumours. However, only Leydig cell and Sertoli cell tumours are of clinical relevance. As no general recommendations have been published to date, the Testicular Cancer Working Group of the European Association of Urology (EAU) has decided to include these tumours in the EAU Germ Cell Tumour Guidelines. Recommendations for diagnosis and treatment are given only for Leydig and Sertoli cell tumours.

9.2 Methods
A Medline search for Leydig cell tumours (synonym: interstitial cell tumour) and Sertoli cell tumours (synonym: androblastoma) was performed. Approximately 850 papers were found. After excluding pure laboratory work without clinical data, female and paediatric tumours and animal cases, 371 papers and abstracts were reviewed. Double publications and papers with unclear histology or missing data on clinical course were excluded. The majority of the remaining 285 publications are case reports, with only a few papers reporting series of more than 10 cases, most of them published in the pathology literature. The true incidence of stromal tumours therefore remains uncertain, and the proportion of metastatic tumours can only be given approximately.

Nevertheless, the symptoms for pre-operative suspicion of testicular stromal tumours and the characteristics of tumours at high risk for metastases are sufficiently well established (LE: 2a/2b) to enable recommendations to be made regarding diagnosis and surgical approach. However, no recommendations for appropriate follow-up can be given due to the absence of follow-up data in most reported cases, and the fatal outcome of metastatic tumours, irrespective of the therapy chosen.

The individual publications have been rated according to level of evidence (see above).

The literature research for clinical data on Leydig cell tumours resulted in 193 publications dealing with more than 480 tumours in adults, including three publications (1-3) reporting larger series on a total of 90 patients. Follow-up data of more than 2 years are available for about 80 patients.

The literature research for clinical data on Sertoli cell tumours resulted in 93 publications dealing with more than 260 tumours in adults, including three publications (from the same group) (4-6) reporting on a total of 80 patients. Follow-up data of more than 2 years are available in fewer than 40 patients.

9.3 Classification
The non-germ cell tumours of the testicle include the sex cord/gonadal stromal tumours and the miscellaneous non-specific stromal tumours. The different histological subtypes of testicular tumours are defined according to the WHO classification 2004 (adapted) (7).

9.4 Leydig cell tumours
9.4.1 Epidemiology
Leydig cell tumours constitute about 1-3% of adult testicular tumours (2,8) and 3% of testicular tumours in infants and children (8). The tumour is most common in the third to sixth decade in adults, with a similar incidence observed in every decade. Another peak incidence is seen in children aged between 3 and 9 years. Only 3% of Leydig cell tumours are bilateral (2). Occasionally, they occur in patients with Klinefelter’s syndrome (8).
9.4.2 Pathology of Leydig cell tumours

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well outlined and usually up to 5 cm in diameter. They are also solid, coloured yellow to tan, with haemorrhage and/or necrosis present in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm with occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S-100, steroid hormones, calretinin and cytokeratin (focally) (7).

About 10% of Leydig cell tumours are malignant tumours, which present with the following parameters:

- large size (> 5 cm);
- cytological atypia;
- increased mitotic activity (> 3 per 10 high-power field [HPF]);
- increased MIB-1 expression (18.6% vs 1.2% in benign);
- necrosis;
- vascular invasion (9);
- infiltrative margins;
- extension beyond the testicular parenchyma;
- DNA aneuploidy (1,10).

9.4.3 Diagnosis

Patients either present with a painless enlarged testis or the tumour is an incidental US finding. In up to 80% of cases, hormonal disorders with high oestrogen and oestradiol levels and low testosterone, increased levels of LH and FSH are reported (11,12), while negative results are always obtained for the testicular germ cell tumour-markers AFP, hCG, LDH and PLAP. Approximately 30% of patients present with gynaecomastia (13,14). Only 3% of tumours are bilateral (2). Leydig cell tumours must be distinguished from the multinodular tumour-like and often bilaterally occurring lesions of the androgenital syndrome (15).

Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH; if not conclusive, additionally oestrogen, oestradiol, progesterone and cortisol), US of both testes, and CT of chest and abdomen. On US, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularisation, but the appearance is variable and is indistinguishable from germ cell tumours (16,17). The proportion of metastatic tumours in all published case reports is only 10%. Within three larger series with longer follow-up, 18 metastatic tumours were found in a total of 83 cases (21.7%) (1-3). Histopathological signs of malignancy have been depicted above (see 4.2) (1,10). In addition, patients of older age have a greater risk of harbouring a tumour of malignant potential.

9.4.4 Treatment

Asymptomatic testicular tumours of small volume are often misinterpreted as germ cell tumours, and inguinal orchidectomy is performed. It is highly recommended to perform an organ-sparing procedure in every small intraparenchymal lesion in order to obtain the histological diagnosis. Especially in patients with symptoms of gynaecomastia or hormonal disorders, a non germ-cell tumour should be considered and immediate orchidectomy avoided (18). In cases of germ cell tumour in either frozen (fresh tissue) section or paraffin histology, orchidectomy is recommended as long as a contralateral normal testicle is present.

In stromal tumours with histological signs of malignancy, especially in patients of older age, orchidectomy and retroperitoneal lymphadenectomy is recommended to prevent metastases (19). Without histological signs of malignancy, an individualised surveillance strategy after orchidectomy is recommended (CT follow-up may be most appropriate since specific tumour markers are not available).

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor (19).

9.4.5 Follow-up

Recommendations for appropriate follow-up cannot be given because of the lack of follow-up data in most reported cases and the lethal outcome of metastatic tumours, irrespective of the therapy chosen.

9.5 Sertoli cell tumour

9.5.1 Epidemiology

Sertoli cell tumours account for fewer than 1% of testicular tumours, and the mean age at diagnosis is around 45 years, with rare cases under 20 years of age (4,20). On rare occasions, these tumours may develop in patients with androgen insensitivity syndrome and Peutz-Jeghers syndrome.
9.5.2 Pathology of Sertoli cell tumours

The tumour is well circumscribed, yellow, tan or white, with an average diameter of 3.5 cm (4). Microscopically, the cells are eosinophilic to pale with vacuolated cytoplasm. The nuclei are regular with grooves and there may be inclusions. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine and capillary, but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) (4).

The rate of malignant tumours ranges between 10% and 22%, and fewer than 50 cases have been reported (21-23). Signs of a malignant Sertoli tumour are:

- large size (> 5 cm);
- pleomorphic nuclei with nucleoli;
- increased mitotic activity (> 5 per 10 HPF);
- necrosis;
- vascular invasion.

9.5.2.1 Classification

Three subtypes have been described (20):

- the classic Sertoli cell tumour (4);
- the large cell calcifying form with characteristic calcifications (5,24);
- the rare sclerosing form (6,25).

9.5.3 Diagnosis

Patients present either with an enlarged testis or the tumour is an incidental US finding (26). Most classic Sertoli tumours are unilateral and unifocal. Hormonal disorders are infrequent, although gynaecomastia is sometimes seen (4). The testicular tumour-markers AFP, hCG, LDH and PLAP are always negative.

Diagnostic work-up must include tumour markers, hormones (at least testosterone, LH and FSH; if not conclusive, additionally oestrogen, oestradiol, progesterone and cortisol), US of both testes and CT of chest and abdomen.

Sertoli cell tumours are generally hypoechoic on US, but they can be of variant appearance and therefore cannot be safely distinguished from germ cell tumours (20). Only the large cell calcifying form has a characteristic image with brightly echogenic foci due to calcification (27,28).

The large cell calcifying form is diagnosed in younger men and is associated with genetic syndromes (Carney’s complex [29] and Peutz-Jeghers syndrome [30]) or, in about 40% of cases, endocrine disorders. A total of 44% of cases are bilateral, either synchronous or metachronous, and 28% show multifocality (24).

The characteristics of metastatic tumours have been depicted above (24,25). However, among patients whose tumours have been histopathologically classified as ‘malignant’ using these or similar characteristics (i.e. 18.8% of tumours in all reported cases), only 7% showed metastatic disease during follow-up.

In the largest series with the longest follow-up, 7.5% of patients had been classified as ‘malignant’ at primary diagnosis and 11.7% showed metastatic disease long-term (4). In general, affected patients are of higher age, tumours are nearly always palpable, and show more than one sign of malignancy (4).

Up to 20% of the large cell sclerosing form are malignant. There are some hints that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared with 23%) (20). Metastases in the infrequent sclerosing subtype are rare.

9.5.4 Treatment

Testicular tumours of small volume, otherwise asymptomatic, are often misinterpreted as germ cell tumours and inguinal orchidectomy is performed. It is highly recommended to proceed with an organ-sparing approach in small intraparenchymal testicular lesions until final histology is available. Especially in patients with symptoms of gynaecomastia or hormonal disorders or typical imaging on ultrasound (calcifications, small circumscribed tumours), organ-sparing surgery should be considered. Secondary orchidectomy can be performed if final pathology reveals a non-stromal (e.g. germ cell) tumour. Organ-sparing surgical approaches are justified as long as the remaining testicular parenchyma is sufficient for endocrine (and in stromal tumours also exocrine) function.

In tumours with histological signs of malignancy, especially in patients of older age, orchidectomy and
retroperitoneal lymphadenectomy are recommended to prevent metastases (19). Without signs of malignancy, an individualised surveillance strategy after orchidectomy is recommended (CT may be most appropriate since specific tumour-markers are not available). Tumours metastasising to lymph nodes, lung or bone respond poorly to chemotherapy or radiation, and survival is poor.

9.5.5 **Follow-up**
Recommendations for appropriate follow-up cannot be given because of the lack of follow-up data in most reported cases and the lethal outcome of metastatic tumours, irrespective of the therapy chosen.

9.6 **Granulosa cell tumour**
This is a rare tumour, with two variants: juvenile and adult.
- The juvenile type is benign. It is the most frequent congenital testicle tumour and represents 6.6% of all prepubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type (31).
- With the adult type, the average age at presentation is 44 years. The typical morphology is of a homogeneous, yellow-grey tumour, with elongated cells with grooves in microfollicular and Call-Exner body arrangements.

Malignant tumours represent around 20% of cases. They are usually > 7 cm diameter. Vascular invasion and necrosis are features suggestive of malignant biology (32).

9.7 **Thecoma/fibroma group of tumours**
These tumours are very rare and benign (7).

9.8 **Other sex cord/gonadal stromal tumours**
Sex cord/gonadal stromal tumours may be incompletely differentiated or mixed forms. There is limited experience with incompletely differentiated sex cord/gonadal stromal tumours and no cases of reported metastasis (7). In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour is most likely to reflect the predominant pattern or the most aggressive component of the tumour (33).

9.9 **Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)**
If the arrangement of the germ cells are in a nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. It is most frequent in gonadal dysgenesis with ambiguous genitalia. Bilateral tumours are present in 40% of cases. The prognosis correlates with the invasive growth of the germinal component (34).

In the case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider them to be entrapped rather than neoplastic (35).

9.10 **Miscellaneous tumours of the testis**

9.10.1 **Tumours of ovarian epithelial types**
These tumours resemble the epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts, and their evolution is similar to that of the different epithelial ovarian subtypes. Some Brenner types can be malignant (7).

9.10.2 **Tumours of the collecting ducts and rete testis**
These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) have been reported, with malignant tumours showing local growth with a mortality rate of 56% (18).

9.10.3 **Tumours (benign and malignant) of non-specific stroma**
These are very uncommon and have a similar criteria, prognosis and treatment as do the soft tissue sarcomas.
10. REFERENCES

10.1 Germ cell tumours


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376019/?tool=pubmed


242. Weinknecht S, Hartmann M, Weissbach L. [In which marker-positive patients with germ cell tumors is residual tumor resection of value?] Urologe A 1998 Nov;37(6):621-4. [Article in German]


308. Schmoll HJ, Weissbach L. [Diagnostik und Therapie von Hodentumoren.] Interdisziplinäre Konsensus-Konferenz, Halle (Saale), 1996. EBM Ila, Iib, III. [Diagnosis and therapy for germ cell tumours] [Article in German]


10.2 Non-germ cell tumours


   http://www.ncbi.nlm.nih.gov/pubmed/7541015


11. ABBREVIATIONS USED IN THE TEXT

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<th>Definition</th>
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<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
</tr>
<tr>
<td>AUC</td>
<td>area under curve</td>
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<tr>
<td>Cg A</td>
<td>chromogranine A</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CS</td>
<td>clinical stage</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>EBM</td>
<td>evidence-based medicine</td>
</tr>
<tr>
<td>EP</td>
<td>etoposide, cisplatin</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>fluorodeoxyglucose-positron emission tomography</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony-stimulating factor</td>
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<td>GR</td>
<td>grade of recommendation</td>
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<tr>
<td>hCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HPF</td>
<td>high-power field</td>
</tr>
<tr>
<td>IGCCCG</td>
<td>International Germ Cell Cancer Collaborative Group</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
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<tr>
<td>LH</td>
<td>luteinising hormone</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NSGCT</td>
<td>non-seminomatous germ cell tumour</td>
</tr>
<tr>
<td>PA</td>
<td>para-aortic</td>
</tr>
<tr>
<td>PEB</td>
<td>cisplatin, etoposide, bleomycin</td>
</tr>
<tr>
<td>PEI</td>
<td>cisplatin, etoposide, ifosfamide</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
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<tr>
<td>PS</td>
<td>pathological stage</td>
</tr>
<tr>
<td>PLAP</td>
<td>placental alkaline phosphatase</td>
</tr>
<tr>
<td>PVB</td>
<td>cisplatin, vinblastine, bleomycin</td>
</tr>
<tr>
<td>RPLND</td>
<td>retroperitoneal lymph node dissection</td>
</tr>
<tr>
<td>SWENOTECA</td>
<td>Swedish-Norwegian Testicular Cancer Project</td>
</tr>
<tr>
<td>TIN</td>
<td>testicular intraepithelial neoplasia</td>
</tr>
<tr>
<td>TIP</td>
<td>paclitaxel, ifosfamide, cisplatin</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour Node Metastasis</td>
</tr>
<tr>
<td>UICC</td>
<td>International Union Against Cancer</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>VelP</td>
<td>vinblastine, ifosfamide, cisplatin</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>VIP</td>
<td>(VP-16) etoposide, ifosfamide, cisplatin</td>
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</tbody>
</table>

Conflict of interest

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Penile Cancer

G. Pizzocaro (past-chair), F. Algaba, E. Solsona, S. Tana, H. Van Der Poel, N. Watkin, S. Horenblas (chair)

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<td>10.2</td>
<td>Sexual mutilation, relapse, and death</td>
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<td>11.</td>
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1. INTRODUCTION

The European Association of Urology (EAU) Guidelines Group on Penile Cancer has prepared this guidelines document to assist medical professionals in the management of penile cancer. The guidelines aim to provide detailed, up-to-date information, based on recent developments in our understanding and management of penile squamous cell carcinoma (SCC). However, it must be emphasised that these guidelines provide an updated, but not yet standardised general approach to treatment and that they provide guidance and recommendations without legal implications.

Publication history information: The Penile Cancer Guidelines were first published in 2001 and updated in 2004 and 2009. The literature search for the 2009 update covered the period from October 2004 to December 2008. The reason to present such an early update can also be attributed to the recent publication of the 2009 Tumour Node Metastasis (TNM) classification which, for penile cancer, had remained unchanged since 1987. Additionally, this update allowed inclusion of relevant new references.

2. METHODOLOGY

A systematic literature search on penile cancer was performed by all members of the EAU Penile Cancer Working Panel which covered the period between October 2004 and December 2008. At the onset of the project, each member was assigned one or two topics in accordance with their particular expertise. Each panel member was teamed up with another panel member who acted as a reviewer of a section. The panel decided to avoid rare diseases and to restrict the guidelines to SCC only. Since new publications became available in the first 3 years, the initial literature acquisition resulted in a first draft for discussion in 2008. This document was reviewed and updated by the panel and published in the 2009 edition of the EAU guidelines book and as an ultra-short (pocket) edition at the Annual EAU Congress in Stockholm, Sweden. For this 2010 print, the results of the updated search performed by the panel for their scientific publication (1) covering the period between December 2008 and December 2009 was supplemented by a second search with a cut-off date of March 2010.

To date the physician data query on ‘Penile Cancer Treatment’ (Health Professional Version) published by the National Cancer Institute, National Institutes of Health in Bethesda, MD, USA (2), remains the only evidence-based, peer-reviewed document available. No randomised controlled trials or Cochrane reviews have been published.

References used in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. As a result of the lack of randomised studies, the levels of evidence (LE) and grades of recommendation (GR) provided in the document are low.

Additionally, a quick reference guide is available. All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/guidelines/online-guidelines/.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (3).
Table 2: Grade of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (3).

2.1 References


3. DEFINITION OF PENILE CANCER

Penile cancer is a relatively rare SCC. It usually originates in the epithelium of the inner prepuce and glans. It shares similar pathology and natural history with SCC of the oropharynx, female genitalia (cervix, vagina and vulva), and anus. Phimosis, poor hygiene, and smoking are the major risk factors for penile cancer. Typing has been done of the human papillomaviruses (HPVs) that are responsible for the sexual transmission of genital warts, condyloma acuminata, and SCC.

An improved understanding of the natural history of the disease, earlier diagnosis, better technology, research group collaboration, and centralisation of patients in centres of excellence has improved the cure rate for penile cancer from 50% in the 1990s to 80% in recent years.

4. EPIDEMIOLOGY

In Western countries, primary malignant penile cancer is uncommon, with an incidence of less than 1.00 per 100,000 males in Europe and the United States (1,2). However, there are significant geographical variations within Europe (Figure 1), reporting an incidence greater than 1.00 per 100,000 men (3). Incidence is also affected by race and ethnicity in North America (1), with the highest incidence of penile cancer found in white Hispanics (1.01 per 100,000), followed by Alaskan, Native/American Indians (0.77 per 100,000), Blacks (0.62 per 100,000) and white non-Hispanics (0.51 per 100,000).

In contrast, in the non-Western world, the incidence of penile cancer is much higher and can represent 10-20% of malignant diseases in men ranging from an age-adjusted incidence of 0.7-3 per 100,000 people in India to 8.3 per 100,000 men in Brazil, and even higher in Uganda, where it is the most commonly diagnosed cancer.

Important risk factors include social and cultural habits, and hygienic and religious practices (4). Penile carcinoma is rare in communities that practise circumcision in newborns or before puberty (Jews, Muslims, and the Ibos of Nigeria). Early circumcision reduces the risk of penile cancer by 3-5 times. Adult circumcision does not protect against penile cancer.
In the USA, the overall age-adjusted incidence rate decreased considerably between 1973 and 2002 from 0.84 per 100,000 in 1973-1982 to 0.69 per 100,000 in 1983-1992, and further to 0.58 per 100,000 in 1993-2002 (1). In European countries, the incidence during the 1980s and 1990s was stable or increased only slightly (2). Incidence increases with age (2); however, the disease has been reported in younger men and even in children in non-western countries (3).

Figure 1: Annual incidence rate (world standardised) by European region/country*

*From Parkin et al. (2003) (3).

4.1 References
5. **RISK FACTORS AND PREVENTION**

Risk factors for penile cancer were identified by the Karolinska Institute based on a Medline search of published literature from 1966 to 2000 (1). Strong risk factors (OR > 10) identified by case-control studies included (LE: 2a):

- Phimosis;
- Chronic inflammatory conditions, e.g., balanoposthitis, lichen sclerosus, and atrophicus (balanitis xerotica obliterans);
- Treatment with sporalene and ultraviolet A photochemotherapy.

Sexual history (multiple partners, early age of first intercourse) and a self-reported history of condylomata are associated with a 3-5-fold increased risk of penile cancer. Smoking is also a risk factor. Cervical cancer in female sexual partners is not consistently associated with penile cancer in their male partners.

In many case series, HPV DNA has been identified in 70-100% of intraepithelial neoplasia and in 40-50% of cases with invasive penile cancer. These results have been confirmed by a population-based case-control study (2). Among men not circumcised in childhood, phimosis was strongly associated with the development of invasive penile cancer (OR: 11.4; 95% CI: 5.0-25.9) and cigarette smoking was associated with a 4.5-fold increased risk (95% CI: 2.0-10.1). Human papillomavirus DNA was detected in 80% of tumour specimens and 69% were positive for HPV-16 (LE: 2a).

Smegma as a carcinogen has been clearly excluded (3). The risk of cancer of the vulva, vagina, penis, and anus is increased in patients with condylomata acuminata (4) (LE: 2b).

Human papillomavirus-16 and 18 have a causal role in 70% of cancers of the cervix, vagina, and anus and 40-50% of cancers of the vulva, penis, and oropharynx. Other cofactors are very likely to be necessary for progression from HPV infection to cancer (5). Verrucous carcinoma is not related to HPV infection (6).

In June 2006, the US Food and Drug Administration (FDA) licensed the first vaccine to prevent cervical cancer and other HPV-associated diseases in women (7). The vaccine protects against infection with HPV-6, 11, 16 and 18, which together are responsible for 70% of cervical cancers and 90% of genital warts.

Human papillomavirus is highly transmissible, with a peak incidence soon after the onset of sexual activity. The recommended age for vaccination in girls is 11-12 years (8), with catch-up vaccination recommended in females aged 13-26 years.

However, vaccination is not a substitute for routine cervical cancer screening and vaccinated women should continue to have cervical cancer screening. Vaccination against HPV has also been recommended in men (9). Although one study has found that mid-adult women (≥ 25 years) have a high level of acceptance of HPV vaccination (10), only 33% of men wanted the HPV vaccine, 27% did not, and 40% were undecided (11). It has been decided that vaccination in men must wait for results of female HPV vaccination (12).

Interestingly, the presence of high-risk HPV DNA in penile cancer does not compromise prognosis. An early study has found no difference between HPV DNA-negative and -positive patients for lymph node metastases and 10-year survival rate (13). In a more recent study (14), disease-specific 5-year survival in the high-risk HPV-negative group was 78% versus 93% in the high-risk HPV-positive group (log rank test P = 0.03). This suggests the presence of high-risk HPV confers a survival advantage in patients with penile cancer. The virus plays an important role in oncogenesis through interaction with oncogenes and tumour suppressor genes (P53 and Rb genes) (15).

5.1 **References**


### 6. TNM CLASSIFICATION AND PATHOLOGY

#### 6.1 TNM classification

The new 2009 TNM classification for penile cancer (1) includes a change for the T1 category (Table 3). This classification needs a further update for the definition of the T2 category*. Two recent publications have shown that the prognosis for corpus spongiosum invasion is much better than for corpora cavernosa invasion (2,3).

**Table 3: 2009 TNM clinical and pathological classification of penile cancer**

<table>
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<th>Clinical classification</th>
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<tbody>
<tr>
<td><strong>T - Primary tumour</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive verrucous carcinoma, not associated with destructive invasion</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour invades subepithelial connective tissue without lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)</td>
</tr>
<tr>
<td>T2*</td>
<td>Tumour invades corpus spongiosum/corpora cavernosa</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades urethra</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades other adjacent structures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
<th></th>
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</thead>
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<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No palpable or visibly enlarged inguinal lymph node</td>
</tr>
<tr>
<td>N1</td>
<td>Palpable mobile unilateral inguinal lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>Palpable mobile multiple or bilateral inguinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pN - Regional lymph nodes</strong></td>
<td></td>
</tr>
<tr>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>pN1</td>
<td>Intranodal metastasis in a single inguinal lymph node</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastasis in multiple or bilateral inguinal lymph nodes</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastasis in pelvic lymph nodes, unilateral or bilateral or extranodal extension of regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological classification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pN - Regional lymph nodes</strong></td>
<td></td>
</tr>
<tr>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>pN1</td>
<td>Intranodal metastasis in a single inguinal lymph node</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastasis in multiple or bilateral inguinal lymph nodes</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pM0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>pM1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G - Histopathological grading</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GX - Grade of differentiation cannot be assessed</strong></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3-4</td>
<td>Poorly differentiated/undifferentiated</td>
</tr>
</tbody>
</table>
Rees et al. (2) have investigated 72 patients with T2 tumours. Local recurrence (35% vs. 17%) and mortality (30% vs. 21%) rates were higher in patients with tunica or cavernosal involvement versus glands-only invasion after a mean follow-up of 3 years (LE: 2b). The authors have proposed defining T2a patients by spongiosum-only invasion and T2b patients by involvement of tunica or corpus cavernosum.

A retrospective analysis of the records of 513 patients treated between 1956 and 2006 has confirmed the above-mentioned difference between tumour invasion of the corpus spongiosum only versus corpus cavernosum (3). It also has confirmed that there are no differences in long-term survival between patients with T2 and T3 tumours, and no significant differences between N1 and N2 tumours in the 1987-2002 TNM classification (LE: 2a).

In the new UICC 2009 TNM classification (1), retroperitoneal node metastases are correctly and accurately defined as extraregional nodal and distant metastases. The difference between corpus spongiosum and corpora cavernosa invasion is not considered.

6.1.1 References

6.2 Pathology
Squamous cell carcinoma accounts for more than 95% of cases of malignant disease of the penis. Malignant melanoma and basal cell carcinoma are much less common. It is not known how often SCC is preceded by premalignant lesions (1-4). Although SCC is the most common penile neoplasia, different types and varying growth patterns have been identified (5-7) (Tables 4 and 5).

Table 4: Premalignant lesions

<table>
<thead>
<tr>
<th>Lesions sporadically associated with SCC of the penis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cutaneous horn of the penis</td>
</tr>
<tr>
<td>• Bowenoid papulosis of the penis</td>
</tr>
<tr>
<td>• Balanitis xerotica obliterans (lichen sclerosus et atrophicus)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesions at high risk of developing SCC of the penis (up to one-third transform to invasive SCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Penile intraepithelial neoplasia (carcinoma in situ): erythroplasia of Queyrat and Bowen’s disease</td>
</tr>
</tbody>
</table>

Table 5: Penile SCC

<table>
<thead>
<tr>
<th>Types of SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Classic</td>
</tr>
<tr>
<td>• Basaloid</td>
</tr>
<tr>
<td>• Verrucous and its varieties:</td>
</tr>
<tr>
<td>• Warty (condylomatous) carcinoma</td>
</tr>
<tr>
<td>• Verrucous carcinoma</td>
</tr>
<tr>
<td>• Papillary carcinoma</td>
</tr>
<tr>
<td>• Hybrid verrucous carcinoma</td>
</tr>
<tr>
<td>• Mixed carcinomas (warty basaloid and adenobasaloid carcinoma)</td>
</tr>
<tr>
<td>• Sarcomatoid</td>
</tr>
<tr>
<td>• Adenosquamous</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Growth patterns of SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Superficial spread</td>
</tr>
<tr>
<td>• Nodular or vertical-phase growth</td>
</tr>
<tr>
<td>• Verrucous</td>
</tr>
</tbody>
</table>
Differentiation grading systems for SCC
- Broders’ grading system (8)
- Maiche’s system score (9)

6.2.1 **Penile biopsy**
There is no need for biopsy if:
- there is no doubt about the diagnosis and/or;
- treatment of the lymph nodes is postponed after treatment of the primary tumour and/or after histological examination of the sentinel node(s).

There is a need for histological confirmation if:
- there is doubt about the exact nature of the lesion (e.g. metastasis or melanoma) and/or;
- treatment of the lymph nodes is based on preoperative histological information (risk-adapted strategy).

In these cases an adequate biopsy is advised. When performing a biopsy, it is important to consider the findings from a study of biopsy size. Studies of biopsies with an average size of 0.1 cm found the following difficulties:
- difficulty in evaluating the extent of depth in 91% of biopsies;
- discordance between the grade at biopsy and in the final specimen in 30% of cases;
- failure to detect cancer in 3.5% of cases (1).

Thus, although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy is preferred.

6.2.2 **Pathological categories**
Traditionally, SCC has been considered as superficial or invasive. However, Cubilla et al. (5) have divided penile carcinoma into four categories:
- superficial spreading;
- vertical growth;
- verrucous;
- multicentric.

Different types of growth pattern have different prognoses (10) and different ways of dissemination. The limits of partial surgical resection must therefore be set according to the growth pattern at the time of evaluation of the frozen sections (11). If the margins are studied following these criteria (including urethral and periurethral tissue), only 3-4 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative (12). Basaloid SSC is a cellular subtype that is better recognised than before, and it is highly aggressive (13).

6.2.3 **Histology and metastatic risk**
Histological subtypes carry different risks of developing metastatic lymph nodes:
- Condylomatous: 18.2%;
- SCC: 56.7%;
- Sarcomatoid carcinoma: 89%.

Perineural (14) and lymphovascular invasion (14,15) are correlated with lymph node metastases, with 23.1% of positive lymph nodes associated with a nodular pattern, and 64.6% with an infiltrative pattern. Perineural invasion, lymphovascular invasion, and high histological grade appear to be the most important adverse pathological prognostic factors, reaching 80% mortality (15).

6.2.4 **References**
7. DIAGNOSIS AND STAGING

The primary tumour and regional lymph nodes must be staged correctly to enable the most appropriate treatment.

7.1 Primary lesion

Physical examination of a patient with penile cancer includes:
- diameter of the penile lesion or suspicious areas;
- location of lesion on the penis;
- number of lesions;
- morphology of lesion: papillary, nodular, ulcerous or flat;
- relationship of lesion to other structures, e.g. submucosa, tunica albuginea, and urethra;
- corpus spongiosum and corpus cavernosum;
- colour and boundaries of lesion;
- penis length.
Accurate histological diagnosis and staging of the primary tumour and regional nodes are necessary for making treatment decisions (1). In a small series, physical examination alone proved more reliable than imaging with ultrasound (US) to judge infiltration into the corpora cavernosa (2). Artificial erection with prostaglandin E1 (alprostadil) in combination with magnetic resonance imaging (MRI) is helpful in excluding tumour invasion into the corpora cavernosa, and deciding whether limited surgery (e.g. glansectomy) can be performed (3,4).

7.2 Regional lymph nodes

7.2.1 Lymphatic drainage of the penis

Primary lymphatic drainage of penile cancer occurs to the inguinal nodes. A recent single photon emission computed tomography (CT) study (5) has shown that all sentinel nodes were located in the superior and central inguinal zones, with most found in the medial superior zone. No lymphatic drainage was observed from the penis to the two inferior regions of the groin, and no direct drainage to the pelvic nodes was visualised. These findings confirm earlier studies (6-8).

7.2.2 Non-palpable nodes

Careful inguinal physical examination is necessary. In the absence of palpable abnormalities, inguinal US (7.5 MHz) can reveal abnormal nodes and can be used as a guide for fine-needle aspiration biopsy (FNAB) (9,10). A sentinel node biopsy (SNB) (8) was not recommended until 10 years ago because of a high rate of false-negative results (25%, range: 9-50%) (11). However, recent reports have suggested that dynamic sentinel node biopsy (DSNB) using indocyanine green (ICG) and/or Tc99m-colloid isosulphan blue improves survival compared to a ‘wait-and-see’ policy (LE: 3), and reduces side effects compared to those with inguinal lymphadenectomy (LAD) (12,13). Prospective studies on DSNB have obtained 100% specificity and 95% sensitivity (14-18) (LE: 2b). As analysis of dynamic SNB is operator-dependent (19) and relies on experience, the procedure is only available in a few centres. Nevertheless, a two-centre evaluation of DSNB has demonstrated the reproducibility of the technique, with a short learning curve (20).

Iliac lymph node metastases do not occur in the absence of inguinal metastases (19), therefore pelvic CT is not necessary in patients with no inguinal node metastases.

Conventional CT or MRI cannot detect micrometastases (21). No further studies have been performed to confirm the promising results reported with nanoparticle-enhanced MRI (22), but positron emission tomography (PET/CT) can detect pelvic and distant metastases (23).

7.2.3 Risk factors and metastasis detection

Patients with T1G1 category tumours do not need further therapy after local treatment, but in 13% up to 29% of cases those with intermediate T1G2 tumours can develop lymph node metastases (23,24). The risk for lymph node involvement can be evaluated by T and G categories and from other tumour characteristics.

Risk factors identified from retrospective studies include several pathological parameters, such as: perineural invasion, lymphovascular invasion, tumour depth or thickness, anatomical site, size and growth pattern, infiltrative front of invasion, positive resection margins, and urethral invasion (25). Several large series have identified lymphovascular invasion alone, lymphovascular invasion with absence of koilocytosis, lymphovascular invasion plus palpable inguinal nodes, and high histological grade plus perineural invasion as the most important risk factors (26-28).

Finally, the most adverse pathological prognostic factors appears to be lymphovascular invasion and high histological grade (28).

Nomograms have been used to evaluate the predictive value of clinical and pathological indicators, but pathological parameters and nomograms (23-30) cannot achieve more than 80% prediction (23-30). Only 18fluorodeoxyglucose (FDG) PET/CT can improve the detection of early regional and distant metastases (31).

7.2.4 Palpable nodes

Palpable nodes should be described as follows:

• node consistency;
• node location;
• diameter of nodes or masses;
• unilateral or bilateral location;
• number of nodes identified in each inguinal area;
• mobile or fixed nodes or masses;
• relationship (e.g. infiltration or perforation) to other structures, such as the skin or cooper ligament;
• oedema of leg and/or scrotum.

Palpable lymph node metastases can be diagnosed using percutaneous FNAB (cytology and/or histology
At the time of diagnosis of penile cancer, as many as 50% of palpable inguinal nodes will be reactive for concomitant infection rather than due to lymph node metastasis. In contrast, during follow-up, nearly 100% of enlarged nodes are metastatic (32) (LE: 2b).

Thus, after allowing time for inflammatory reactions to subside, regional nodes should be evaluated within a few weeks after treatment of the primary tumour. Histological diagnosis can be done using fine-needle aspiration, tissue core, or open biopsy, according to the preference of the pathologist (32,33) (LE: 2b). In the case of a negative biopsy and clinically suspicious nodes, a repeat or excisional biopsy should be performed.

### Conclusion

Imaging techniques (e.g. CT and MRI) are widely used, but they are only useful for staging patients with centrimetrical, or lymph node metastases ≥ 1 cm. So far, no current imaging modality can identify microscopic invasion. Imaging using 18FDG-PET/CT have some minor limitations (0.5 cm) (31). The use of molecular biological techniques is experimental (37-41).

### Distant metastases

An assessment of distant metastases should be performed in patients with positive inguinal nodes (23-35) (LE: 2b). PET/CT is reliable for identification of pelvic and distant metastases in patients with positive inguinal nodes (31). Routine blood analysis and plain radiography chest are usually performed, despite the fact that they have limited use and lung metastases are exceptionally rare. The value of SCC antigen determination as a staging tool is unclear and therefore not recommended for routine use (37). Biological studies are investigational (38-41).

A diagnostic schedule is summarised below.

### Guidelines for the diagnosis and staging of penile cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumour</strong></td>
<td></td>
</tr>
<tr>
<td>Physical examination, recording morphological and physical characteristics of the lesion.</td>
<td>C</td>
</tr>
<tr>
<td>Cytological and/or histological diagnosis.</td>
<td></td>
</tr>
<tr>
<td><strong>Inguinal lymph nodes</strong></td>
<td></td>
</tr>
<tr>
<td>Physical examination of both groins, recording nodal morphological and physical characteristics:</td>
<td>C</td>
</tr>
<tr>
<td>- If nodes are non-palpable, DSNB is indicated; if DSNB not available, US-guided FNAC/risk factors.</td>
<td></td>
</tr>
<tr>
<td>- If nodes are palpable, FNAC for cytological diagnosis.</td>
<td></td>
</tr>
<tr>
<td><strong>Regional metastases (inguinal and pelvic nodes)</strong></td>
<td></td>
</tr>
<tr>
<td>A pelvic CT/PET/CT is indicated in patients with metastatic inguinal nodes.</td>
<td>C</td>
</tr>
<tr>
<td><strong>Distant metastases (beside inguinal and pelvic nodes)</strong></td>
<td></td>
</tr>
<tr>
<td>PET/CT also allows evidence of distant metastasis.</td>
<td>C</td>
</tr>
<tr>
<td>If PET/CT is not available, abdominal CT and plain radiography chest are advisable, and in symptomatic M1 patients a bone scan is also advisable.</td>
<td></td>
</tr>
<tr>
<td><strong>Biological laboratory</strong></td>
<td></td>
</tr>
<tr>
<td>Determinations for penile cancer are investigational and not for clinical use.</td>
<td>C</td>
</tr>
</tbody>
</table>

CT = computed tomography; DSNB = dynamic sentinel node biopsy; FNAC = fine-needle aspiration cytology; PET = positron emission tomography.

### References


8. TREATMENT

The primary tumour and regional lymph nodes are usually treated separately. Although it is important to avoid overtreatment, which can lead to loss of penile tissue and adverse effects of an unnecessary lymphadenectomy, it is essential to remove all cancerous tissue with healthy margins.

8.1 Primary tumour

Guidelines on treatment strategies for primary tumour in penile cancer are outlined in Table 6. For small lesions, a penis-preserving strategy is recommended (GR: B). There is a variety of treatment modalities, which have not been compared in a scientifically rigorous manner, and providing recommendations based on published data is therefore difficult. However, treatment choice is influenced by tumour size, its position on the glans or in the corpora cavernosa, and experience of the treating urologist. There are no documented differences in the local recurrence rate between surgery, laser therapy, and radiotherapy. Although conservative surgery improves quality of life, the risk of local recurrence is higher than after ablative surgery (27% vs. 5%). The pathological assessment of surgical margins is essential to guarantee tumour-free margins (1). Tumour-positive margins lead inevitably to local recurrence. Total removal of the glans (glansectomy) and prepuce does have the lowest recurrence rate among the treatment modalities for small penile lesions (2%) (2).

8.1.1 Categories Tis, Ta, and T1a

Superficial lesions can be treated with one of the following penis-sparing techniques: LE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local excision with (or without) circumcision.</td>
<td>3</td>
</tr>
<tr>
<td>Laser therapy with CO(_2) laser (peniscopically controlled) or neodymium:yttrium:aluminium:garnet (Nd:YAG) laser (3-5). Small recurrences can be retreated in the same way.</td>
<td>2b</td>
</tr>
<tr>
<td>Mohs’ micrographic surgery (for verrucous carcinoma) (6).</td>
<td>3</td>
</tr>
<tr>
<td>Photodynamic and topical therapy with 5-fluorouracil (5-FU) or 5% imiquimod cream and other agents have been reported for superficial lesions with relatively high recurrence rates (7).</td>
<td>4</td>
</tr>
</tbody>
</table>

8.1.2 Category T1b tumours of the glans with deeper infiltration (> 1 mm)

These tumours can be treated with the following techniques: LE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide local (laser) excision plus reconstructive surgery or total glans resurfacing with or without skin transplantation (8).</td>
<td>2b</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy [vinblastine, bleomycin, and methotrexate (VBM)] followed by CO(_2) laser excision and spontaneous glans re-epithelialisation (3).</td>
<td>2b</td>
</tr>
<tr>
<td>Radiotherapy (see section 8.1.7).</td>
<td></td>
</tr>
<tr>
<td>Glansectomy (2,8-11).</td>
<td>2b</td>
</tr>
</tbody>
</table>

Conservative treatment may be less suitable in cases of multifocal lesions, which are responsible for 15% of recurrences. Total treatment of the glans surface combined with concomitant circumcision is recommended to avoid multiple recurrences (3) (GR: C).
Negative surgical margins are imperative when using penile-conserving treatments. Pathological assessment of the surgical margins is recommended (GR: C). In general, a margin of 3 mm is considered safe (1).

8.1.3  **Category T2 (limited to the glans)**
Total glansectomy, with or without resurfacing of the corporeal heads, is recommended (8, 10) (LE: 2b; GR: B). Radiotherapy is also an option (see section 8.1.7). Partial amputation should be considered in patients who are unfit for more conservative reconstructive surgery (11) (GR: C).

8.1.4  **Local disease recurrence after conservative surgery**
A second conservative procedure is advised if there is no corpus cavernosum invasion (2-8) (GR: C). If there is a large or deep infiltrating recurrence, partial or total amputation is inevitable (11) (GR: B). For those cases a total phallic reconstruction should be considered (12, 13).

8.1.5  **Category T2 with invasion into the corpus cavernosum**
Partial amputation with a tumour-free margin is considered standard treatment (11) (GR: B). A surgical margin of 5-10 mm is considered safe (1). Reconstruction may alleviate the mutilation (10, 12, 13).

8.1.6  **Categories T3 and T4**
These categories of patients are rare (e.g., 5% in Europe and 13% in Brazil) (13). Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumours (14) (GR: B). Spatulating the urethra is helpful in preventing stenosis. In more advanced disease (T4), neoadjuvant chemotherapy is advised, followed by surgery in responding patients (as for management of patients with fixed or relapsed inguinal nodes (see section 8.2.4) (GR: B). Otherwise, adjuvant chemotherapy or consolidating radiation is advised (GR: C; see sections 8.2.4 and 8.1.7).

8.1.7  **Radiotherapy**
Radiotherapy of the primary tumour is an alternative organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter (15-18) (LE: 2b). Best results have been obtained with brachytherapy with local control rates ranging from 70-90% (15, 17). Patients with lesions > 4 cm are not candidates for brachytherapy.

A minimum dose of 60 Gy is given for external radiotherapy combined with a brachytherapy boost, or brachytherapy alone (15-18). The penile preservation rate after radiotherapy is approximately 80%. Local failure rates after radiotherapy are higher than after partial penectomy, but salvage surgery can restore local control (16). The following complications are the most prevalent: urethral stenosis (20-35%), glans necrosis (10-20%), and late fibrosis of the corpora cavernosa (18) (LE: 3).

No scientifically sound recommendations can be given regarding surgical procedures versus radiotherapy. Institutional experience and available techniques play an important role in decision making.

8.1.8  **Guidelines for treatment strategies for penile cancer**
Table 6 provides a graded treatment schedule, also including the level of the underlying evidence on which the recommendations are based.

### Table 6: Treatment strategies for penile cancer

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>Conservative treatment is to be considered whenever possible</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category Tis, Ta, T1a (G1, G2)</td>
<td>CO₂ or Nd:YAG laser surgery, wide local excision, glans resurfacing, or glans resection, depending on size and location of the tumour.</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Mohs’ micrographic surgery or photodynamic therapy for well differentiated superficial lesions (Tis, G1 Ta).</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Category: T1b (G3) and T2 (glans only)</td>
<td>Glansectomy, with or without tips amputation or reconstruction.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Category T2 (invasion of the corpora)</td>
<td>Partial amputation.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Category T3 (invasion of urethra)</td>
<td>Total amputation with perineal urethrostomy.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
**Category T4**
(Other adj. structures)
Eligible patients: neoadjuvant chemotherapy followed by surgery in responders.
Alternative: external radiation.

**Local disease recurrence after conservative therapy**
Salvage surgery, consisting of penis-sparing treatment in small recurrences.
Larger recurrence: some form of amputation.

**Radiotherapy**
Organ-preserving treatment in selected patients with T1-T2 of glans or coronal sulcus, lesions < 4 cm.

**Chemotherapy**
Neoadjuvant, before surgery.
Palliation in advanced or metastatic disease.

CO₂ = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminum-garnet.

**8.2 Regional lymph nodes**
Guidelines on treatment strategies for nodal metastases are presented in section 8.2.7. Lymphadenectomy is the treatment of choice for patients with inguinal lymph node metastases (GR: B). The procedure requires careful skin-flap management, meticulous lymph node dissection, prophylactic antibiotics, compression stockings, and early ambulation. Prolonged lymph leakage, leg and scrotal lymphoedema, skin-flap necrosis, and wound infection can occur in 30-70% of patients (14) (LE: 2b). Recent studies have shown a decrease in complications, which suggests that these procedures should be done by experienced surgeons (19).

**8.2.1 Surveillance**
Surveillance can be recommended only in patients with Tis, Ta, and T1G1 tumours (14,19,20).

**8.2.2 Management of patients with non-palpable inguinal nodes**
All non-invasive diagnostic procedures miss approximately 20% of microscopic metastases. Also, the sensitivity of a published nomogram does not exceed 80% (21) (LE: 2b). Various risk factors have been helpful in stratifying node-negative patients for lymph node dissection (14,19-21) (LE: 2b). This approach was the basis for the 2004 guideline recommendations for the management of clinically node-negative patients (22). In centres without sentinel node diagnostics, these recommendations can still be useful. In addition, T1G2 tumours should be considered intermediate risk, based on a recent analysis (23). The experience from Brazil can be used as a gold standard for survival rates that can only be attained by surgery (14,19). Only DSNB has better sensitivity (94%) (24) (LE: 2b).

To identify the sentinel nodes reliably, preoperative mapping is essential. Tc99m nanocolloid is injected the day before surgery, patent blue is injected, and a γ-ray detection probe is used intraoperatively. Complete inguinal LAD is performed only in tumour-positive patients. The current protocol has a sensitivity of 95% (24). The technique is now reproducible with a short learning curve (25) (GR: B).

Considering the rarity of the disease and possible improvements in diagnosis and treatment, centralisation of patients is recommended. Centralisation of patients with penile SCC in 10 centres in the United Kingdom allowed improvement in the cure of the disease within a few years (26).

**8.2.3 Management of patients with palpable inguinal nodes**
US-guided FNAB provides an excellent, rapid, and easy way to detect metastatic nodal involvement (27) (LE: 3). In suspected cases with tumour-negative findings, various strategies can be followed:
(1) Antibiotics are given;
(2) FNAB is repeated;
(3) Suspected nodes are surgically removed;
(4) Inguinal LAD is performed. Dynamic sentinel node biopsy is not reliable in patients with palpable suspected nodes and should not be used (28) (LE: 3); DSNB can be used for the clinically uninvolved side and LAD is performed at the tumour-positive sites. Inguinal LAD has been shown to have significant morbidity and it is to be limited to positive sides.

In advanced cases, reconstructive surgery is often necessary for primary wound closure (29). Modified inguinal LAD is associated with less morbidity, but reducing the field of dissection increases the possibility of false-negative results. Current knowledge on lymphatic drainage of the penis suggests that modified LAD should dissect at least the central and both superior Daseler’s zones (30,31) (LE: 3).

There is no direct lymphatic drainage from penile tumours to the pelvic lymph nodes (30), therefore, pelvic LAD is not needed if there is no involvement of inguinal nodes or there is only one intranodal metastasis (14,19) (LE: 3).

In contrast, pelvic LAD is recommended if the node of Cloquet or two or more inguinal nodes are involved.
are involved. The rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes, and 56% for those with more than three positive inguinal nodes, or if there was extracapsular involvement in at least one inguinal node (14,19) (LE: 2b). Pelvic LAD can be performed as a secondary procedure.

If bilateral dissection is indicated, it can be performed though a midline suprapubic extraperitoneal incision. It is also important to avoid delay for LAD (31). Laparoscopy is not suitable for radical surgery.

8.2.4 Adjuvant chemotherapy
Adjuvant chemotherapy after resection of nodal metastases has been reported in a few small heterogeneous series. Nevertheless, at the National Cancer Institute in Milan, Italy, a long-term disease-free survival (DFS) rate of 84% was obtained in 25 consecutive node-positive patients treated with 12 adjuvant weekly courses of VBM during the period 1979-1990 (32,33). This compares with a DFS rate of only 39% for 38 consecutive patients who underwent radical LAD, with or without complementary radiotherapy, in the period 1960-1978 (32).

Since 1991, category pN2-3 patients have received three courses of adjuvant cisplatin and 5-FU, with lower toxicity and even better results compared to VBM (33) (LE: 2b). Category pN1 patients do not need adjuvant chemotherapy (33) (LE: 2b).

8.2.5 Management of patients with fixed or relapsed inguinal nodes
Upfront surgery is not recommended (GR: B) because cure is unlikely, survival is short, and the surgery is usually quite destructive. Upfront chemotherapy followed by surgery is promising, and these procedures should be performed by experienced medical oncologists and surgeons (14,32,33).

Multiple regimens have been used in a small number of patients. Cisplatin, methotrexate, and bleomycin (BMP) at Memorial Sloan-Kettering Cancer Center in New York have shown promising results, but a confirmatory study by the Southwest Oncology Group has reported unacceptable toxicity and only modest results (34).

Leijte et al. have reported on 20 patients with five different neoadjuvant chemotherapy regimens in the 1972-2005 period (36). Responders underwent post-chemotherapy surgery and achieved a 37% long-term survival rate. At the MD Anderson Cancer Center, combination therapy with paclitaxel, carboplatin or paclitaxel, cisplatin, and ifosfamide has been used in seven patients, followed by surgery (37). Four patients were long-term survivors (48-84 months) but none of the other three patients treated with BMP achieved significant remission.

A preliminary study on taxol combined with cisplatin and 5-FU has shown significant responses in five of six patients with fixed or relapsed inguinal nodes, but only the three who underwent post-chemotherapy surgery achieved durable complete remission (38).

Conclusions

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>Adjuvant chemotherapy is recommended in patients with pN2-3 tumours (33).</td>
<td>C</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy followed by radical surgery is advisable in patients with non-resectable or recurrent lymph node metastases (36-38).</td>
<td>C</td>
</tr>
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</table>

8.2.6 The role of radiotherapy
Prophylactic radiotherapy in patients with N0 tumours is not recommended (GR: C) because of:
- failure to prevent the development of metastatic lymph nodes;
- complications of radiotherapy;
- more difficult follow-up due to fibrotic changes.

Adjuvant radiotherapy may improve locoregional control in patients with extensive metastases and/or extranodal spread, but control is achieved at the cost of severe side effects including severe oedema and pain (GR: C).

8.2.7 Guidelines for treatment strategies for nodal metastases

<table>
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<tr>
<th>Regional lymph nodes</th>
<th>Management of regional lymph nodes is fundamental in the treatment of penile cancer</th>
<th>LE</th>
<th>GR</th>
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<tr>
<td>No palpable inguinal nodes</td>
<td>Tis, Ta G1, T1G1: surveillance. &gt; T1G2: DSNB. (NB: Inguinal LAD if histology is positive). If DSNB not available: risk factors / nomogram decision-making.</td>
<td>2a</td>
<td>B</td>
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20 PENILE CANCER - UPDATE APRIL 2010
Palpable inguinal nodes

US-guided FNAB (DSNB is unsuitable for palpable nodes).

Negative biopsy: surveillance (repeat biopsy).

Positive biopsy: inguinal LAD on positive side.

(NB: Modified LAD must include the central zone and both superior Daseler’s zones).

Pelvic nodes

Pelvic LAD if there is: extranodal metastasis; Cloquet node involved; > 2 inguinal node metastases.

Unilateral pelvic LAD if unilateral lymph node metastases with prolonged inguinal incision.

Bilateral pelvic LAD if bilateral inguinal metastases.

Adjuvant chemotherapy

In patients with > 1 intranodal metastasis (pN2 pN3) after radical LAD, survival is improved by adjuvant chemotherapy (3 courses of cisplatin, fluorouracil [PF] chemotherapy).

Patients with fixed or relapsed inguinal nodes

Neo-adjuvant chemotherapy is strongly recommended in patients with unresectable or recurrent lymph node metastases.

Taxanes seems to improve the efficacy of standard PF chemotherapy (or carboplatin).

Radiotherapy

Curative radiotherapy may be used for primary tumours of the glans penis and sulcus < 4 cm or for palliation.

Prophylactic radiotherapy in clinical N0 patients is not indicated.

DSNB = dynamic sentinel node biopsy; FNAB = fine-needle aspiration biopsy; LAD = lymphadenectomy.

8.3 References


9. FOLLOW-UP

Follow-up in penile carcinoma is important for several reasons:
• It enables early detection of recurrence, which is important because most local and/or loco-regional recurrences are potentially curable.
• It is the only way to assess treatment and anticipate early and late complications.
• It is important for patient (and physician) education.

A rational follow-up scheme requires an understanding of the patterns of recurrence. Preferably, follow-up should be introduced within the framework of a controlled study. Based on a retrospective study, a follow-up schedule for penile cancer has been published (1).

9.1 How to follow-up

The aim of follow-up is to detect local and/or regional recurrences because they can be cured. In contrast, metastases at distant sites are always fatal (2). Risk stratification for recurrence is also helpful. Traditional follow-up methods are inspection and physical evaluation. Modern US is a useful adjunct, with promising results from new imaging modalities, such as PET/CT (3).

9.2 When to follow-up

The follow-up interval and strategies for patients with penile cancer are directed by the initial treatment of the primary lesion and regional lymph nodes. In the above-mentioned multicentre study (1), during the first 2 years of follow-up, the following occurred:
• 74.3% of all recurrences;
• 66.4% of local recurrences;
• 86.1% of regional recurrences;
• 100% of distant recurrences.

Of all recurrences, 92.2% occurred within the first 5 years (1). All recurrences after 5 years were
local recurrences or new primary lesions. Thus, an intensive programme of follow-up during the first 2 years is rational, with less intensive follow-up needed thereafter. In well-educated and motivated patients, follow-up can stop after 5 years, although they must continue to carry out regular self-examination.

### 9.3 Primary tumour

Local recurrence has been reported in up to 30% of patients treated with penis-preserving surgery, during the first 2 years following treatment. Local recurrence is more likely with all types of local therapy, that is, local resection, laser therapy, brachytherapy, Mohs’ procedure, and associated therapies (1,4). However, in contrast to regional recurrence, local recurrence does not have an impact on survival (1,4).

Local recurrences are easily detected by the patient, his partner or doctor. Patient education is an important part of follow-up and the patient should be urged to visit a specialist if any changes are seen. Despite the fact that late local recurrences are well documented, it is reasonable to stop follow-up after 5 years, provided the patient will report local changes immediately (5). This is possible because life-threatening regional and distant metastases no longer occur, while recurrences that are local only are not life-threatening. The emphasis should be placed on patient self-examination. In patients who are unlikely to self-examine, long-term follow-up may be necessary.

Following penis-preserving treatment, a follow-up visit every 3 months is advised in the first 2 years. We then advise a follow-up visit every 6 months, provided that the patient and his partner have been well instructed to examine the penis regularly and to return if any abnormality is observed. It is important to stress that the patient must continue to carry out regular self-examination even after 5 years’ follow-up. After amputation, a less frequent time interval of every 6 months is advised. The risk of local recurrence is no more than 5% (1,4).

### 9.4 Regional recurrences

Stringent follow-up is advised for the 2 years following surgery. This is because most regional recurrences occur within that time, whether a ‘wait-and-see’ policy has been followed or the patient has undergone SNB or inguinal LAD.

Previous follow-up recommendations have relied heavily on physical examination of the inguinal regions. However, experience with ‘wait and see’ and DSNB have shown that, despite intensive follow-up, regional recurrences have shown up unexpectedly (6). US and immediate FNAB have been encouraging in finding occult metastases (6,7), and it seems reasonable to add US to physical examination.

Patients managed with a ‘wait-and-see’ policy have a higher risk of recurrence (9%) than patients staged surgically (2.3%), irrespective whether staging has been performed by LAD or DSNB. This finding only applies to patients without histopathological evidence of lymph node metastases.

Patients treated surgically because of lymph node metastases have an increased risk of recurrence (19%) (1). Based on these findings, a change in the follow-up scheme is proposed. For patients in a ‘wait-and-see’ programme and those treated with LAD for proven lymph node metastases, follow-up should be every 3 months and should include US investigation of the groin. This intensive follow-up programme should be observed for 2 years, which is the period when recurrence is most likely. Imaging using CT has been replaced by US scanning with immediate FNAB, and PET/CT is used in patients at risk of regional recurrence and distant metastases. Bone scan and other tests are only recommended in symptomatic patients.

### 9.5 Guidelines for follow-up in penile cancer

Table 7 provides a follow-up schedule for penile cancer with grades of recommendation.

#### Table 7: Follow-up schedule for penile cancer

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<td>Penile preserving treatment</td>
<td>3 months</td>
<td>6 months</td>
<td>Regular physician or self-examination</td>
</tr>
<tr>
<td>Amputation</td>
<td>6 months</td>
<td>1 year</td>
<td>Regular physician or self-examination</td>
</tr>
<tr>
<td><strong>Recommendations for follow-up of the inguinal lymph nodes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Wait-and-see’</td>
<td>3 months</td>
<td>6 months</td>
<td>Regular physician or self-examination</td>
</tr>
<tr>
<td>pN0</td>
<td>6 months</td>
<td>1 year</td>
<td>Regular physician or self-examination US with FNAB</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>--------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>pN+</td>
<td>3 months</td>
<td>6 months</td>
<td>Regular physician or self-examination US with FNAB</td>
</tr>
</tbody>
</table>

FNAB = fine-needle aspiration biopsy.

9.6 References

10. QUALITY OF LIFE

10.1 Sexuality and fertility after cancer
As more people achieve long-term survival after cancer, sexual dysfunction and infertility are increasingly recognised as negative consequences that affect the quality of life (1).

10.1.1 Sexual activity and quality of life after penile cancer laser treatment
A retrospective, face-to-face, structured interview study was carried out on Swedish patients treated with laser for localised penile carcinoma during 1986 to 2000 (2). Sixty-seven patients were treated, with 58 of them (mean age 63 years) still alive in 2006. Forty-six (79%) agreed to participate in the interview. Nearly all patients could recall their first symptom, with 37% reporting that they delayed seeking treatment for > 6 months. Patients had a greater lifetime number of sexual partners and a greater lifetime prevalence of sexually transmitted infections than the comparable general Swedish population. Following laser treatment, there was a marked decrease in some sexual practices, such as manual stimulation or caressing and fellatio. Patient satisfaction with life overall was similar to that of the general population.

In conclusion, some patients delayed seeking treatment for a considerable period despite awareness of the first local symptoms. Men with laser-treated localised penile carcinoma resumed their sexual activities to a large extent. Except for satisfaction with somatic health, a similar (or higher) proportion of patients were satisfied with life overall and with other domains of life including their sex life.

10.1.2 Sexual function after partial penectomy for penile cancer
To compare sexual function and satisfaction before and after partial penectomy, 18 Brazilian patients were given a personal interview and answered the International Index of Erectile Function questionnaire to determine erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction with sexual activity (3). The median patient age was 52 years. The median penile length after partial penectomy was
4 cm in the flaccid state, with 55.6% of patients reporting erectile function that allowed sexual intercourse. The main reason given for not resuming sexual intercourse in 50% of sexually abstinent patients was feeling shame because of a small penis and the absence of the glans penis. Surgical complications also compromised resumption of sexual activity after amputation in 33.3% of these patients. However, 66.7% sustained the same frequency and level of sexual desire prior to surgery, and 72.2% continued to have ejaculation and orgasm every time they had sexual stimulation or intercourse. Nevertheless, only 33.3% maintained their preoperative frequency of sexual intercourse and were satisfied with their sexual relationships with their partners and their overall sex life. In conclusion, the preoperative and postoperative scores were statistically worse for all domains of sexual function after partial penectomy.

10.2 Sexual mutilation, relapse, and death
Today, nearly 80% of penile cancer patients can be cured. Experience in management of this rare tumour is helpful (4). Referral to centres with experience is recommended. Psychological support is very important for these patients. Penis-sparing surgery obviously allows a better quality of life than penile amputation and must be considered whenever feasible.

10.3 References
11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

<table>
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<th>Description</th>
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<td>5-FU</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>BMP</td>
<td>cisplatin, methotrexate and bleomycin</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DFS</td>
<td>disease-free survival</td>
</tr>
<tr>
<td>DSNB</td>
<td>dynamic sentinel node biopsy</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>FDA</td>
<td>[US] Food and Drug Administration</td>
</tr>
<tr>
<td>FDG</td>
<td>fluorodeoxyglucose</td>
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<tr>
<td>FNAB</td>
<td>fine-needle aspiration biopsy</td>
</tr>
<tr>
<td>FNAC</td>
<td>fine-needle aspiration cytology</td>
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<tr>
<td>GR</td>
<td>grade of recommendation</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<tr>
<td>LAD</td>
<td>lymphadenectomy</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>Nd:YAG</td>
<td>neodymium:yttrium-aluminum-garnet</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>PF</td>
<td>cisplatin and fluorouracil</td>
</tr>
<tr>
<td>SCC</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>SNB</td>
<td>sentinel node biopsy</td>
</tr>
<tr>
<td>TC99m</td>
<td>technetium 99m</td>
</tr>
<tr>
<td>TNM</td>
<td>tumour, node, metastasis</td>
</tr>
<tr>
<td>VBM</td>
<td>vinblastine, bleomycin, methotrexate</td>
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Conflict of interest

All members of the Penile Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on the Management of Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)


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7. ABBREVIATIONS USED IN THE TEXT
1. INTRODUCTION

Lower urinary tract symptoms (LUTS) in elderly men were traditionally attributed to the enlarging prostate. The mechanisms invoked were one or all of the following: histological benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), or benign prostatic obstruction (BPO). However, during the last decade the causal link between the prostate and the pathogenesis of LUTS has come into question (1). Although the enlarged prostate can contribute to the onset of LUTS in a proportion of men over 40 years of age, other factors are of equal importance. Latest knowledge suggests that LUTS may be linked to the prostate (BPH-LUTS), bladder (detrusor overactivity-overactive bladder syndrome [OAB], detrusor underactivity) or kidney (nocturnal polyuria) (1). Because of the great prevalence of BPH in elderly men, which is as high as 40% in men in their fifth decade and 90% in men in their ninth decade (2), microscopical changes of the prostate seem to co-exist silently with other bladder or kidney malfunctions in some men. The many causes of LUTS are illustrated in Figure 1. In any single person complaining of LUTS it is common for more than one of these factors to be present. This multi-factorial view of the aetiology of LUTS has led most experts to regard the whole urinary tract as a single functional unit. This broader, more complex approach to the pathogenesis of LUTS meant that we modified the title - to reflect the change in perspective - from the former EAU Guidelines on LUTS suggestive of BPO (3) to the more contemporary and precise EAU Guidelines on Male LUTS, including BPO.

![Figure 1: Multifactorial aetiology of lower urinary tract symptoms (LUTS). The EAU Guidelines on Male LUTS mainly cover LUTS secondary to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO), detrusor overactivity or overactive bladder (OAB), and nocturia due to nocturnal polyuria. Other causes of male LUTS are covered by separate EAU Guidelines.](image-url)

Because patients seek help for LUTS and not an underlying attribute of the prostate such as BPH or BPE, these updated guidelines have been written from the perspective of men who complain about a variety of bladder storage, voiding and/or post-micturition symptoms. The recommendations made within the guidelines are based on the best available evidence. These recommendations apply to men aged 40 years or older who seek professional help for various forms of non-neurogenic benign forms of LUTS, e.g. LUTS/BPO, detrusor...
overactivity—overactive bladder (OAB), or nocturnal polyuria. Assessment and treatment of neurogenic LUTS has been published elsewhere and is valid only for men and women with bladder symptoms due to neurological diseases (4). EAU Guidelines on LUTS due to urinary incontinence, urogenital infections, ureteral stones, or malignant diseases of the lower urinary tract have been published elsewhere.

The recommendations of these guidelines are based on a structured literature search using articles in English language published in the PubMed/Medline, Web of Science, and Cochrane databases between 1966 and 1st January 2010, including the search terms “lower urinary tract symptoms”, “benign prostatic hyperplasia”, “detrusor overactivity”, “overactive bladder”, “nocturia”, and “nocturnal polyuria” in combination with the various treatment modalities and the search limits “humans”, “adult men”, “review”, “randomised clinical trials”, “clinical trials”, and “meta-analysis”. There have been no new drugs licensed since the literature search.


Language: English

Literature Search: conducted 1st February - 1st March 2010

Search Period: 1966 - 1st January 2010

<table>
<thead>
<tr>
<th>Search limits …</th>
<th>for group search terms …</th>
<th>in combination with investigated drugs, operations, or synonyms</th>
</tr>
</thead>
</table>

Each extracted article was separately analysed, classified, and labelled with a Level of Evidence (LE), according to a classification system modified from the Oxford Centre for Evidence-based Medicine in 2001 (LE: 1a, highest evidence level) to expert opinion (LE: 4, lowest evidence level) (5). Subsections for the various types of conservative treatments, drugs, and operations are presented in a homogeneous structure listing (1) “mechanism of action”, (2) “available drugs” with a table of key pharmacokinetic profiles or “operative procedure” in case of surgical intervention, (3) “efficacy” with a table of trials with the highest LE, (4) “tolerability and safety”, (5) “practical considerations”, and (6) “recommendations”, which were drawn from the relevant articles using a Grade of Recommendation (GR) according to a classification system modified from the Oxford Centre for Evidence-based Medicine, ranging from a strong (Grade A) to a weak (Grade C) recommendation. (5).

The working panel consisted of urologists, a pharmacologist, and an epidemiologist and statistician who have been working on the topic for the last 4 years. The guidelines are primarily written for urologists but can also be used by general practitioners, patients, or other stakeholders. The working panel intends to update the content and recommendations, according to the given structure and classification systems, every 2 years.

An update of these guidelines will be presented on the website of the EAU in the course of 2013. A complete revision will be included in the 2014 print version of the EAU Guidelines.

1.1 References


2. ASSESSMENT

Systematic diagnostic work-up should be done by history, validated symptom questionnaires (e.g. IPSS), both ideally proactively, physical examination, urinalysis, blood analysis, ultrasound (US) of the prostate, bladder and kidneys, uroflowmetry and US measurement of post-void residual urine, and bladder diary in cases of urinary frequency or nocturia. Only the diagnosis of nocturnal polyuria (> 33% of the 24-hour urine excretion overnight) can be made by the bladder diary, whereas the diagnosis of all other forms of non-neurogenic benign forms of LUTS in men aged 40 years or older is mainly made by exclusion. The systematic work-up should exclude relevant diseases or conditions also causing LUTS in adult men. An assessment algorithm is proposed in figure 2.

---

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older. Systematic work-up can exclude other diseases or conditions also associated with LUTS. The assessment may be interrupted or stopped when relevant pathologies have been identified.
Benign prostatic obstruction and detrusor overactivity are urodynamic diagnoses. Filling cystometry and pressure-flow measurement are optional tests usually indicated before surgical treatment in men who:

- cannot void ≥ 150 mL;
- have a maximum flow rate ≥ 15 mL/s;
- are < 50 or > 80 years of age;
- can void but have post-void residual urine > 300 mL;
- are suspicious of having neurogenic bladder dysfunction;
- have bilateral hydronephrosis;
- had radical pelvic surgery or;
- had previous unsuccessful (invasive) treatment.

3. CONSERVATIVE TREATMENT

3.1 Watchful waiting - behavioural treatment
Many men with LUTS do not complain of high levels of bother and are therefore suitable for non-medical and non-surgical management - a policy of care known as watchful waiting (WW). It is customary for this type of management to include the following components: education, reassurance, periodic monitoring, and lifestyle advice. In many patients, it is regarded as the first tier in the therapeutic cascade and most men will have been offered WW at some point. Watchful waiting is a viable option for many men as few, if left untreated, will progress to acute urinary retention and complications such as renal insufficiency and stones (1,2). Similarly, some symptoms may improve spontaneously, while other symptoms remain stable for many years (3).

3.2 Patient selection
All men with LUTS should be formally assessed prior to starting any form of management in order to identify those with complications that may benefit from intervention therapy. Men with mild to moderate uncomplicated LUTS (causing no serious health threat), who are not too bothered by their symptoms, are suitable for a trial of WW. A large study comparing WW and transurethral resection of the prostate (TURP) in men with moderate symptoms showed that those who had undergone surgery had improved bladder function over the WW group (flow rates and post-void residual volumes), with the best results being in those with high levels of bother. Thirty-six per cent of patients crossed over to surgery in 5 years, leaving 64% doing well in the WW group (4). Approximately 85% of men will be stable on WW at 1 year, deteriorating progressively to 65% at 5 years (5, 6). The reason why some men deteriorate with WW and others do not is not well understood; increasing symptom bother and PVR volumes appeared to be the strongest predictors of failure.

3.3 Education, reassurance, and periodic monitoring
There now exists LE 1b that self-management as part of WW reduces both symptoms and progression (7, 8) (Table 1). In this study, men randomised to three self-management sessions in addition to standard care had better symptom improvement and improved quality of life at 3 and 6 months when compared to men treated with standard care only. These differences were maintained at 12 months. Nobody is quite sure which key components of self-management are effective, but most experts believe the key components are:

- education about the patient’s condition;
- reassurance that cancer is not a cause of the urinary symptoms;
- framework of periodic monitoring.

Table 1: Self-management as part of watchful waiting reduces symptoms and progression (7)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>Patients</th>
<th>IPSS</th>
<th>Qmax (mL/s)</th>
<th>PVR (mL)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (2007) (7)</td>
<td>52</td>
<td>Standard care</td>
<td>67</td>
<td>-1.3</td>
<td>-</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard care plus self-management</td>
<td>73</td>
<td>-5.7</td>
<td>*†</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

IPSS = International Prostate Symptom Score; Qmax = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual

* significant compared to standard care (p < 0.05); † significant compared to baseline (p < 0.05)
3.4 Lifestyle advice

The precise role of lifestyle advice in conferring benefit seen in the studies reported to date remains uncertain. Minor changes in lifestyle and behaviour can have a beneficial effect on symptoms and may prevent deterioration requiring medical or surgical treatment. Lifestyle advice can be obtained through informal and formal routes. If it is offered to men, it should probably comprise the following:

- Reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient, e.g. at night or going out in public. The recommended total daily fluid intake of 1500 mL should not be reduced.
- Avoidance or moderation of caffeine and alcohol which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia.
- Use of relaxed and double-voiding techniques.
- Urethral stripping to prevent post-micturition dribble.
- Distraction techniques, such as penile squeeze, breathing exercises, perineal pressure and mental ‘tricks’ to take the mind off the bladder and toilet, to help control irritative symptoms.
- Bladder re-training, by which men are encouraged to ‘hold on’ when they have sensory urgency to increase their bladder capacity (to around 400 mL) and the time between voids.
- Reviewing a man’s medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects.
- Providing necessary assistance when there is impairment of dexterity, mobility or mental state.
- Treatment of constipation.

3.5 Practical considerations

The components of self-management have not been individually subjected to study. The above components of lifestyle advice have been derived from formal consensus methodology (9). Further research in this area is required.

3.6 Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men with mild symptoms are suitable for watchful waiting.</td>
<td>1b A</td>
</tr>
<tr>
<td>Men with lower urinary tract symptoms should be offered lifestyle advice prior to or concurrent with treatment.</td>
<td>1b A</td>
</tr>
</tbody>
</table>

3.7 References


4. DRUG TREATMENT

4.1 \(\alpha_1\)-adrenoceptor antagonists (\(\alpha_1\)-blockers)

4.1.1 Mechanism of action

Historically, it was assumed that \(\alpha_1\)-blockers act by inhibiting the effect of endogenously released noradrenaline on prostate smooth muscle cells, thereby reducing prostate tone and bladder outlet obstruction. Contraction of the human prostate is mediated predominantly, if not exclusively, by \(\alpha_1\)A-adrenoceptors (1). However, it has been shown that \(\alpha_1\)-blockers have little effect on urodynamically determined bladder outlet resistance (2) and treatment-associated improvement of LUTS is correlated only poorly with obstruction (3). Hence, there has been a lot of discussion about the role of \(\alpha_1\)-adrenoceptors located outside the prostate (e.g. in the urinary bladder and/or spinal cord) and other \(\alpha\)-adrenoceptor subtypes (\(\alpha_1\)B- or \(\alpha_1\)D-adrenoceptors) as mediators of beneficial effects of \(\alpha_1\)-blockers. \(\alpha_1\)-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and central nervous system are considered to be mediators of side-effects during \(\alpha\)-blocker treatment, and all three receptor subtypes seem to be involved. This concept has favoured the use of \(\alpha_1\)A-selective adrenoceptor antagonists. However, it remains to be determined whether \(\alpha_1\)A-selectivity is the only and main factor determining good tolerability.

4.1.2 Available drugs

Following the early use of phenoxybenzamine and prazosin in BPH-LUTS treatment, four \(\alpha_1\)-blockers are currently in mainstream use:

- alfuzosin HCL (alfuzosin);
- doxazosin mesylate (doxazosin);
- tamsulosin HCL (tamsulosin);
- terazosin HCL (terazosin).

Over a period of time, alfuzosin has been clinically available in Europe in three formulations, doxazosin and tamsulosin in two formulations each, and terazosin in one formulation (Table 2). Although different formulations result in different pharmacokinetic behaviours and, perhaps, tolerability profiles, the overall clinical impact of the different formulations is modest. Although some countries also have available indoramin, naftopidil and more recently silodosin, there have been only limited clinical data for these agents at the time of the literature search and, hence, they will not be discussed in these guidelines.
Table 2: Key pharmacokinetic properties and standard doses of α1-blockers licensed in Europe for treating symptoms of BPH

<table>
<thead>
<tr>
<th>Drug</th>
<th>t\text{max} (hours)</th>
<th>t\text{½} (hours)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin IR</td>
<td>1.5</td>
<td>4-6</td>
<td>3 x 2.5 mg</td>
</tr>
<tr>
<td>Alfuzosin SR</td>
<td>3</td>
<td>8</td>
<td>2 x 5 mg</td>
</tr>
<tr>
<td>Alfuzosin XL</td>
<td>9</td>
<td>11</td>
<td>1 x 10 mg</td>
</tr>
<tr>
<td>Doxazosin IR</td>
<td>2-3</td>
<td>20</td>
<td>1 x 2-8 mg</td>
</tr>
<tr>
<td>Doxazosin GITS</td>
<td>8-12</td>
<td>20</td>
<td>1 x 4-8 mg</td>
</tr>
<tr>
<td>Silodosin</td>
<td>2.5</td>
<td>11-18</td>
<td>1 x 4-8 mg</td>
</tr>
<tr>
<td>Tamsulosin MR</td>
<td>6</td>
<td>10-13</td>
<td>1 x 0.4 mg</td>
</tr>
<tr>
<td>Tamsulosin OCAS</td>
<td>4-6</td>
<td>14-15</td>
<td>1 x 0.4 mg</td>
</tr>
<tr>
<td>Terazosin</td>
<td>1-2</td>
<td>8-14</td>
<td>1 x 5-10 mg</td>
</tr>
</tbody>
</table>

\(t\text{max} = \text{time to maximum plasma concentration; } t\text{½} = \text{elimination half-life; } IR = \text{immediate release; } SR = \text{sustained release; GITS = Gastrointestinal Therapeutic System; MR = Modified Release; OCAS = Oral Controlled Absorption System.}\)

4.1.3 **Efficacy**

Indirect comparisons between α1-blockers, and limited direct comparisons, demonstrate that all α1-blockers have a similar efficacy in appropriate doses (4). Controlled studies have shown that α1-blockers typically reduce the International Prostate Symptom Score (IPSS), after a run-in period, by approximately 35-40% and increase the maximum urinary flow rate (Q\text{max}) by approximately 20-25% (Table 3). However, considerable improvements also occurred in the corresponding placebo arms (4,5). In open-label studies (without a run-in period), an IPSS improvement of up to 50% and Q\text{max} increase of up to 40% were documented (4,6).

Although these improvements take a few weeks to develop fully, statistically significant efficacy over placebo was demonstrated within hours to days. α1-blockers seem to have a similar efficacy, expressed as a percent improvement in IPPS, in patients with mild, moderate and severe symptoms (6). Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of <1 year, but patients with smaller prostates (<40 mL) seem to have better efficacy compared to those with larger glands in longer-term and is similar across age groups (6). α1-blockers do not reduce prostate size and do not prevent acute urinary retention in long-term studies (8), so that eventually some patients will have to be surgically treated. Nevertheless, the efficacy of α1-blockers appears to be maintained over at least 4 years.

Table 3: Randomised, placebo-controlled trials with α1-blockers in men with LUTS (drugs in chronological order; selection of trials)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment (daily dose)</th>
<th>Patients (n)</th>
<th>Change in symptoms (%)</th>
<th>Change in Q\text{max} (mL/s)</th>
<th>PVR change (%)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jardin et al. (1991) [14]</td>
<td>24</td>
<td>Placebo Alfuzosin 3 x 2.5 mg</td>
<td>267 251</td>
<td>-32 a -42 ab</td>
<td>+1.3 a +1.4 a</td>
<td>-9 -39 ab</td>
<td>1b</td>
</tr>
<tr>
<td>Buzelin et al. (1997) [15]</td>
<td>12</td>
<td>Placebo Alfuzosin 2 x 5 mg</td>
<td>196 194</td>
<td>-18 -31 ab</td>
<td>+1.1 +2.4 ab</td>
<td>0 -17 ab</td>
<td>1b</td>
</tr>
<tr>
<td>van Kerrebroeck et al. (2000) [16]</td>
<td>12</td>
<td>Placebo Alfuzosin 3 x 2.5 mg</td>
<td>154 150 143</td>
<td>-27.7 -38.1 ab -39.9 ab</td>
<td>+1.4 +3.2 ab +2.3 ab</td>
<td>- -</td>
<td>1b</td>
</tr>
<tr>
<td>MacDonald and Witt (2005) [17]</td>
<td>4-26</td>
<td>Placebo: all formulations</td>
<td>1039 1928</td>
<td>-0.9 b (Boyarski) † -1.8 b (IPSS) †</td>
<td>+1.2 b</td>
<td>-</td>
<td>1a</td>
</tr>
<tr>
<td>Kirby et al. (2001) [18]</td>
<td>13</td>
<td>Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS</td>
<td>155 640 651</td>
<td>-34 a -45 ab -45 ab</td>
<td>+1.1 a +2.6 ab +2.8 ab</td>
<td>- -</td>
<td>1b</td>
</tr>
<tr>
<td>McConnell et al. (2003) [8]</td>
<td>234</td>
<td>Placebo Doxazosin 1 x 4-8 mg</td>
<td>737 756</td>
<td>-29 b -39 b</td>
<td>+1.4 +2.5 ab</td>
<td>- -</td>
<td>1b</td>
</tr>
<tr>
<td>Study References</td>
<td>Participants</td>
<td>Placebo</td>
<td>Tamsulosin MR 1 x 0.4 mg</td>
<td>Tamsulosin MR 1 x 0.8 mg</td>
<td>PVR</td>
<td>Qmax</td>
<td>Comparison</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>---------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>-----</td>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>Chapple et al. (1996) [19]</td>
<td>12 Placebo</td>
<td>185</td>
<td>-25.5</td>
<td>+0.6</td>
<td>-13.4</td>
<td>12 Placebo</td>
<td>Tamsulosin MR 1 x 0.4 mg</td>
</tr>
<tr>
<td>Lepor (1998) [20]</td>
<td>13 Placebo</td>
<td>253</td>
<td>-28.1</td>
<td>+0.5</td>
<td>- -</td>
<td>13 Placebo</td>
<td>Tamsulosin MR 1 x 0.4 mg</td>
</tr>
<tr>
<td>Tamsulosin MR 1 x 0.8 mg</td>
<td>247</td>
<td>-48.2</td>
<td>- -</td>
<td>+1.8</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapple et al. (2005) [21]</td>
<td>12 Placebo</td>
<td>350</td>
<td>-32</td>
<td>- -</td>
<td>-</td>
<td>12 Placebo</td>
<td>Tamsulosin MR 1 x 0.4 mg</td>
</tr>
<tr>
<td>Tamsulosin OCAS 1 x 0.4 mg</td>
<td>354</td>
<td>-41.7</td>
<td>- -</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamsulosin OCAS 1 x 0.8 mg</td>
<td>707</td>
<td>-42.4</td>
<td>- -</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilt et al. (2002) [22]</td>
<td>4-26 Placebo</td>
<td>4122</td>
<td>-12 b (-1.1 Boyarski †)</td>
<td>+1.1 b</td>
<td>-</td>
<td>4-26 Placebo</td>
<td>Tamsulosin 1 x 0.4-0.8 mg</td>
</tr>
<tr>
<td>Brawer et al. (1993) [23]</td>
<td>24 Placebo</td>
<td>72</td>
<td>-11 a,b</td>
<td>+1.2</td>
<td>-</td>
<td>24 Placebo</td>
<td>Terazosin 1 x 1-10 mg</td>
</tr>
<tr>
<td>Roehrborn et al. (1996) [24]</td>
<td>52 Placebo</td>
<td>973</td>
<td>-18.4</td>
<td>+0.8 a</td>
<td>-</td>
<td>52 Placebo</td>
<td>Terazosin 1 x 1-10 mg</td>
</tr>
<tr>
<td>Wilt et al. (2000) [25]</td>
<td>4-52 Placebo</td>
<td>5151</td>
<td>-37 b (-2.9 Boyarski †)</td>
<td>+1.7 b</td>
<td>-</td>
<td>4-52 Placebo</td>
<td>Terazosin</td>
</tr>
</tbody>
</table>

Qmax = maximum urinary flow rate (free uroflowmetry); PVR = post-void residual; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo; † = absolute value

4.1.4 Tolerability and safety

Although alfuzosin, doxazosin, and terazosin are similar in terms of molecular structure and lack of α1-adrenoceptor subtype selectivity, the side-effect profile of alfuzosin is more similar to tamsulosin than to doxazosin and terazosin. The mechanisms underlying such differential tolerability are not fully understood, but may involve better distribution into lower urinary tract tissues by alfuzosin and tamsulosin. Other factors, such as subtype selectivity and the pharmacokinetic profiles of certain formulations, may also contribute to the tolerability profile of specific drugs.

The most frequent side-effects of α1-blockers are asthenia, dizziness and (orthostatic) hypotension. Although a reduction in blood pressure may benefit hypertensive patients, at least some of the observed asthenia and dizziness can be attributed to a decrease in blood pressure. Vasodilating effects are most pronounced with doxazosin and terazosin, and are much less common for alfuzosin and tamsulosin. The mechanisms underlying such differential tolerability are not fully understood, but may involve better distribution into lower urinary tract tissues by alfuzosin and tamsulosin. Other factors, such as subtype selectivity and the pharmacokinetic profiles of certain formulations, may also contribute to the tolerability profile of specific drugs.

Despite the long-standing and widespread use of α1-blockers, an adverse ocular event, termed intraoperative floppy iris syndrome (IFIS), has been discovered only recently in the context of cataract surgery (10). Although IFIS has been observed with all α1-blockers, most reports have been related to tamsulosin. Whether this reflects a greater risk with tamsulosin than with other α1-blockers, or rather its more widespread use, is not clear, particularly as the ratio between doses yielding ocular effects and those acting on the lower urinary tract are similar for all α1-blockers (11). It therefore appears prudent not to initiate α1-blocker treatment prior to cataract surgery, while existing α1-blocker treatment should be stopped though it is not clear how long before surgery takes place. It should be noted that the occurrence of IFIS complicates cataract surgery and makes it technically more demanding, however, there are no reports about increased health risks of these patients.

As LUTS and ED often co-exist, medical BPH treatment should not further impair sexual function. A systematic review concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation (12). Originally, the abnormal ejaculation...
was thought to be retrograde, but more recent data demonstrate that it is due to (relative) anejaculation, with young age being an apparent risk factor. Although abnormal ejaculation has been observed more frequently with tamsulosin than with other \(\alpha_1\)-blockers, this difference did not reach statistical significance in direct comparative studies with alfuzosin and is not associated with an overall reduction of overall sexual function (12). The apparently greater risk for abnormal ejaculation with tamsulosin is intriguing as even more \(\alpha_1\)-selective drugs, such as silodosin, carry a greater risk (13), however, all \(\alpha_1\)-blockers are dosed to block \(\alpha_1\)-adrenoceptors effectively. Hence, the mechanism underlying abnormal ejaculation remains to be elucidated.

4.1.5 Practical considerations
\(\alpha_1\)-blockers are often considered the first-line drug treatment of moderate-to-severe male LUTS. All \(\alpha_1\)-blockers are available in formulations, which are suitable for once-daily administration. To minimise adverse events, it is recommended that dose titration is used to initiate treatment with doxazosin and terazosin, however, this is not necessary with alfuzosin and tamsulosin. Because of their rapid onset of action, \(\alpha_1\)-blockers can be considered for intermittent use in patients with fluctuating intensity of symptoms not needing long-term treatment.

4.1.6 Recommendation

<table>
<thead>
<tr>
<th>(\alpha_1)-blockers should be offered to men with moderate-to-severe lower urinary tract symptoms</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

4.1.7 References

4.2 5α-reductase inhibitors

4.2.1 Mechanism of action
Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted primarily in the prostatic stroma cells from its precursor testosterone by the enzyme 5α-reductase, a nuclear-bound steroid enzyme (1). Two isoforms of this enzyme exist:
• 5α-reductase type 1, with minor expression and activity in the prostate but predominant activity in...
extraprostatic tissues, such as skin and liver.

- 5α-reductase type 2, with predominant expression and activity in the prostate.

Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5α-reductase inhibitor). However, the clinical role of dual inhibition remains unclear. 5α-reductase inhibitors act by inducing apoptosis of prostate epithelial cells (2) leading to prostate size reduction of about 18-28% and circulating PSA levels of about 50% after 6-12 months of treatment (3). Mean prostate volume reduction may be even more pronounced after long-term treatment.

### 4.2.2 Available drugs

Two 5α-reductase inhibitors are available for clinical use: dutasteride and finasteride (Table 4). The elimination half-time is longer for dutasteride (3-5 weeks). Both 5α-reductase inhibitors are metabolised by the liver and excreted in the faeces. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5α-reductase inhibitors.

**Table 4: 5α-reductase inhibitors licensed in Europe for treating benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH); key pharmacokinetic properties and standard doses**

<table>
<thead>
<tr>
<th>Drug</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (hours)</th>
<th>t½ (weeks)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutasteride</td>
<td>1-3</td>
<td>3-5</td>
<td>1 x 0.5 mg</td>
</tr>
<tr>
<td>Finasteride</td>
<td>2</td>
<td>6-8</td>
<td>1 x 5 mg</td>
</tr>
</tbody>
</table>

<sub>t<sub>max</sub> = time to maximum plasma concentration; t½ = elimination half-life</sub>

### 4.2.3 Efficacy

Clinical effects relative to placebo are seen after minimum treatment duration of at least 6 to 12 months. After 2 to 4 years of treatment, 5α-reductase inhibitors reduce LUTS (IPSS) by approximately 15-30%, decrease prostate volume by approximately 18-28% and increase Q<sub>max</sub> of free uroflowmetry by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement (Table 5) (4-13).

Symptom reduction by finasteride depends on initial prostate size and may not be more efficacious than placebo in patients with prostates smaller than 40 mL (14). However, dutasteride seems to reduce IPSS, prostate volume, and the risk of acute urinary retention. It also increases Q<sub>max</sub> even in patients with prostate volumes between 30 and 40 mL at baseline (15,16). Indirect comparison between individual studies and one unpublished direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS (3). Comparative studies with α<sub>1</sub>-blockers have demonstrated that 5α-reductase inhibitors reduce symptoms more slowly and, for finasteride, less effectively (5,10,17,18). A long-term trial with dutasteride in symptomatic men with a prostate volume greater than 30 mL (average prostate volume in the CombAT trial was approximately 55 mL) showed that the 5α-reductase inhibitor reduced LUTS in these patients at least as much or even more effectively than tamsulosin (11,12). The greater the baseline prostate volume (serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride (19). International prostate symptom score reduction was significantly greater in men with prostate volumes of 58 mL or more (PSA > 4.4) at treatment month 15 or later compared to men with lower baseline prostate volumes (PSA concentrations).

5α-reductase inhibitors, but not α<sub>1</sub>-blockers, reduce the long-term (> 1 year) risk of acute urinary retention or need for surgery (8,10,19,20). Prevention of disease progression by 5α-reductase inhibitors is already detectable with prostate sizes considerably smaller than 40 mL (12,13,20). The precise mechanism of action of 5α-reductase inhibitors in reducing disease progression remains to be determined, but it is most likely attributable to reduction of bladder outlet resistance. Open-label trials demonstrated relevant reductions of voiding parameters after computer-urodynamic re-evaluation in men who were treated at least 3 years with finasteride (21,22).
Table 5: Randomised trials with 5α-reductase inhibitors in men with LUTS and benign prostatic enlargement due to BPH

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment (daily dose)</th>
<th>Patients (n)</th>
<th>Change in symptoms (% IPSS)</th>
<th>Change in Qmax (mL/s)</th>
<th>Change in prostate volume (%)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepor et al. (1996) [4]</td>
<td>52</td>
<td>Placebo 305 Finasteride 1 x 5 mg</td>
<td>310</td>
<td>-16.5 a⁺</td>
<td>+1.6</td>
<td>-16.9 b⁻</td>
<td>1b</td>
</tr>
<tr>
<td>Kirby et al. (2003) [5]</td>
<td>52</td>
<td>Placebo 253 Finasteride 1 x 5 mg</td>
<td>239</td>
<td>-38.6 a⁻</td>
<td>+1.8</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td>Andersen et al. (1995) [6]</td>
<td>104</td>
<td>Placebo 346 Finasteride 1 x 5 mg</td>
<td>348</td>
<td>-14.9 a,b⁻</td>
<td>+1.5 a,b⁻</td>
<td>-19.2 a,b⁻</td>
<td>1b</td>
</tr>
<tr>
<td>Nickel et al. (1996) [7]</td>
<td>104</td>
<td>Placebo 226 Finasteride 1 x 5 mg</td>
<td>246</td>
<td>-13.3 a,b⁻</td>
<td>+1.4 a,b⁻</td>
<td>-21</td>
<td>1b</td>
</tr>
<tr>
<td>McConnell et al. (1998) [8]</td>
<td>208</td>
<td>Placebo 1503 Finasteride 1 x 5 mg</td>
<td>1513</td>
<td>-22 a,b⁻</td>
<td>+1.9 a,b⁻</td>
<td>-18 a,b⁻</td>
<td>1b</td>
</tr>
<tr>
<td>Marberger et al. (1998) [9]</td>
<td>104</td>
<td>Placebo 1452 Finasteride 1 x 5 mg</td>
<td>1450</td>
<td>-21.4 a,b⁻</td>
<td>+1.4 b⁻</td>
<td>-15 b⁻</td>
<td>1b</td>
</tr>
<tr>
<td>McConnell et al. (2003) [10]</td>
<td>234</td>
<td>Placebo 737 Finasteride 1 x 5 mg</td>
<td>768</td>
<td>-28.4 a,b⁻</td>
<td>+2.2 a,b⁻</td>
<td>-19 a,b⁻</td>
<td>1b</td>
</tr>
<tr>
<td>Roehrborn et al. (2002) [11]</td>
<td>104</td>
<td>Placebo 2158 Dutasteride 1 x 0.5 mg</td>
<td>2167</td>
<td>-26.5 a,b⁻</td>
<td>+2.2 a,b⁻</td>
<td>-25.7 a,b⁻</td>
<td>1b</td>
</tr>
<tr>
<td>Roehrborn et al. (2008) [12]</td>
<td>104</td>
<td>Tamsulosin 1 x 0.4 mg Dutasteride 1 x 0.5 mg</td>
<td>1611</td>
<td>-27.4 a</td>
<td>+0.9</td>
<td>0</td>
<td>1b</td>
</tr>
<tr>
<td>Roehrborn et al. (2010) [13]</td>
<td>208</td>
<td>Tamsulosin 1 x 0.4 mg Dutasteride 1 x 0.5 mg</td>
<td>1611</td>
<td>-23.2 a</td>
<td>+0.7</td>
<td>+4.6</td>
<td>1b</td>
</tr>
</tbody>
</table>

Qmax = maximum urinary flow rate (free uroflowmetry); IPSS = International Prostate Symptom Score; Boyarski Score; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo/active control.

4.2.4 Tolerability and safety
The most relevant adverse effects of 5α-reductase inhibitors are related to sexual function and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders, such as retrograde ejaculation, ejaculation failure, or decreased semen volume (3,10,13). The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (breast enlargement with breast or nipple tenderness) develops in approximately 1-2% of patients.

4.2.5 Practical considerations
Treatment with 5α-reductase inhibitors should only be considered in men with moderate-to-severe LUTS and enlarged prostates (> 40 mL) or elevated PSA concentrations (> 1.4 – 1.6 µg/L). Due to the slow onset of action, 5α-reductase inhibitors are only suitable for long-term treatment (many years). Their effect on the serum
PSA concentration needs to be considered for prostate cancer screening. Of interest, 5α-reductase inhibitors (finasteride) might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularisation (23).

4.2.6 Recommendations

<table>
<thead>
<tr>
<th></th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5α-reductase inhibitors should be offered to men who have moderate-to-severe lower urinary tract symptoms and enlarged prostates (&gt; 40 mL) or elevated prostate specific antigen concentrations (&gt; 1.4 – 1.6 µg/L). 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

4.2.7 References


4.3 Muscarinic receptor antagonists

4.3.1 Mechanism of action

The predominant neurotransmitter of the urinary bladder is acetylcholine that is able to stimulate muscarinic receptors (m-cholinoreceptors) on the surface of detrusor smooth muscle cells. However, muscarinic receptors are not only densely expressed on smooth muscle cells but also on other cell types, such as epithelial cells of the salivary glands, urothelial cells of the urinary bladder, or nerve cells of the peripheral or central nervous system. Five muscarinic receptor subtypes (M1-M5) have been described in humans, of which the M2 and M3 subtypes are predominantly expressed in the detrusor. Although approximately 80% of these muscarinic receptors are M2 and 20% M3 subtypes, only M3 seems to be involved in bladder contractions in healthy humans (1,2). The role of M2 subtypes remains unclear. However, in men with neurogenic bladder dysfunction and in experimental animals with neurogenic bladders or bladder outlet obstruction M2 receptors seem to be involved in smooth muscle contractions as well (3).

The detrusor is innervated by parasympathetic nerves which have their origin in the lateral columns of sacral spinal cord on the level S2-S4 which itself is modulated by supraspinal micturition centres. The sacral micturition centre is connected with the urinary bladder by the pelvic nerves which release acetylcholine after depolarisation. Acetylcholine stimulates postsynaptic muscarinic receptors leading to G-protein mediated calcium release in the sarcoplasmatic reticulum and opening of calcium channels of the cell membrane and,
finally, smooth muscle contraction. Inhibition of muscarinic receptors by muscarinic receptor antagonists inhibit/decrease muscarinic receptor stimulation and, hence, reduce smooth muscle cell contractions of the bladder. Antimuscarinic effects might also be induced or modulated by the urothelium of the bladder and/or by the central nervous system (4,5).

4.3.2 **Available drugs**
The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms in men and women (Table 6):

- darifenacin hydrobromide (darifenacin);
- fesoterodine fumarate (fesoterodine);
- oxybutynin HCl (oxybutynin);
- propiverine HCl (propiverine);
- solifenacin succinate (solifenacin);
- tolterodine tartrate (tolterodine);
- trospium chloride.

This drug class is still officially contraindicated in men with BPH/BOO due to the possibility of incomplete bladder emptying or development of urinary retention.

**Table 6: Antimuscarinic drugs licensed in Europe for treating overactive bladder/storage symptoms; key pharmacokinetic properties and standard doses**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax [h]</th>
<th>T ½ [h]</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin ER³</td>
<td>7 h</td>
<td>12 h</td>
<td>1 x 7.5-15 mg</td>
</tr>
<tr>
<td>Fesoterodina,b</td>
<td>5 h</td>
<td>7 h</td>
<td>1 x 4-8 mg</td>
</tr>
<tr>
<td>Oxybutynin IR</td>
<td>1 h</td>
<td>2-5 h²</td>
<td>2-3 x 5 mg</td>
</tr>
<tr>
<td>Oxybutynin ER</td>
<td>4-6 h</td>
<td>13 h</td>
<td>1 x 5-30 mg</td>
</tr>
<tr>
<td>Propiverine IR</td>
<td>2 h</td>
<td>14-22 h</td>
<td>2 x 15 mg</td>
</tr>
<tr>
<td>Propiverine ER</td>
<td>10 h</td>
<td>20 h</td>
<td>1 x 30 mg</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>3-8 h</td>
<td>45-68 h</td>
<td>1 x 5-10 mg</td>
</tr>
<tr>
<td>Tolterodine IR³</td>
<td>1-2 h</td>
<td>2 h</td>
<td>2 x 2 mg</td>
</tr>
<tr>
<td>Tolterodine ER³</td>
<td>4 h</td>
<td>7-10 h</td>
<td>1 x 4 mg</td>
</tr>
<tr>
<td>Trospium IR</td>
<td>5 h</td>
<td>18 h</td>
<td>2 x 20 mg</td>
</tr>
<tr>
<td>Trospium ER</td>
<td>5 h</td>
<td>36 h</td>
<td>1 x 60 mg</td>
</tr>
</tbody>
</table>

IR = immediate release; ER = extended release (in some countries some manufacturers may have assigned different designators to the ER formulation). The gel and patch formulations of oxybutynin were not included in this table. All information is based on the most recent corresponding US Summary of Product Characteristics as accessed on 18.4.2012, except for propiverine where the corresponding German form was used. Detailed information on other pharmacokinetic parameters and its alterations with renal or hepatic impairment, on drug metabolism and on pharmacokinetic drug-drug interactions has been summarised (6). All data refer to use in adults; where applicable, pharmacokinetic properties may differ in pediatric populations.

³Higher exposure can occur in CYP 2D6 poor metabolisers.

bOnly the active metabolite 5-hydroxy-methyl-tolterodine is detectable in blood after oral administration of fesoterodine.

²T1/2 is age-dependent, values taken from (7).

4.3.3 **Efficacy**
Muscarinic receptor antagonists have been predominantly tested in females in the past because it was believed that LUTS in women are caused by the bladder and, therefore, have to be treated with bladder-specific drugs. In contrast, it was believed that LUTS in men are caused by the prostate and need to be treated with prostate specific drugs. However, there is no scientific data for that assumption (8). A sub-analysis of an open-label trial of 2,250 male or female patients with OAB symptoms treated with tolterodine showed that age but not gender has a significant impact on urgency, frequency, or urge incontinence (9).

The efficacy of the anticholinergic drug tolterodine, and lately also fesoterodine, was tested as a single agent in adult men with bladder storage symptoms (OAB symptoms) but without bladder outlet

obstruction (BOO) (Table 7). Maximum trial duration was 25 weeks, but most of the trials lasted for only 12 weeks. In open-label trials with tolterodine, daytime frequency, nocturia, urge incontinence, and IPSS were all significantly reduced compared to baseline values after 12-25 weeks (10,11). In an open-label study with \(\alpha_1\)-blocker nonresponders, each answer of the IPSS questionnaire was improved during tolterodine treatment irrespective of storage or voiding symptoms (10). Randomised, placebo-controlled trials demonstrated that tolterodine can significantly reduce urge incontinence and daytime or 24-hour frequency compared to placebo. It was also demonstrated that urgency related voiding is significantly reduced by tolterodine (12-14). Although nocturia, urgency, or IPSS were reduced in the majority of patients, these parameters did not reach statistical significance in most of the trials. However, if treatment outcome was stratified by PSA-concentration (prostate volume) tolterodine significantly reduced daytime frequency, 24h voiding frequency and IPSS storage symptoms in those men with PSA concentrations below 1.3 ng/mL, which was not the case in men with PSA concentrations of 1.3 ng/mL or more, indicating that men with smaller prostates might profit more from antimuscarinic drugs (15).

### Table 7: Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with overactive bladder symptoms (trials in chronological order)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>Patients</th>
<th>Voiding frequency [%]</th>
<th>Nocturia [%]</th>
<th>Urgency incontinence</th>
<th>IPSS [%]</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaplan et al. (2005) [10]</td>
<td>25</td>
<td>Tolterodine 1 x 4 mg/d (after (\alpha_1)-blocker failure)</td>
<td>43</td>
<td>-35.7(^a)</td>
<td>-29.3(^a)</td>
<td>-</td>
<td>-35.3(^a)</td>
<td>2b</td>
</tr>
<tr>
<td>Roehrborn et al. (2006) [18]</td>
<td>12</td>
<td>Placebo 1 x 4 mg/d</td>
<td>86</td>
<td>-4</td>
<td>-</td>
<td>-40</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>77</td>
<td>-12</td>
<td>-</td>
<td>-71(^b)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (2006) [13]</td>
<td>12</td>
<td>Placebo 1 x 4 mg/d</td>
<td>374</td>
<td>-7.9</td>
<td>-17.6</td>
<td>-</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>371</td>
<td>-10.8(^b)</td>
<td>-18.8</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (2006) [19]</td>
<td>12</td>
<td>Placebo 1 x 4 mg/d</td>
<td>215</td>
<td>-13.5</td>
<td>-23.9</td>
<td>-13</td>
<td>-44.9</td>
<td>1b</td>
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<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>210</td>
<td>-16.5</td>
<td>-20.1</td>
<td>-85(^b)</td>
<td>-54</td>
<td></td>
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<tr>
<td>Dmochowski et al. (2007) [14]</td>
<td>12</td>
<td>Placebo 1 x 4 mg/d</td>
<td>374</td>
<td>-5.6</td>
<td>-17.6</td>
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<td>1b</td>
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<td></td>
<td></td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>371</td>
<td>-8.7(^b)</td>
<td>-18.8</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Höfner et al. (2007) [11]</td>
<td>12</td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>741</td>
<td>-20(^a)</td>
<td>-42.9(^a)</td>
<td>-100</td>
<td>-37.9(^a)</td>
<td>2b</td>
</tr>
<tr>
<td>Herschorn et al. (2009) [16]</td>
<td>12</td>
<td>Placebo 1 x 4 mg/d</td>
<td>124</td>
<td>-10.2</td>
<td>-59.3</td>
<td>-</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fesoterodine 1 x 4 mg/d</td>
<td>111</td>
<td>-13.2(^b)</td>
<td>-</td>
<td>-84.5(^b)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fesoterodine 1 x 8 mg/d</td>
<td>109</td>
<td>-15.6(^b)</td>
<td>-</td>
<td>-100(^b,c)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**IPSS** = International Prostate Symptom Score; \(^a\) = significant compared to baseline \((p < 0.01; indexed wherever evaluated); \(^b\) = significant compared to placebo \((p < 0.05); c = significant compared to fesoterodine 4 mg \((p < 0.05)\)

### 4.3.4 Tolerability and safety

Muscarinic receptor antagonists are generally well tolerated and associated with approx. 3-10% study withdrawals which were not significantly different compared to placebo in most of the studies. Compared to placebo, drug-related adverse events appear with higher frequencies for dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%) nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increase of PVR urine in men without bladder outlet obstruction is minimal and not significantly different compared to placebo (0 to 5 mL vs. -3.6 to 0 mL). Nevertheless, fesoterodine 8 mg showed higher post-void residuals (+20.2 mL) compared to placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) (16). The incidence of urinary retention in men without BOO was comparable with placebo in trials with tolterodine (0
to 1.3 vs. 0 to 1.4%). In men under fesoterodine 8 mg treatment, 5.3% had symptoms suggestive of urinary retention that was higher compared to placebo or fesoterodine 4 mg (0.8% each). These symptoms appeared during the first 2 weeks of treatment and affected men aged 66 years or older.

In men with BOO, antimuscarinic drugs are not recommended due to the theoretical decrease of bladder strength which might be associated with PVR urine or urinary retention. A 12-week placebo-controlled safety study dealing with men who had mild to moderate BOO (median bladder outlet obstruction index, BOOI, in the placebo or tolterodine group 43 and 49 cm H2O, respectively) demonstrated that tolterodine significantly increased the amount of PVR urine (49 vs. 16 mL) but was not associated with increased events of acute urinary retention (3% in both study arms) (17). Urodynamic effects of tolterodine included significant larger bladder volumes to first detrusor contraction, higher maximum cystometric bladder capacity, and decreased bladder contractility index. Maximum urinary flow remained unchanged in both the tolterodine and placebo groups. This single trial indicated that the short-term treatment with antimuscarinic drugs in men with BOO is safe.

4.3.5 Practical considerations
Although studies in elderly men with LUTS and overactive bladder symptoms were exclusively carried out with tolterodine or fesoterodine it is likely that similar efficacy and adverse events will also appear with other antimuscarinic agents. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are still missing, therefore, these drugs should be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised.

4.3.6 Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscarinic receptor antagonists might be considered in men with moderate to severe lower urinary tract symptoms who have predominantly bladder storage symptoms.</td>
<td>1b</td>
</tr>
<tr>
<td>Caution is advised in men with bladder outlet obstruction.</td>
<td>4</td>
</tr>
</tbody>
</table>

4.3.7 References


4.4 **Plant extracts - Phytotherapy**

4.4.1 **Mechanism of action**

Phytotherapy comprises the medical use of various extracts of different plants. It remains controversial which components of the extracts are responsible for symptom relief in male LUTS. The most important compounds are believed to be phytosterols, ß-sitosterol, fatty acids, and lectins (1). In vitro studies have shown that plant extracts:

- have anti-inflammatory, antiandrogenic, or oestrogenic effects;
- decrease sexual hormone binding globulin (SHBG);
- inhibit aromatase, lipooxygenase, growth-factor stimulated proliferation of prostatic cells, α-adrenoceptors, 5α-reductase, muscarinic cholinoeceptors, dihydropyridine receptors, or vanilloid receptors;
- improve detrusor function;
- neutralise free radicals (1-3).

However, most in vitro effects have not been confirmed in vivo and the precise mechanisms of action of plant extracts remain unclear.

4.4.2 **Available drugs**

Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits of a single plant (monopreparations); others combine the extracts of two or more plants to one pill (combination preparations). A large number of different plants are used for the preparation of extracts. The most widely used plants are:

- *Cucurbita pepo* (pumpkin seeds)
- *Hypoxis rooperi* (South African star grass)
- *Pygeum africanum* (bark of the African plum tree)
- *Secale cereale* (rye pollen)
- *Serenoa repens* (syn. *Sabal serrulata*; berries of the American dwarf palm, saw palmetto)
- *Urtica dioica* (roots of the stinging nettle).
Different producers use different extraction techniques, distribute active ingredients with different qualitative and quantitative properties, or combine two or more herbal compounds in one pill. The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects so that the effects of one brand cannot be extrapolated to others (4). To complicate matters even, two different batches of the same producer might contain different concentrations of active ingredients and cause different biological effects (5). Thus, the pharmacokinetic properties can differ significantly between different plant extracts.

4.4.3 Efficacy
Each class of plant extract is discussed separately because of the above-mentioned reasons (Table 8). Whenever possible, the brand name is mentioned to demonstrate possible differences between products. In general, no phytotherapeutic agent has been shown to significantly reduce prostate size and no trial has proven reduction of BOO or decreased disease progression.

- **Cucurbita pepo**: Only one trial has evaluated the efficacy of pumpkin seeds extracts (Prosta Fink™ forte) in patients with BPH-LUTS (6). A total of 476 patients were randomly assigned to placebo or Prostat Fink™ forte. After a follow-up of 12 months, IPSS and daytime voiding frequency were significantly reduced in the pumpkin seed group. However, uroflowmetry parameters (Q\text{max}, PVR urine, prostate volume, PSA concentration, nocturia, or quality of life (QoL) Score were not statistically different between the groups.

- **Hypoxis rooperi**: These phytopharmacological extracts contain a mixture of phytosterols bonded with glycosides of which β-sitosterol is the most important compound (Harzol™, Azuprostat™). Four randomised, placebo-controlled trials with durations between 4 and 26 weeks were published and summarised in a Cochrane report (7). Daily doses of plant extracts ranged from 60 to 195 mg. Two trials evaluated symptoms (8,9) and all four trials investigated Q\text{max} and PVR urine. A meta-analysis calculated weighted mean differences of -4.9 IPSS points, +3.9 mL/s in terms of Q\text{max} and -28.6 mL in terms of PVR urine in favour of β-sitosterol. Prostate size remained unchanged in all trials. No further trials have been carried out since the Cochrane report was published in 2000.

- **Pygeum africanum**: A Cochrane report dealing with the clinical results of *Pygeum africanum* extracts (mono- or combination preparations) summarised the results of 18 randomised, placebo-controlled trials (10). Most trials used the *Pygeum africanum* extract Tadenan™. The meta-analysis comprised 1,562 men, but individual trials were small in size and lasted only between 30 and 122 days. Most trials were performed in the 1970s and 1980s and did not use validated questionnaires such as the IPSS. Men treated with *Pygeum africanum* were twice as likely to report symptom improvement (relative risk [RR] 2.07) compared to men treated with placebo. The mean weighted difference of Q\text{max} was +2.5 mL/s and of PVR volume -13.2 mL in favour of *Pygeum africanum*. No further trials have been published since the Cochrane report in 2002.

- **Secale cereale**: A Cochrane report dealt with the clinical results of the main *Secale cereale* product Cernilton™ and comprised 444 men who were enrolled in two placebo-controlled and two comparative trials (Tadenan™, Paraprost™) lasting between 12 and 24 weeks (11). Men treated with Cernilton™ reported that they were twice as likely to benefit from therapy compared to placebo (RR 2.4). However, there were no significant differences between Cernilton™ and placebo with regard to Q\text{max}, PVR urine, or prostate volume. No additional placebo-controlled trial with the mono preparation of *Secale cereale* has been published since the Cochrane report in 2000.

- **Sabal serrulata/Serenoa repens**: A recently updated Cochrane report summarised the clinical results of 30 randomised trials comprising 5,222 men (12). *Serenoa repens* (mainly Permixon™ or Prostasereene™) was compared as mono or combination preparations either with placebo, other plant extracts (*Pygeum africanum, Urtica dioica*), the 5-reductase inhibitor finasteride, or the α\text{-blocker} tamsulosin. Mean follow-up of these trials varied between 4 and 60 weeks. The Cochrane report concluded that *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q\text{max} or prostate size reduction. Similar levels of IPSS or Q\text{max} improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence (13). For nocturia, *Serenoa repens* was significantly better than placebo (mean weighted difference -0.78).

- **Urtica dioica**: Two trials investigated the efficacy of stinging nettle mono preparations compared to placebo (14,15). One trial investigated 246 men with BPH-LUTS over a period of 52 weeks (14); only IPSS decreased significantly in the phytotherapy group (Bazoton™ uno), whereas Q\text{max} and PVR urine were not statistically different between the groups at the end of the trial. The second trial investigated 620 patients with BPH-LUTS over a period of 26 weeks (15); IPSS, Q\text{max} and PVR urine significantly improved compared to placebo.

- **Combination preparations**: Trials have been carried out, especially with the extract combination of *Sabal serrulata* and *Urtica dioica* (PRO 160/120, Prostatgutt™ forte). A 24-weeks placebo-controlled trial investigated the efficacy of Bazoton™ uno compared to placebo, finasteride, or tamsulosin. Mean follow-up of these trials varied between 4 and 60 weeks. The Cochrane report concluded that Bazoton™ uno was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q\text{max} or prostate size reduction. Similar levels of IPSS or Q\text{max} improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence (13). For nocturia, *Serenoa repens* was significantly better than placebo (mean weighted difference -0.78).
A 24-week open label extension trial of the same patients, in which all patients were treated with PRO 160/120, showed similar improvements of IPSS at week 48 in both groups (-7 IPSS points). A second trial, in which PRO 160/120 was randomised against finasteride, showed similar results for IPSS and Qmax in both groups (17).

Table 8: Trials with plant extracts in patients with BPH-LUTS (selection; in alphabetical order)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Change in symptoms (IPSS) †</th>
<th>Change in Qmax [mL/s]</th>
<th>PVR [mL]</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bach (2000) (6)</td>
<td>52</td>
<td>placebo Cucurbita pepo (Prosta Fink™ forte)</td>
<td>243/233</td>
<td>-5.5/-6.7 a</td>
<td>n.s./n.s.</td>
<td>n.s./n.s.</td>
<td>1b</td>
</tr>
<tr>
<td>Berges et al. (1995) (8)</td>
<td>24</td>
<td>placebo Hypoxis rooperi (Harzol™)</td>
<td>100/100</td>
<td>-2.3/-7.4 a</td>
<td>+1.1/5.2 a</td>
<td>-16.8/-35.4 a</td>
<td>1b</td>
</tr>
<tr>
<td>Klippel et al. (1997) (9)</td>
<td>26</td>
<td>placebo Hypoxis rooperi (Azuprostat™)</td>
<td>89/88</td>
<td>-2.8/-8.2 a</td>
<td>+4.3/8.8 a</td>
<td>-4.1/-37.5 a</td>
<td>1b</td>
</tr>
<tr>
<td>Wilt et al. (2000) (7)</td>
<td>4-26</td>
<td>placebo Hypoxis rooperi</td>
<td>475</td>
<td>-4.9 b/3.9 b</td>
<td>n.s./n.s.</td>
<td>-28.6 b</td>
<td>1a</td>
</tr>
<tr>
<td>Wilt et al. (2002) (10)</td>
<td>4-18</td>
<td>placebo Pygeum africanum (β-sitosterol)</td>
<td>1562</td>
<td>RR 2.07 b/2.5 b</td>
<td>-13.2 b</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Wilt et al. (2000) (11)</td>
<td>12-24</td>
<td>placebo Secale cereale (Cernilton™)</td>
<td>444</td>
<td>RR 2.4 b/1.6</td>
<td>-14.4 b</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Wilt et al. (2002) (18)</td>
<td>4-48</td>
<td>placebo Serenoa repens/ Sabal cerrulata</td>
<td>3139</td>
<td>-1.41 b/1.86 b</td>
<td>-23 b</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Bent et al. (2006) (19)</td>
<td>52</td>
<td>placebo Serenoa repens</td>
<td>113/112</td>
<td>-0.7/-0.7</td>
<td>0.01/0.42</td>
<td>-19/-14</td>
<td>1b</td>
</tr>
<tr>
<td>Carraro et al. (1996) (20)</td>
<td>26</td>
<td>finasteride Serenoa repens (Permixon™)</td>
<td>545/553</td>
<td>-6.2/-5.8</td>
<td>3.2 a/2.7</td>
<td>-/-</td>
<td>1b</td>
</tr>
<tr>
<td>Debruyne et al. (2002) (21)</td>
<td>52</td>
<td>tamsulosin Serenoa repens (Permixon™)</td>
<td>354/350</td>
<td>-4.4/-4.4</td>
<td>1.9/-1.8</td>
<td>-/-</td>
<td>1b</td>
</tr>
<tr>
<td>Schneider &amp; Rübben (2004) (14)</td>
<td>52</td>
<td>placebo Urtica dioica (Bazoton uno™)</td>
<td>122/124</td>
<td>-4.7/-5.7 a</td>
<td>2.9/-3.0</td>
<td>-/-</td>
<td>1b</td>
</tr>
<tr>
<td>Safarinejad (2005) (15)</td>
<td>26</td>
<td>placebo Urtica dioica</td>
<td>316/305</td>
<td>-1.5/-8.0 a</td>
<td>3.4/-8.2 a</td>
<td>0/-37</td>
<td>1b</td>
</tr>
<tr>
<td>Lopatkin et al. (2005) (16)</td>
<td>24</td>
<td>placebo Sabal cerrulata + Urtica dioica (Prostatgutt™ forte)</td>
<td>126/127</td>
<td>-6 b/-4</td>
<td>1.9/-1.8</td>
<td>-/-</td>
<td>1b</td>
</tr>
<tr>
<td>Sökeland &amp; Albrecht (1997) (17)</td>
<td>48</td>
<td>finasteride Sabal cerrulata + Urtica dioica (Prostatgutt™ forte)</td>
<td>244/245</td>
<td>-5.6/-4.8</td>
<td>2.8/-2.0</td>
<td>-17.1/-10.2</td>
<td>1b</td>
</tr>
</tbody>
</table>

IPSS = International Prostate Symptom Score; Qmax = maximal urinary flow rate (free uroflowmetry); PVR = post-void residual; n.s. = not significant; RR = relative risk
† absolute values; a = significant reduction compared to placebo/comparison treatment arm (p<0.05); b = in favour of plant extract.
4.4.4 **Tolerability and safety**

Side-effects during phytotherapy are generally mild and comparable to placebo with regard to severity and frequency. Serious adverse events were not related to study medication. Gastrointestinal complaints were the most commonly reported side-effects. In formulations with *Hypoxis rooperi*, ED appeared in 0.5% of patients. Trial withdrawals were almost equal in both placebo and phytotherapy groups.

4.4.5 **Practical considerations**

Phytotherapeutic agents are a heterogeneous group of plant extracts used to improve BPH-LUTS. Phytotherapy remains problematic to use because of different concentrations of the active ingredient(s) in different brands of the same phytotherapeutic agent. Hence, meta-analyses of extracts of the same plant do not seem to be justified and results of these analyses have to be interpreted with caution.

4.4.6 **Recommendations**

The guidelines committee is unable to make specific recommendations about phytotherapy of male lower urinary tract symptoms because of the heterogeneity of the products and the methodological problems associated with meta-analyses.

4.4.7 **References**


4.5 Vasopressin analogue - desmopressin

4.5.1 Mechanism of action

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and the control of urine production by binding to the V2 receptor in the renal collecting ducts. Arginine vasopressin increases water re-absorption as well as urinary osmolality and decreases water excretion as well as total urine volume. Arginine vasopressin might be therapeutically used to manipulate the amount of urine excretion but, however, AVP also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for the treatment of nocturia/nocturnal polyuria.

4.5.2 Available drugs

Desmopressin acetate (desmopressin) is a synthetic analogue of AVP with high V2 receptor affinity and antidiuretic properties. It is the only registered drug for antidiuretic treatment (Table 9). In contrast to AVP, desmopressin has no relevant V1 receptor affinity and hypertensive effects. Desmopressin may be used by intravenous infusion, nasal spray, tablet, or MELT formulation. Nasally or orally administered desmopressin is rapidly absorbed and, later, excreted 55% unchanged by the kidneys (1). Desmopressin has been used for over 30 years in the treatment of diabetes insipidus or primary nocturnal enuresis and has recently been approved in most European countries for the treatment of nocturia polyuria for adult male and female patients. After intake before sleeping, urine excretion during the night decreases and, therefore, the urge to void is postponed and the number of voids at night is reduced (2,3). The clinical effects - in terms of urine volume decrease and an increase in urine osmolality - last for approximately 8-12 hours (2).

Table 9: Antidiuretics licensed in Europe for treating nocturia due to nocturnal polyuria; key pharmacokinetic properties and standard doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_{\text{max}}$ (hours)</th>
<th>$t_{\frac{1}{2}}$ (hours)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin</td>
<td>1-2</td>
<td>3</td>
<td>1 x 0.1-0.4 mg orally before sleeping</td>
</tr>
</tbody>
</table>

$t_{\text{max}} = \text{time to maximum plasma concentration}; t_{\frac{1}{2}} = \text{elimination half-life}.$
4.5.3 Efficacy
The majority of clinical trials have used desmopressin in an oral formulation. A dose-finding study showed that the nocturnal urine volume/nocturnal diuresis was more reduced by oral desmopressin 0.2 mg than 0.1 mg; however, this study also showed that a 0.4 mg dose taken once before sleeping had no additional effects on the nocturnal diuresis compared to a 0.2 mg dose (4). In the pivotal clinical trials, the drug was titrated from 0.1 to 0.4 mg according to the individual clinical response. Desmopressin significantly reduced nocturnal diuresis by approximately 0.6-0.8 mL/min (-40%), decreased the number of nocturnal voids by approximately 0.8-1.3 (-40%) (-2 in the long-term open-label trial), and extended the time until the first nocturnal void by approximately 1.6 hours (-2.3 in the long-term open-label trial) (Table 10). Furthermore, desmopressin significantly reduced night-time urine volume as well as the percentage of urine volume excreted at night (5,8).

The clinical effects of desmopressin were more pronounced in patients with more severe nocturnal polyuria and bladder capacity within the normal range at baseline. The 24-hour diuresis remained unchanged during desmopressin treatment (6). The clinical effects were stable over a follow-up period of 10-12 months and returned to baseline values after trial discontinuation (12). A significantly higher proportion of patients felt fresh in the morning-time after desmopressin use (odds ratio 2.71) (11).

Table 10: Clinical trials with desmopressin in adult men with nocturnal polyuria

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment, i.e. oral daily dose before bedtime unless otherwise indicated</th>
<th>Patients (n)</th>
<th>Change nocturnal urine volume (mL/min)</th>
<th>Change nocturnal voids (n)</th>
<th>Time to first void (hours)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asplund et al. (1998) [4]</td>
<td>3</td>
<td>1 x 0.1 mg 1 x 0.2 mg 2 x 0.2 mg</td>
<td>23*</td>
<td>-0.5 (-31%)</td>
<td>-</td>
<td>-</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23*</td>
<td>-0.7 (-44%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23*</td>
<td>-0.6 (-38%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cannon et al. (1999) [5]</td>
<td>6</td>
<td>Placebo 1 x 20 µg intranasal 1 x 40 µg intranasal</td>
<td>20</td>
<td>-</td>
<td>+0.1 (+3%)</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>-</td>
<td>-0.3 (-10%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>-</td>
<td>-0.7 (-23%)a</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Asplund et al. (1999) [6]</td>
<td>2</td>
<td>Placebo 1 x 0.1-0.4 mg</td>
<td>17*</td>
<td>-0.2 (-11%)</td>
<td>-0.2 (-11%)</td>
<td>+0.2</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17*</td>
<td>-0.8 (-44%)a</td>
<td>-0.8 (-42%)a</td>
<td>+1.6</td>
<td></td>
</tr>
<tr>
<td>Chancellor et al. (1999) [7]</td>
<td>12</td>
<td>1 x 20-40 µg intranasal</td>
<td>12</td>
<td>-</td>
<td>-1.8 (-50%)</td>
<td>-</td>
<td>2b</td>
</tr>
<tr>
<td>Mattiasson et al. (2002) [8]</td>
<td>3</td>
<td>Placebo 1 x 0.1-0.4 mg</td>
<td>65</td>
<td>-0.2 (-6%)</td>
<td>-0.5 (-12%)</td>
<td>+0.4</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>86</td>
<td>-0.6 (-36%)a</td>
<td>-1.3 (-43%)a</td>
<td>+1.8a</td>
<td></td>
</tr>
<tr>
<td>Kuo 2002 [9]</td>
<td>4</td>
<td>1 x 0.1 mg</td>
<td>30*</td>
<td>-</td>
<td>-2.72 (-48.5)</td>
<td>-</td>
<td>2b</td>
</tr>
<tr>
<td>Rembratt et al. (2003) [10]</td>
<td>0.5</td>
<td>1 x 0.2 mg</td>
<td>72*</td>
<td>-0.5</td>
<td>-1.0</td>
<td>+1.9</td>
<td>2b</td>
</tr>
<tr>
<td>van Kerrebroeck et al. (2007) [11]</td>
<td>3</td>
<td>Placebo 1 x 0.1-0.4 mg</td>
<td>66</td>
<td>-</td>
<td>-0.4 (-15%)</td>
<td>+0.55</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61</td>
<td>-</td>
<td>-1.25 (-39%)a</td>
<td>+1.66a</td>
<td></td>
</tr>
<tr>
<td>Lose et al. (2004) [12] ‡</td>
<td>52</td>
<td>1 x 0.1-0.4 mg</td>
<td>132</td>
<td>-</td>
<td>-2</td>
<td>+2.3</td>
<td>2b</td>
</tr>
</tbody>
</table>

*Majority of study participants were men; ‡ only male data; a = significant compared to placebo.

4.5.4 Tolerability
The absolute number of adverse events associated with desmopressin treatment were higher compared to placebo but usually mild in nature. The most frequent adverse events in short-term (up to 3 weeks) and long-term studies (12 months) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth, and hyponatraemia. These events were comparable with the established safety profile of desmopressin in the treatment of polyuria due to other conditions. Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial (12).

Hyponatraemia (serum sodium concentration < 130 mmol/L) was observed mainly in patients aged
65 years or older and seemed to occur less frequently in men compared to women of the same age (3). Hyponatraemia of all degrees, not necessarily associated with symptoms, occurs in approximately 5% (13) to 7.6% of patients (14) early after treatment initiation. The risk of developing hyponatraemia significantly increases with age (odds ratio 1.16 per year of age), lower serum sodium concentration at baseline (odds ratio 0.76), and higher basal 24-hour urine volume per bodyweight (odds ratio 1.09) (13). The chance of developing hyponatraemia in patients younger than 65 years is less than 1%, whereas the risk for older patients increases to 8% with normal sodium concentration and up to 75% in patients with low sodium concentration at baseline (13).

Therefore, the treatment of men aged 65 years or older should not be initiated without monitoring the serum sodium concentration. At the time of treatment initiation or dose change, older men with normal values of serum sodium should be monitored by Na⁺ measurement at day 3 and day 7 of treatment as well as at 1 month later. If serum sodium concentration has remained normal and no dose adjustment is intended, Na⁺ should be monitored every 3-6 months thereafter (15). Furthermore, patients should be informed about the prodromal symptoms of hyponatraemia, such as headache, nausea, or insomnia.

### 4.5.5 Practical considerations

Desmopressin should be taken once daily before sleeping. As the optimal dose differs between patients, desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased every week until maximum efficacy is reached. The maximal daily dose recommended is 0.4 mg/day. Patients should avoid drinking fluids at least 1 hour before using desmopressin until 8 hours thereafter. In men aged 65 years or older, desmopressin should not be used if the serum sodium concentration is below the normal value. In all other men aged 65 years or older, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month and, if serum sodium concentration has remained normal, every 3-6 months subsequently.

### 4.5.6 Recommendations

<table>
<thead>
<tr>
<th>Desmopressin can be used for the treatment of nocturia secondary to nocturnal polyuria.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

### 4.5.7 References


4.6 Combination therapies

4.6.1 \(\alpha_1\)-blockers + 5\(\alpha\)-reductase inhibitors

4.6.1.1 Mechanism of action

Combination therapy of \(\alpha_1\)-blockers and 5\(\alpha\)-reductase inhibitors aims to combine the differential effects of both drug classes to create synergistic efficacy in symptom improvement and prevention of disease progression.

4.6.1.2 Available drugs

Combination therapy consists of an \(\alpha_1\)-blocker (alfuzosin, doxazosin, tamsulosin, or terazosin; pharmacokinetic properties see Section 3.1.2) together with a 5\(\alpha\)-reductase inhibitor (dutasteride or finasteride; pharmacokinetic properties see Section 3.2.2). The \(\alpha_1\)-blocker exhibits clinical effects within hours or days, whereas the 5\(\alpha\)-reductase inhibitor needs several months to develop significant clinical efficacy. Of all drug combinations possible, so far finasteride together with alfuzosin, doxazosin, or terazosin, and dutasteride together with tamsulosin, have been tested in clinical trials. Both compounds show class effects with regard to efficacy and adverse events. No differences in pharmacokinetic or pharmacodynamic properties of the combined use of both drugs have been reported compared to single drug.

4.6.1.3 Efficacy

Several studies have investigated the efficacy of combination therapy against the efficacy of an \(\alpha_1\)-blocker, 5\(\alpha\)-reductase inhibitor, or placebo alone (Table 11). Initial studies with follow-up periods between 6 and 12 months used symptom (IPSS) change as their primary endpoint (1-3). These trials consistently demonstrated that the \(\alpha_1\)-blocker was superior to finasteride in symptom reduction, whereas the combination treatment was not superior to the \(\alpha_1\)-blocker alone. In studies which included a placebo arm, the \(\alpha_1\)-blocker was consistently more effective than placebo, whereas finasteride was consistently not more effective than placebo. Data from the 1-year time point of the MTOPS (Medical Therapy of Prostatic Symptoms) study, which have been published but not specifically analysed for this time point, showed similar results (4).

More recently, 4-year data analysis from MTOPS as well as the 2- and 4-year results from the CombAT (Combination of Avodart® and Tamsulosin) trials, have been reported (4-6). The latter trial included older men with larger prostates and higher serum PSA concentrations and therefore appears to represent men at greater risk of disease progression. In contrast to earlier studies with only 6 to 12 months follow-up, long-term data have demonstrated that combination treatment is superior to either monotherapy with regard to symptom reduction and Q\(\text{max}\) improvement and superior to \(\alpha_1\)-blocker in reducing the risk of acute urinary retention and the need for surgery (4-6). The CombAT study demonstrated that combination treatment is superior to either monotherapy with regard to symptom improvement and Q\(\text{max}\) starting from month 9 and superior to \(\alpha_1\)-blocker with regard to the reduction in the risk of acute urinary retention and the need for surgery after month 8 (6). The different results between the CombAT and MTOPS trials appear to arise from different inclusion and exclusion criteria rather than the types of \(\alpha_1\)-blockers or 5\(\alpha\)-reductase inhibitors. Dutasteride or finasteride alone reduced prostate volume as effectively as combination treatment (-20 to -27%).
Three studies addressed the issue of discontinuation of the $\alpha_1$-blocker (7-9). One trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after 6 months (7). After cessation of the $\alpha_1$-blocker, almost three-quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy. A more recently published trial evaluated the symptomatic outcome of finasteride monotherapy at 3 and 9 months after discontinuation of 9-month combination therapy (finasteride plus $\alpha_1$-blocker) (8). LUTS improvement after combination therapy was sustained at 3 months (IPSS difference 1.24) and 9 months (IPSS difference -0.44).

In a retrospective study, the likelihood of $\alpha_1$-blocker discontinuation, which was based on the individual decision of the patient, was evaluated over a 12-month period in men aged > 65 years receiving $\alpha_1$-blockers in combination with either dutasteride or finasteride (9). Dutasteride patients discontinued $\alpha_1$-blocker therapy 64% faster than finasteride patients at any time point. At 12 months, 62% of patients were treated with dutasteride alone compared to 43.7% of men treated with finasteride alone.

Combination therapy was shown to be superior to monotherapy in both the MTOPS and CombAT trials in preventing overall clinical progression, as defined by an IPSS increase of at least 4 points, acute urinary retention, urinary tract infection (UTI), incontinence, or an increase in serum creatinine > 50% compared to baseline values. For combination therapy in the MTOPS trial versus the CombAT trial, the following reductions were observed:

- overall risk of disease progression was 66% versus 44%;
- symptomatic progression, 64% vs. 41%;
- acute urinary retention, 81% vs. 68%;
- urinary incontinence, 65% vs. 26%;
- BPH-related surgery, 67% vs. 71%.

Monotherapy with 5α-reductase inhibitor appeared to reduce the risks of acute urinary retention and prostate-related surgery as effectively as combination treatment (differences not significant), although the preventive effects were more pronounced with combination therapy (4,6). The MTOPS trial results suggested that the $\alpha_1$-blocker alone might also reduce the risk of symptom progression.

**Table 11: Randomised trials using $\alpha_1$-blocker, 5α-reductase inhibitor, and the combination of both drugs in men with LUTS and benign prostatic enlargement due to benign prostatic hyperplasia**

(Of note: references 5 and 6 reflect different time points of the same study.)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment (daily dose)</th>
<th>Patients (n)</th>
<th>Symptom change (% IPSS)</th>
<th>Change in $Q_{\text{max}}$ (mL/s)</th>
<th>Change in prostate volume (%)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepor et al. (1996) [1]</td>
<td>52</td>
<td>Placebo 305 Terazosin 1 x 10 mg 305 Finasteride 1 x 5 mg 310</td>
<td>-16.5&lt;sup&gt;a&lt;/sup&gt; -37.7&lt;sup&gt;a,b,d&lt;/sup&gt; -19.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+1.4 +2.7&lt;sup&gt;b,d&lt;/sup&gt; +1.6</td>
<td>+1.3 +1.3 -16.9&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terazosin 1 x 10 mg + Finasteride 1 x 5 mg 309</td>
<td>-39&lt;sup&gt;a,b,d&lt;/sup&gt;</td>
<td>+3.2&lt;sup&gt;b,d&lt;/sup&gt; +18.8&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debruyne et al. (1998) [2]</td>
<td>26</td>
<td>Alfuzosin 2 x 5 mg 358 Finasteride 1 x 5 mg 344 Alfuzosin 2 x 5 mg + Finasteride 1 x 5 mg 349</td>
<td>-41.2&lt;sup&gt;d&lt;/sup&gt; -33.5 -39.1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>+1.8 +1.8 +2.3</td>
<td>-0.5 -10.5&lt;sup&gt;c&lt;/sup&gt; -11.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirby et al. (2003) [3]</td>
<td>52</td>
<td>Placebo 253 Doxazosin 1 x 1-8 mg 250 Finasteride 1 x 5 mg 239 Doxazosin 1 x 1-8 mg + Finasteride 1 x 5 mg 265</td>
<td>-33.1 -49.1&lt;sup&gt;b,d&lt;/sup&gt; -38.6 -49.7&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>+1.4 +3.6&lt;sup&gt;b,d&lt;/sup&gt; +1.8 +3.8&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McConnell et al. (2003) [4]</td>
<td>234</td>
<td>Placebo 737 Doxazosin 1 x 1-8 mg 756 Finasteride 1 x 5 mg 768 Doxazosin 1 x 1-8 mg + Finasteride 1 x 5 mg 786</td>
<td>-23.8&lt;sup&gt;a&lt;/sup&gt; -35.3&lt;sup&gt;a,b,d&lt;/sup&gt; -28.4&lt;sup&gt;a,b&lt;/sup&gt; -41.7&lt;sup&gt;a,b,c,d&lt;/sup&gt;</td>
<td>+1.4&lt;sup&gt;a&lt;/sup&gt; +2.5&lt;sup&gt;a,b&lt;/sup&gt; +2.2&lt;sup&gt;a,b&lt;/sup&gt; +3.7&lt;sup&gt;a,b,c,d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.6.1.4  Tolerability and safety
In both the CombAT and MTOPS trials, overall drug-related adverse events were significantly more frequent during combination treatment than during either monotherapy. The adverse events observed during combination treatment were typical of an \( \alpha_1 \)-blocker and 5\( \alpha \)-reductase inhibitor. The frequencies of adverse events were significantly higher for combination therapy for most adverse events (4).

4.6.1.5  Practical considerations
Compared to \( \alpha_1 \)-blockers or 5\( \alpha \)-reductase inhibitor monotherapy, combination therapy results in a greater improvement in LUTS and increase in \( Q_{\text{max}} \), and is superior prevention of disease progression. However, combination therapy is also associated with more adverse events. Combination therapy should therefore be used primarily in men who have moderate to severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, etc.). Combination therapy should only be used when long-term treatment (more than 12 months) is intended; this issue should be discussed with the patient before treatment. Discontinuation of the \( \alpha_1 \)-blocker after 6 months might be considered in men with moderate LUTS.

4.6.1.6  Recommendations

| Combination treatment with \( \alpha_1 \)-blocker together with 5\( \alpha \)-reductase inhibitor should be offered to men with moderate-to-severe lower urinary tract symptoms, enlarged prostates (> 40 mL), and reduced \( Q_{\text{max}} \) (men likely to develop disease progression). Combination treatment is not recommended for short-term therapy (< 1 year). |
|---|---|---|
| LE | GR |
| 1b | A |

4.6.1.7  References


4.6.2 \(\alpha_1\)-blockers + muscarinic receptor antagonists

4.6.2.1 Mechanism of action
Combination therapy of an \(\alpha_1\)-blocker together with a muscarinic receptor antagonist aims to antagonize both \(\alpha_1\)-adrenoceptor and muscarinic cholinoreceptors (M2 and M3) in the lower urinary tract, hereby using the efficacy of both drug classes to achieve synergistic effects.

4.6.2.2 Available drugs
Combination treatment consists of an \(\alpha_1\)-blocker (alfuzosin, doxazosin, tamsulosin, or terazosin; pharmacokinetic properties chapter 3.1.2) together with a muscarinic receptor antagonist (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, or trospium chloride; pharmacokinetic properties chapter 3.3.2). However, only the combinations of the \(\alpha_1\)-blocker doxazosin, tamsulosin, or terazosin and the muscarinic receptor antagonist oxybutynin, propiverine, solifenacin, or tolterodine have been tested in clinical trials so far. Until now, both drug classes have to be taken as separate pills as no combination pill is yet available. No differences in terms of pharmacokinetic or pharmacodynamic properties of the combined use of both drugs have been described compared to the use of the single drugs.

4.6.2.3 Efficacy
At least nine trials have been published investigating the efficacy of the combination treatment with \(\alpha_1\)-blockers and muscarinic receptor antagonists in adult male patients with LUTS (1-8). Additionally, one trial was published using the \(\alpha_1\)-blocker naftopidil (not registered in most European countries) with and without anticholinergic agents (9). Only one of those trials had a placebo arm (LE: 1b) and also tested the drug combination against the \(\alpha_1\)-blocker as well as against the muscarinic receptor antagonist (4); all other trials compared the efficacy of the combination therapy with the efficacy of an \(\alpha_1\)-blocker alone (Table 12) (LE: 2b). Maximum trial duration was 25 weeks but the majority of trials lasted 4-12 weeks only.

The combination of drugs was in general more efficacious in reducing voiding frequency, nocturia, or IPSS compared to \(\alpha_1\)-blockers or placebo alone. Furthermore, the combination treatment significantly reduced urge urinary incontinence episodes as well as urgency and significantly increased QoL (4).

Overall symptom improvement in the combination therapy arm was significantly higher compared to placebo regardless of PSA serum concentration, whereas tolterodine alone significantly improved symptoms predominantly in men with a serum PSA concentration less than 1.3 ng/mL (10). Three trials investigated the efficacy of combination treatment in patients with persistent LUTS during \(\alpha_1\)-blocker treatment by adding a muscarinic receptor antagonist to the existing \(\alpha_1\)-blocker therapy (add-on approach) (6-8). These trials demonstrated that persistent LUTS can be significantly reduced by the additional use of a muscarinic receptor antagonist (tolterodine) especially if detrusor overactivity had been demonstrated (Table 12). Patient reported QoL, treatment benefit, symptom bother, or patient perception of bladder condition was significantly improved in the combination treatment arm.
Table 12: Efficacy of muscarinic receptor antagonists together with $\alpha_1$-blockers

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>Patients</th>
<th>Voiding frequency [%]</th>
<th>Nocturia [%]</th>
<th>IPSS [%]</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al. (1999) [1]</td>
<td>4</td>
<td>Tamsulosin 1 x 0.2 mg/d</td>
<td>59</td>
<td>-29.6</td>
<td>-22.5</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20 mg/d</td>
<td>75</td>
<td>-44.7</td>
<td>-44.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2005) [3]</td>
<td>8</td>
<td>Doxazosin 1 x 4 mg/d</td>
<td>67</td>
<td>-11.8</td>
<td>-37.5</td>
<td>-54.9</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxazosin 1 x 4 mg/d + propiverine 1 x 20 mg/d</td>
<td>131</td>
<td>-27.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-46.7</td>
<td>-50.7</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (2006) [4]</td>
<td>12</td>
<td>Placebo</td>
<td>215</td>
<td>-13.5</td>
<td>-23.9</td>
<td>-44.9</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>210</td>
<td>-16.5</td>
<td>-20.1</td>
<td>-54</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamsulosin 1 x 0.4 mg/d</td>
<td>209</td>
<td>-16.9</td>
<td>-40.3</td>
<td>-64.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4 mg/d + tamsulosin 1 x 0.4 mg/d</td>
<td>217</td>
<td>-27.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-39.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-66.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>MacDiarmid et al. (2008) [5]</td>
<td>12</td>
<td>Tamsulosin 1 x 0.4 mg/d + placebo</td>
<td>209</td>
<td>-</td>
<td>-</td>
<td>-34.9</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamsulosin 1 x 0.4 mg/d + oxybutynine 1 x 10 mg/d</td>
<td>209</td>
<td>-</td>
<td>-</td>
<td>-51.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (2005) [7] ‡</td>
<td>25</td>
<td>Tolterodine 1 x 4 mg/d</td>
<td>43</td>
<td>-35.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-29.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-35.3</td>
<td>2b</td>
</tr>
<tr>
<td>Yang et al. (2007) [8] ‡</td>
<td>6</td>
<td>Tolterodine 2 x 2 mg/d</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>-35.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2b</td>
</tr>
<tr>
<td>Kaplan et al. (2009) [11] ‡</td>
<td>12</td>
<td>Tamsulosin 1 x 0.4 mg/d + placebo</td>
<td>195</td>
<td>-6.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-29</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d</td>
<td>202</td>
<td>-9.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-31.8</td>
<td></td>
</tr>
</tbody>
</table>

IPSS = International Prostate Symptom Score
† persisting LUTS during $\alpha_1$-blocker treatment (add-on approach)

<sup>a</sup> = significant compared to baseline ($p \leq 0.05$, indexed wherever evaluated)
<sup>b</sup> = significant reduction compared to placebo ($p < 0.05$)

4.6.2.4 Tolerability and safety

Adverse events of both drug classes appear during combination treatment of $\alpha_1$-blockers and muscarinic receptor antagonists. The most frequently reported side effect in all trials was xerostomia. Some side effects (e.g. xerostomia or ejaculation failure) appear with increased frequency and cannot simply be explained by adding the frequencies of adverse events of either drug. Post-void residual urine increased in most trials. Although the mean increase of PVR urine was low (+6 to +24 mL) some men developed higher PVRs or even urinary retention (0.9 to 3.3%). It remains unknown which men are at risk of developing PVR urine or urinary retention during the combination treatment.

4.6.2.5 Practical considerations

Class effects are likely to be responsible for increased efficacy and QoL in patients treated with $\alpha_1$-blocker and muscarinic receptor antagonist. Measuring of PVR urine is recommended during combination treatment to assess increase or urinary retention.
4.6.2.6 Recommendations

<table>
<thead>
<tr>
<th>Combination treatment with $\alpha_1$-blocker and muscarinic receptor antagonist might be considered in patients with moderate to severe lower urinary tract symptoms if symptom relief has been insufficient with the monotherapy of either drug.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

Combination treatment should cautiously be prescribed in men who are suspicious of having bladder outlet obstruction.

4.6.2.7 References


4.7 Emerging drugs

4.7.1 Phosphodiesterase (PDE) 5 Inhibitors (with or without $\alpha_1$-blockers)

4.7.1.1 Mechanism of action

Nitric oxide (NO) represents an important non-adrenergic, non-cholinergic neurotransmitter in the human body and is involved in signal transmission in the human urinary tract. Nitric oxide is synthesised from the amino acid L-arginine by NO synthases (NOS), which are classified based on their original tissues of detection as neuronal (nNOS), endothelial (eNOS), and immune cells (inducible NOS, iNOS). After being synthesised, NO diffuses...
into cells and stimulates the synthesis of cyclic guanosine monophosphate (cGMP) mediated by the enzyme guanylyl-cyclase. cGMP can activate protein kinases, ion channels, and cGMP-binding phosphodiesterases (PDEs) leading to smooth muscle cell relaxation via depletion of intracellular Ca\(^{2+}\) and desensitisation of contractile proteins (1). The effects of cGMP are terminated by PDE isoenzymes catalysing the hydrolysis of cGMP to an inactive form. Phosphodiesterase inhibitors increase the concentration and prolong the activity of intracellular cGMP; hereby reducing smooth muscle tone of the detrusor, prostate, and urethra. Until now, 11 different PDEs have been identified of which the PDEs 4 and 5 are the predominant ones in the transition zone of the human prostate, bladder, and urethra (2,3). Nitric oxide might also be involved in the micturition cycle by inhibiting reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder (4).

4.7.1.2 Available drugs
Three selective oral PDE5Is (sildenafil citrate [sildenafil], tadalafil, and vardenafil hcl [vardenafil]) have been licensed in Europe for the treatment of ED or pulmonary arterial hypertension (sildenafil and tadalafil), but these drugs have not yet been officially registered for the treatment of male LUTS (Table 13). The available PDE5Is differ primarily in their pharmacokinetic profiles (5). All PDE5Is are rapidly resorbed from the gastrointestinal tract, have a high protein binding in plasma, and are metabolised primarily by the liver and eliminated predominantly by the faeces. However, their half-lives differ markedly. PDE5Is are taken on-demand by patients with erectile dysfunction but tadalafil is also registered for daily use in lower dose (5 mg) than for on-demand use.

Table 13: PDE5Is licensed in Europe for treating erectile dysfunction; key pharmacokinetic properties and doses used in clinical trials

<table>
<thead>
<tr>
<th>Drugs</th>
<th>t(_{\text{max}}) (hours)</th>
<th>t(_{\frac{1}{2}}) (hours)</th>
<th>Daily doses in clinical trials of patients with male LUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>1 * (0.5-2)</td>
<td>3-5</td>
<td>1 x 25-100 mg</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>2 (0.5-12)</td>
<td>17.5</td>
<td>1 x 2.5-20 mg</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>1 * (0.5-2)</td>
<td>4-5</td>
<td>2 x 10 mg</td>
</tr>
</tbody>
</table>

\(t_{\text{max}}\) = time to maximum plasma concentration; \(t_{\frac{1}{2}}\) = elimination half-life; * dependent on food intake (i.e. slower resorption of the drug and an increase in \(t_{\text{max}}\) by approximately 1 hour after a fatty meal).

4.7.1.3 Efficacy
A post-hoc analysis of patients with ED treated with sildenafil initially showed that the PDE5I was capable of significantly reducing concomitant LUTS and increasing bladder symptoms-related QoL, as measured by the IPSS questionnaire (6,7). LUTS improvement was found to be independent of improvement of erectile function. Randomised, placebo-controlled trials on the efficacy of all three available oral PDE5Is have been published during the last years and have investigated changes in symptoms (IPSS), uroflowmetry parameters (Q\(_{\text{max}}\)), and PVR urine (6-16). The maximum trial duration was 12 weeks. These trials demonstrated that all PDE5Is significantly and consistently reduced IPSS by approximately 17-35% (Table 14). Both bladder storage and voiding symptoms decreased equally during treatment with PDE5Is. Post-void residual urine remained unchanged in most of the trials. Q\(_{\text{max}}\) of free uroflowmetry increased in a dose-dependent fashion (tadalafil [16]), but was not significantly different to placebo (sildenafil, tadalafil, and vardenafil). In contrast to the EBM level 1b-trials listed in Table 14, two singlecentre uroflowmetry studies documented improvements of Q\(_{\text{max}}\) and Q\(_{\text{ave}}\) following oral administration of 50 or 100 mg sildenafil in up to 76% of men (mean Q\(_{\text{max}}\) increase 3.7-4.3 mLs or 24-38%) (17,18). Phosphodiesterase 5 inhibitors significantly improved QoL compared to placebo-treated patients.

Three trials compared the efficacy of PDE5Is (sildenafil or tadalafil) with or without \(\alpha_1\)-blockers (alfuzosin or tamsulosin) (9,12,13). These trials were conducted in a small number of patients and with a limited follow-up of 6 to 12 weeks. The drug combination improved IPSS, Q\(_{\text{max}}\), and PVR urine to a greater extent than the single drug alone of each class (Table 14), although the difference compared to PDE5I or \(\alpha_1\)-blocker alone was only statistically significant in one of the three trials (12).
<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>Patients</th>
<th>IPSS (mL/s)</th>
<th>Qmax (mL/s)</th>
<th>PVR (mL)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>McVary et al. 2007 [8] ‡</td>
<td>12</td>
<td>Placebo</td>
<td>180</td>
<td>-1.93</td>
<td>+0.16</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sildenafil 1 x 50-100 mg/day or 1 x 50-100 mg before sexual intercourse</td>
<td>189</td>
<td>-6.32 *</td>
<td>+0.32</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. 2007 [9]‡</td>
<td>12</td>
<td>Alfuzosin 1 x 10 mg/day</td>
<td>20</td>
<td>-2.7 (-15.5%) †</td>
<td>+1.1 †</td>
<td>-23 †</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sildenafil 1 x 25 mg/day</td>
<td>21</td>
<td>-2.0 (-16.9%) †</td>
<td>+0.6</td>
<td>-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alfuzosin 1 x 10 mg/day + sildenafil 1 x 25 mg/day</td>
<td>21</td>
<td>-4.3 (-24.1%) †</td>
<td>+4.3 †</td>
<td>-21 †</td>
<td></td>
</tr>
<tr>
<td>McVary et al. 2007 [10]</td>
<td>12</td>
<td>Placebo</td>
<td>143</td>
<td>-1.7 (-9.3%)</td>
<td>+0.9</td>
<td>-2.6</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil 1 x 5-20 mg/day</td>
<td>21</td>
<td>-2.3 (-13.3%)</td>
<td>+1.2</td>
<td>+4.81</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil 1 x 2.5 mg/day</td>
<td>209</td>
<td>-2.7 (-22.2%) *</td>
<td>+1.4</td>
<td>+12.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil 1 x 5 mg/day</td>
<td>212</td>
<td>-4.9 (-28.2%) *</td>
<td>+1.6</td>
<td>+6.6</td>
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<tr>
<td></td>
<td></td>
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<td>216</td>
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<tr>
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<td></td>
<td>Tadalafil 1 x 20 mg/day</td>
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<td>+2.1 †</td>
<td>-35.2 †</td>
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<td>+3.0 †</td>
<td>-38.7 †</td>
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<td>+1.7 †</td>
<td>-</td>
<td>1b</td>
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<tr>
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<td>Tadalafil 1 x 20 mg every 2 days</td>
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<td>-1.3 (-8.4%)</td>
<td>+1.2 †</td>
<td>-</td>
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<tr>
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<td></td>
<td>Alfuzosin 1 x 10 mg/day + tadalafil 1 x 20 mg every 2 days</td>
<td>23</td>
<td>-6.3 † (-41.6%)</td>
<td>+3.1 †</td>
<td>-</td>
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<td>Porst et al. 2009 [14]‡</td>
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<td>-6.8</td>
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<tr>
<td></td>
<td></td>
<td>Tadalafil 1 x 2.5 mg/day</td>
<td>113</td>
<td>-3.6</td>
<td>+1.4</td>
<td>+8.6 *</td>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td>Stief et al. 2008 [15]</td>
<td>8</td>
<td>Placebo</td>
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<td>+1.0</td>
<td>+1.92</td>
<td>1b</td>
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<td></td>
<td></td>
<td>Vardenafil 2 x 10 mg</td>
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<td>+1.6</td>
<td>-1.0</td>
<td></td>
</tr>
</tbody>
</table>

IPSS = International Prostate Symptom Score; Qmax = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual; ‡ trial included patients with both ED and LUTS; * significant compared to placebo (p ≤ 0.05); † significant compared to baseline (p ≤ 0.05 (indexed wherever evaluated); ‡ significant compared to α1-blocker (tamsulosin, p < 0.05).
4.7.1.4 Tolerability and safety
Phosphodiesterase 5 inhibitors in general can cause headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, hypotension, syncope, tinnitus, conjunctivitis, or altered vision (blurred, discoloration). However, the frequencies of side-effects vary between the individual PDE5Is. The probability of developing priapism or acute urinary retention is considered minimal.

Phosphodiesterase 5 inhibitors are contraindicated in patients using nitrates or the potassium channel opener, nicorandil, due to additional vasodilatation, which might cause hypotension, myocardial ischaemia in patients with coronary artery disease, or cerebrovascular strokes (5). Additionally, all PDE5Is should not be used in patients who are taking the α₁-blockers doxazosin or terazosin, have unstable angina pectoris, have had a recent myocardial infarction (previous 3 months) or stroke (previous 6 months), myocardial insufficiency NYHA > 2, hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if non-arteritic anterior ischemic optic neuropathy (NAION) with sudden loss of vision is known or has appeared after previous use of PDE5Is. Sildenafil and vardenafil are also contraindicated in patients with retinitis pigmentosa. Caution is advised if PDE5Is are used together with other drugs which are metabolised by the same hepatic elimination pathway (CYP3A4), which is associated with an increased serum concentration of the PDE5I.

4.7.1.5 Practical considerations
To date, PDE5Is have been officially licensed only for the treatment of ED and pulmonary arterial hypertension. Treatment beyond this indication (e.g. male LUTS) is still experimental and should not be used routinely in the clinical setting. Long-term experience in patients with LUTS is still lacking. The value of PDE5Is in the context of other available potent drugs (e.g. α₁-blockers, 5α-reductase inhibitors, or muscarinic receptor antagonists) remains to be determined. Insufficient information is available about combinations between PDE5Is and other LUTS medications.

4.7.1.6 Recommendations

<table>
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<tr>
<th>Description</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5 inhibitors reduce moderate to severe male lower urinary tract symptoms.</td>
<td>1b</td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitors are currently restricted to men with erectile dysfunction, pulmonary arterial hypertension, or to those who have lower urinary tract symptoms and participate in clinical trials.</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

PDE = Phosphodiesterase

4.7.1.7 References


4.7.2 **Other new drugs**

Several new drugs are currently under clinical investigation (phase II-III trials) of which none have been licensed for male LUTS so far. These new drugs target:

- the prostate, e.g. gonadotrophin-releasing hormone antagonists, oestrogen receptor antagonists, apoptosis-inducing agents, vaccines, vitamin D agonists, or androgen replacement therapies;
- the bladder, e.g. β3-adrenoceptor agonists;
- the nervous system, e.g. neuromuscular blocking agents, tachykinin receptor antagonists. Published results of those drugs are preliminary and sparse. Therefore, these new drugs were excluded from further analyses, but will be re-evaluated for the next version of the guidelines on male LUTS.
5. **SURGICAL TREATMENT**

5.1 **Transurethral Resection of the Prostate (TURP) and Transurethral Incision of the Prostate (TUIP)**

5.1.1 **Mechanism of action**

Transurethral resection of the prostate (TURP) was first performed in 1932. Whereas the material has changed substantially since the first procedure, the basic principle of TURP has remained unchanged. It is still, firstly, the removal of tissue from the transition zone of the prostate to reduce BPO and, secondly, to reduce LUTS.

Transurethral resection of the prostate is still regarded as the gold standard for the treatment of LUTS secondary to BPO in prostates between 30 and 80 mL. However, there is no strong evidence in the literature regarding the upper size limit of the prostate suitable for TURP. The suggested threshold sizes reflect the Panel's opinion that has assumed that this limit depends on the surgeon's experience, resection speed, and resectoscope sizes. During the last decade, there has been a continuous decline in the rate of TURPs performed. In 1999, TURP represented 81% of all surgery for benign prostatic hypertrophy (BPH) in the USA, but by 2005, TURP represented only 39% of surgical procedures for BPH, due to the combined effect of fewer prostatic operations and more minimally-invasive procedures (1).

Transurethral incision of the prostate (TUIP) was initially described by Orandi in 1969. TUIP reduces LUTS secondary to BPO by splitting the bladder outlet without tissue removal. This technique has been rediscovered and may replace TURP as the first choice of treatment in selected men with benign prostate enlargement, especially men with prostate sizes < 30 mL and without prostate middle lobes.

5.1.2 **Operative procedure**

During TURP, hyperplastic prostatic tissue of the transition zone is removed endoscopically using special resectoscopes and cutting loops, which enable ablation of prostatic tissue in small slices that are then removed from the bladder at the end of surgery. The cutting of prostatic tissue and coagulation of blood vessels is achieved by using adaptable electrical current.

During the TUIP procedure, one or two cuts are made into the prostatic parenchyma and capsule, thereby reducing urethral resistance (BPO). The technique has been modified by several authors. The most popular unilateral incision is located at the 6 o’clock position and the most commonly performed bilateral incisions are at the 5 and 7 o’clock positions.

Urinary tract infections (UTIs) should be treated prior to TURP or TUIP (2,3). The routine use of prophylactic antibiotics in TURP has been well evaluated with a considerable number of RCTs. Three systematic reviews of the available RCTs resulted in similar conclusions favouring the use of antibiotic prophylaxis (4-6). Antibiotic prophylaxis significantly reduces bacteriuria, fever, sepsis, and the need for additional antibiotics after TURP. There was also a trend towards higher efficacy in favour of short-course antibiotic administration than for a single-dose regimen (4). However, further studies are required to define the optimal antibiotic regimen and cost-effectiveness of antibiotic prophylaxis in TURP.

5.1.3 **Efficacy**

5.1.3.1 **Symptom improvement**

Transurethral resection of the prostate provides durable clinical outcomes, as shown by studies with a long follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO (7). One study with a mean follow-up of 13 years reported a significant and sustained decrease in most symptoms and improvements in urodynamic parameters following TURP. The study also found that subjective and objective failures were associated with decreased detrusor contractility rather than BPO (8). A study in 577 men who underwent TURP reported excellent functional outcomes with a mean IPSS of 4.9 and a mean QoL score of 1.2 after 10 years of follow-up (9). A meta-analysis of 29 RCTs reported a mean LUTS improvement of 70.6% (95% CI: 66.4-75.5%) after TURP (10).

5.1.3.2 **RCT comparison of TUIP with TURP**

Eleven RCTs comparing TUIP with TURP are currently available (10-14) (Table 15). These studies evaluated similar LUTS improvements in patients with small prostates (< 20-30 mL) and no prostate median lobe (10-14). The findings are reported below.

Uroflowmetry: the mean Q\(_{\text{max}}\) increase following TURP was 125% with an absolute mean improvement of +9.7 mL/s (95% CI: 8.8-11.2 mL/s) (10). All RCTs comparing TUIP with TURP 12 months after the procedure reported a lower mean or median Q\(_{\text{max}}\) following TUIP with an overall mean Q\(_{\text{max}}\) improvement of 70% (95% CI: 27-112) (10,13).

Post-void residual: PVR volume decreased by 60.5% (95% CI: 48-71) after TURP (10). The decrease in PVR after TUIP varied across available studies, but was always lower than with TURP (10,13).

Re-treatment rate: a second prostatic operation, usually performed as TURP again, was reported at a
constant rate of approximately 1-2% per year. The review analysing 29 RCTs found a re-treatment rate of 2.6% (95% CI: 0.5-4.7) after a mean follow-up of 16 months (10). In a recent large-scale study of 20,671 men, who underwent TURP in Austria, the overall reported re-treatment rates (including secondary TURP, urethrotomy, and bladder neck incision) were 5.8%, 12.3%, and 14.7% at 1, 5, and 8 years of follow-up, respectively (14). The incidence of secondary TURP was 2.9%, 5.8%, and 7.4% for the same follow-up periods (14). Analyses of RCTs comparing TURP with TUIP showed that re-treatment was more likely following TUIP (17.5%) than after TURP (9%) (13).

5.1.4 Tolerability and safety

5.1.4.1 Intra- and peri-operative complications
Mortality following prostatectomy has decreased constantly and significantly during the past decades and is less than 0.25% in contemporary series (10,15,16). In the most recent study of 10,564 men who underwent TURP, peri-operative mortality (during the first 30 days) was 0.1% (17). The risk of transurethral resection (TUR) syndrome has also decreased during the last decades to less than 1.1% (10,16). Risk factors associated with TUR syndrome are excessive bleeding with opening of venous sinuses, prolonged operation time, large prostates, and past or present nicotine abuse (17). No cases of TUR syndromes were recorded in patients undergoing TUIP. The incidence of blood transfusion following TURP in the analysis of 29 RCTs was 8.4% (95% CI: 3.9-13.4) (10). Contemporary real-life data from 10,564 TURP procedures reported procedure-related bleeding requiring blood transfusion in 2.9% of patients. The risk of bleeding following TUIP is negligible (10).

5.1.4.2 Long-term risk of mortality
The possibility of an increased long-term risk of mortality after TURP compared to open surgery has been raised by Roos et al. (15). However, these findings have not been replicated by others (18-20). Recently, data from 20,671 TURPs and 2,452 open prostatectomies (OP) showed that the 8-year incidence of myocardial infarction was identical after TURP (4.8%) and OP (4.9%). Similarly, mortality rates at 90 days (0.7% vs. 0.9%), one year (2.8% vs. 2.7%), 5 years (12.7% vs. 11.8%) and 8 years (20% vs. 20.9%) were almost identical (14).

5.1.4.3 Long-term complications
Urinary incontinence: the median probability of postoperative stress urinary incontinence ranges from 1.8% following TUIP to 2.2% following TURP (1-6,13,15). A meta-analysis of three trials investigating urinary incontinence showed no statistically significant difference between the TUIP and TURP groups, although there were fewer events in the TUIP group (13).

Urinary retention and UTIs: a recent meta-analysis found no statistically significant differences between TURP and TUIP in the development of urinary retention and UTIs (13).

Bladder neck stenosis and urethral stricture: the risk of developing urethral strictures after TURP is 3.8% (95% CI: 1.7-5.8) and after TUIP 4.1% (10). The risk of bladder neck stenoses is 4.7% (95% CI: 0.3-9.2) after TURP (10). A systematic review reported an overall incidence of 8.7% for strictures after TUIP, but did not distinguish between urethral strictures and bladder neck stenoses (13).

Sexual function: retrograde ejaculation results from resection/destruction of the bladder neck and is reported by 65.4% (95% CI 53.4-77.5) of patients after TURP and 18.2% after TUIP (10). There is a longstanding controversy on the impact of prostatectomy, particularly TURP, on erectile function. The only RCT that compared TURP to a ‘wait and see’ policy with a follow-up of 2.8 years reported identical rates of ED in both arms (19% and 21%, respectively) (21). In the analysis of 29 RCTs, the incidence of ED following TURP was 6.5% (95% CI: 0.2-12.7%) (10). The frequently reported increase in ED after TURP seems to be caused by confounding factors (e.g. age) rather than being the direct consequence of TURP.

5.1.5 Practical considerations
TURP and TUIP are both effective primary treatments for men with BPO, BPE, and moderate-to-severe LUTS. The choice between TURP and TUIP should be primarily based on prostate volume, with prostates < 30 mL being mainly considered for TUIP and prostates of 30-80 mL for TURP. The advantages of TUIP are reduced bleeding incidents, shorter operation time, avoidance of TUR syndrome, minimal and shorter postoperative bladder irrigation, low risk of retrograde ejaculation, and shorter times for catheterisation and hospitalisation. The disadvantages are a higher rate of symptom recurrence and the need for additional surgery.

5.1.6 Modifications of TURP: bipolar Transurethral Resection of the Prostate

5.1.6.1 Mechanism of action
One of the most important recent improvements in TURP is the incorporation of plasmakinetic bipolar technology (B-TURP). To date, five types of bipolar resection devices have been developed: the plasmakinetic (PK) system (Gyrus), Vista Coblation/CTR (controlled tissue resection) system (ACMI) [withdrawn], transurethral resection in saline (TURis) system (Olympus), Karl Storz, and Wolf (22). The devices differ in the way in which
bipolar current flow is delivered to achieve the plasmakinetic effect.

5.1.6.2 Operative procedure
Prostatic tissue removal during B-TURP is identical to monopolar TURP. In contrast to monopolar TURP, B-TURP uses a specialised resectoscope loop, which incorporates both the active and return electrodes. It permits electrosurgical tissue cutting in a conductive saline medium. After activation of the high frequency current, the physiological saline around the loop is heated up to the boiling point. The resulting bubbles create an environment with high electrical resistance; the voltage between electrode and saline solution spikes forms an arc. The tissue is heated indirectly by the heat of the ignition of the arc; this enables both resection and coagulation. As with other endoscopic operations, UTIs should be treated before the procedure and prophylactic antibiotic therapy is advised.

5.1.6.3 Efficacy
The efficacy of bipolar TURP devices has been demonstrated in case series and RCTs. Three systematic reviews have provided important information on the efficacy of bipolar TURP (23-25). Almost identical outcomes were reported with monopolar and bipolar TURP concerning the improvement of $Q_{\text{max}}$ (10.5 mL/s vs. 10.8 mL/s) and the AUA-SS/IPSS (-15.2 vs. -15.1) (23).

Long-term results of B-TURP are still awaited. In an RCT comparing B-TURP with plasmakinetic energy with a mean follow-up of 18.3 months, the re-operation rate was 4.1% and 2.1% for the PK system and TURP, respectively (26). In a recent study with a follow-up of 3 years, the initially observed significant improvements remained durable for the bipolar and monopolar arm in terms of IPSS (6.8 vs. 6.2) and $Q_{\text{max}}$ (20.5 vs. 21.5 mL/s) (27).

5.1.6.4 Tolerability and safety
The overall rate of adverse events was significantly lower with B-TURP compared to monopolar TURP (28.6% vs. 15.5%) (23). Main advantages of B-TURP include reduced blood loss and decreased incidences of postoperative clot retention and blood transfusions. Both postoperative catheterisation and hospitalisation times were shorter with bipolar TURP compared to monopolar TURP; this was thought to be due to reduced bleeding associated with improved coagulation abilities. Postoperative storage symptoms, particularly dysuria, were less common with B-TURP. However, most of these results were trends favouring B-TURP rather than statistically significant differences (23).

TUR syndrome has not been reported with B-TURP, due to the use of physiological saline irrigation fluid and reduced fluid absorption during the procedure (23,24). Several RCTs have suggested that urethral strictures are more common with B-TURP with possible contributory factors being a larger resectoscope size (27F), the type of return electrode, and higher current densities (22). However, the most recent systematic review of RCTs did not reveal statistically significant differences between monopolar and bipolar TURP treatment arms (1.7% vs 2.4, respectively, $p = 0.280$) (24). Nevertheless, larger studies with increased numbers of patients and/or longer follow-ups may change these results. Regarding the impact of B-TURP on sexual function, it was found that postoperative retrograde ejaculation (57 vs 60%) (24) or ED (both about 14%) (23) did not differ significantly between B-TURP and monopolar TURP.

5.1.6.5 Practical considerations
B-TURP offers an attractive alternative to monopolar TURP in patients with LUTS secondary to BPO with similar efficacy but lower morbidity. Furthermore, the safety of B-TURP allows more time for training and teaching of urology residents. However, since there remains a lack of sufficient long-term data, it is not possible to draw definite conclusions about the duration of improvements and advantages of B-TURP over monopolar TURP. The choice of B-TURP should currently be based on the availability of the bipolar armamentarium, the surgeon’s experience, and the patient’s preference.
5.1.7  **Recommendations**

Monopolar TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL and moderate-to-severe LUTS secondary to BPO. Monopolar TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments. However, the morbidity of monopolar TURP is higher than for transur, bipolar TURP, drugs, or other minimally-invasive procedures.

Bipolar TURP achieves short-term results comparable to monopolar TURP.

TUIP is the surgical therapy of choice for men with LUTS secondary to BPO and prostate sizes < 30 mL without middle lobes.

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**Table 15: Efficacy of transurethral resection of the prostate (TURP) or transurethral incision of the prostate (TUIP) in level 1 trials at 12 or 24 months. Absolute and relative changes compared to baseline with regard to symptoms (Madson-Iverson or IPSS) and maximum urinary flow rate (Q\text{max})**

<table>
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<tr>
<th>Trials</th>
<th>Intervention</th>
<th>Patients (n)</th>
<th>Absolute decrease (%) in symptoms at 12 months</th>
<th>Q\text{max} (mL/s) at 12 months</th>
<th>Blood transfusion</th>
<th>Re-operation rate at 12 months</th>
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<tr>
<td></td>
<td></td>
<td>absolute [%]</td>
<td></td>
<td>absolute [%]</td>
<td></td>
<td>[ %]</td>
<td>[ %]</td>
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<td>Dorflinger et al. (1992) (28)</td>
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<td>31</td>
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<td>-88 a</td>
<td>+22.9 a,b</td>
<td>13</td>
<td>3.2 b</td>
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<td>TUIP</td>
<td>29</td>
<td>-12.6 a</td>
<td>-85 a</td>
<td>+16.3 a</td>
<td>+223 a</td>
<td>0 c</td>
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<tr>
<td>Jahnson et al. (1998) (29)</td>
<td>TURP</td>
<td>43</td>
<td>-13 a</td>
<td>-82 a</td>
<td>+19.5 a,b</td>
<td>+229 a,b</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>TUIP</td>
<td>42</td>
<td>-11.8 a</td>
<td>-77 a</td>
<td>+13.8 a</td>
<td>+148 a</td>
<td>0</td>
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<td>Riehmann et al. (1995) (30)</td>
<td>TURP</td>
<td>61</td>
<td>-9.5 a</td>
<td>-67 a</td>
<td>no significant difference between groups</td>
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<td>TUIP</td>
<td>56</td>
<td>-10 a</td>
<td>-63 a</td>
<td>23</td>
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<td>20</td>
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<td>+17.3 a</td>
<td>+266 a</td>
<td>0 b</td>
</tr>
<tr>
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<td>TUIP</td>
<td>20</td>
<td>-9.3 a</td>
<td>-64 a</td>
<td>+14.6 a</td>
<td>+197 a</td>
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<td>TUIP</td>
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<td>+19.5 a</td>
<td>+246 a</td>
<td>0 c</td>
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<td>50</td>
<td>-12 a</td>
<td>-70*</td>
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<td>+255 a</td>
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<tr>
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<td>TUIP</td>
<td>50</td>
<td>-13 a</td>
<td>-77*</td>
<td>7.6 *a</td>
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<td>Lourenco et al. (2009) (33)</td>
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<td>no significant difference between groups</td>
<td>no significant difference between groups</td>
<td>28.3</td>
<td>7.2 b</td>
<td>1a</td>
</tr>
<tr>
<td></td>
<td>TUIP</td>
<td>346</td>
<td>1.1 c</td>
<td>18</td>
<td>1b</td>
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<tr>
<td>Yang et al. (2001) (11)</td>
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<td>403</td>
<td>-11.2 to -13</td>
<td>-63 to -82</td>
<td>+17.3 to +22.9 b</td>
<td>+266 to +352 b</td>
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<td>TUIP</td>
<td>392</td>
<td>-10 to -13.5</td>
<td>-63 to -83</td>
<td>+13.8 to +16.3</td>
<td>+189 to +223</td>
<td>0.87 c</td>
</tr>
</tbody>
</table>

*24 month postoperatively; a significantly different compared to baseline; b significantly different in favour of TURP; c significantly different in favour of TUIP*
5.1.8 References


5.2 Open prostatectomy

5.2.1 Mechanism of action

Open prostatectomy is the oldest surgical treatment modality for LUTS secondary to BPO. Obstructive prostatic adenomas are enucleated using the index finger, either from the inside of the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure), allowing unobstructed voiding.
5.2.2 Operative procedure

Indications for surgery

The most frequent indication for surgical management is bothersome LUTS refractory to medical management (1,2). The following complications of BPH/BPE/BPO are considered strong indications for surgery:

• refractory urinary retention;
• recurrent urinary infection;
• recurrent haematuria refractory to medical treatment with 5-alpha reductase inhibitors;
• renal insufficiency due to BPE/BPO;
• bladder stones.

Increased PVR volume may also be used as an indication for surgery. However, there is great intra-individual variability and an upper limit requiring intervention has not been defined. Variables most likely to predict the outcome of prostatectomy are severity of LUTS, the degree of bother, and the presence of BPO.

Procedure

A transurethral balloon catheter is inserted and the bladder is filled with saline solution. Access to the bladder or anterior prostatic capsule is obtained through a midline or transverse suprapubic incision.

Transvesical procedure (Freyer)

A transverse incision is made in the anterior bladder wall. The index finger is then placed in the urethra and with forward pressure towards the symphysis, the urethral mucosa is broken, and the plane between the surgical capsule and the adenomas is defined. The prostatic adenomas are then bluntly separated from the capsule with the finger. Special care must be taken when dividing the urethra at the apex in order not to harm the urethral sphincter. Haemostatic sutures are placed in the posterior corners of the cavity and the posterior margin, taking care not to include the ureteral orifices. Postoperative haemostasis might be obtained using gauze packing and/or traction on a large balloon catheter. For sufficient drainage, both a transurethral and a suprapubic catheter are placed.

Transcapsular procedure (Millin)

A transverse incision is made in the anterior prostatic capsule and the adenomas freed bluntly with a scissors and the index finger. Care is taken when dividing the urethra. Many surgeons will resect the posterior bladder neck to avoid late bladder neck stricture. The prostatic capsule is closed after insertion of a transurethral balloon catheter for drainage.

Peri-operative antibiotics

A known UTI should be treated before surgery (10,11). The routine use of prophylactic antibiotics remains controversial. However, antibiotics are recommended in patients on catheterisation prior to surgery.

5.2.3 Efficacy

Open prostatectomy is the treatment of choice for large glands (> 80-100 mL). Associated complications include large bladder stones or bladder diverticula (4-6). Three recent RCTs have shown that Holmium laser enucleation and PVP lead to similar outcomes compared to open prostatectomy in men with large glands (> 70, 80 and 100 mL) at a significantly lower complication rate (7-9).

5.2.3.1 Treatment outcome

The results of open prostatectomy studies for treating BPH-LUTS or BPO are summarised in Table 16.

• LUTS: open prostatectomy results in an improvement of LUTS of 63-86% and in the IPSS Quality of Life score of 60-87% (8,9,12).
• Uroflowmetry: the mean increase of $Q_{\text{max}}$ following open prostatectomy is 375% (range, 88-677%) (8,9,12) in absolute terms +16.5-20.2 mL/s (6,8,9,12).
• PVR: a reduction of 86-98% is seen in the PVR volume after open prostatectomy (8,9,12).

5.2.3.2 Long-term outcome and re-treatment rate

A favourable long-term outcome is common after open prostatectomy. A secondary prostatic operation has not been reported in the open prostatectomy arm in randomised studies up to 5 years follow-up (8,9,12) (Table 17).
5.2.4 **Tolerability and safety**

*Intra-/peri-operative complications*

Mortality following open prostatectomy has decreased significantly during the past two decades and is less than < 0.25% in contemporary series (13) (Table 17). The estimated need for blood transfusion following is about 7-14% (9,12,13).

*Long-term complications*

Long-term complications are incontinence and bladder neck contracture and urethral stricture. The risk of developing stress incontinence is up to 10% (4), while the risk for developing bladder neck contracture and urethral stricture is about 6% (7-9).

5.2.5 **Practical considerations**

Open prostatectomy is the most invasive, but also the most effective and durable, procedure for the treatment of LUTS secondary to BPO. Only Holmium enucleation delivers similar results, but with less morbidity. In the absence of an endourological armamentarium and a Holmium laser, open prostatectomy appears to be the treatment of choice for men with prostates > 80-100 mL and drug-treatment-resistant LUTS secondary to BPO. The choice between the Freyer or Millin procedures depends upon the surgeon’s preference.

Table 16: Results of open prostatectomy studies for treating BPH-LUTS or BPO

<table>
<thead>
<tr>
<th>Studies</th>
<th>Duration (weeks)</th>
<th>Patients (n)</th>
<th>Change in symptoms (IPSS)</th>
<th>Change in Q\text{max}</th>
<th>Change in PVR</th>
<th>Change in prostate volume</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute % mL/s % mL % mL % mL % mL %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuntz et al. 2008 (9)</td>
<td>260</td>
<td>32</td>
<td>-18.2 86 21.4 677 -287 98 1b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skolarikos et al. 2008 (8)</td>
<td>78</td>
<td>60</td>
<td>-12.5 63 7 86 -77 86 86 88 1b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naspro et al. 2006 (7)</td>
<td>104</td>
<td>39</td>
<td>-13.2 62 15.9 291 1b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varkarakis et al. 2004 (12)</td>
<td>151</td>
<td>232</td>
<td>-23.3 84 16.5 329 -104 90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gratzke et al. 2007 (13)</td>
<td>868</td>
<td></td>
<td>13 218 -128 88 85 88 2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IPSS = international prostate symptom score; PVR = post-void residual; Q\text{max} = maximum urinary flow rate (free uroflowmetry)

Table 17: Tolerability and safety of open prostatectomy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Peri-operative mortality (%)</th>
<th>Postoperative stress incontinence (%)</th>
<th>Re-operation for BPO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuntz et al. 2008 (9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skolarikos et al. 2008 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Naspro et al. 2006 (7)</td>
<td>0</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>Varkarakis et al. 2004 (12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gratzke et al. 2007 (13)</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPO = benign prostatic obstruction

5.2.6 **Recommendations**

Open prostatectomy is the first choice of surgical treatment in men with drug-refractory LUTS secondary to benign prostatic obstruction and prostate sizes > 80-100 mL in the absence of Holmium lasers.

LUTS = lower urinary tract symptoms
5.2.7 References


5.3 Transurethral Microwave Therapy (TUMT)

5.3.1 Mechanism of action

Microwave thermotherapy of the prostate works by emitting microwave radiation through an intra-urethral antenna in order to deliver heat into the prostate. Tissue is destroyed by being heated at temperatures above cytotoxic thresholds (> 45°C) (coagulation necrosis). Heat is mainly produced by electrical dipoles (water molecules) oscillating in the microwave field and electric charge carriers (ions) moving back and forth in the microwave field. It is also thought that the heat generated by TUMT also causes apoptosis and denervation of α1-receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

5.3.2 Operative procedure

Transurethral microwave therapy is a registered trademark of Technomed Medical Systems, the pioneer of microwave thermotherapy. Currently, the main devices in the field of microwave thermotherapy are the Prostatron™ device (Urologix, Minneapolis, MN, USA), Targis™ (Urologix, Minneapolis, MN, USA), CoreTherm™ (ProstaLund, Lund, Sweden), and TMx-2000™ (TherMatrx Inc, Northbrook, ILL, USA). Most published data on thermotherapy has been on the Prostatron device.
Conceptually, TUMT devices are all similar in delivering microwave energy to the prostate with some type of feedback system. All TUMT devices consist of a treatment module that contains the microwave generator with a temperature measurement system and a cooling system. The main difference between TUMT devices is the design of the urethral applicator. The applicator consists of a microwave catheter connected to the module, which is inserted into the prostatic urethra. Differences in the characteristics of applicators have a significant effect on the heating profile (1). Other less important differences between TUMT devices are found in the catheter construction, cooling systems, treatment time, and monitoring of TUMT effects (2).

5.3.3  Efficacy

5.3.3.1  Clinical outcome

A systematic review of all available RCTs on TUMT attempted to assess therapeutic efficacy (Table 18) (3) in different TUMT devices and software, including Prostatron (Prostatsoft 2.0 and 2.5) and ProstaLund Feedback. Weighted mean differences (WMD) were calculated with a 95% confidence interval (CI) for the between-treatment differences in pooled means. The review found that TUMT was somewhat less effective than transurethral resection of the prostate (TURP) in reducing LUTS. The pooled mean symptom score for men undergoing TUMT decreased by 65% in 12 months compared to 77% in men undergoing TURP, which is a WMD of -1.83 in favour of TURP. TURP achieved a greater improvement in O\(_{\text{max}}\) (119%) than TUMT (70%), with a WMD of 5.44 mL/s in favour of TURP (3).

Similarly, a pooled analysis of three studies (two RCTs and one open label) of ProstaLund Feedback TUMT (PLFT) with 12-month follow-up showed that the responder rate was 85.3% in the PLFT group and 85.9% in the TURP group (4). In addition, pooled IPSS data indicated that a subjective, non-inferior improvement with PLFT compared to TURP (4). However, one-sided 95% CI analysis showed that the non-inferiority of PLFT compared to TURP did not reach the predetermined level, even though both PLFT and TURP appeared to improve O\(_{\text{max}}\) significantly.

Previously, urinary retention was considered to be a contraindication for TUMT. Nowadays, level 2b evidence studies have reported an 80-93% success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously (5-7). However, these studies had a short follow-up (≤12 months), which makes it difficult to estimate the durability of TUMT outcome in patients with retention. In a study with a longer follow-up of up to 5 years, treatment failure was 37.8% in the retention group, with a cumulative risk of 58.8% at 5 years (8). One RCT compared TUMT with the α\(_1\)-blocker, terazosin (9). After 18 months' follow-up, treatment failure in the terazosin-treated patients (41%) was significantly greater than in TUMT patients (5.9%), with TUMT also achieving a greater improvement in IPSS and O\(_{\text{max}}\) (10).

5.3.3.2  Durability

Low-energy TUMT has disappointing results for durability. Several studies have reported a re-treatment rate after low-energy TUMT as high as 84.4% after 5 years (11-14), while other studies have reported re-treatment rates of 19.8-29.3% after high-energy TUMT, though with a lower mean follow-up of 30-60 months (15-18). The re-treatment rate due to treatment failure has also been estimated by a systematic review of randomised TUMT trials (3). The trials had different follow-up periods and the re-treatment rate was expressed as the number of events per person per year of follow-up. The re-treatment rate was 0.075/person years for patients treated by TUMT and 0.010/person years for TURP.

However, a prospective, randomised, multicentre study after 5 years has obtained comparable clinical results with TUMT to those seen with TRUP. The study compared TUMT (PLFT; the Core-Therm device) and TURP (19). No statistically significant differences were found in O\(_{\text{max}}\) and IPSS between the two treatment groups at 5 years. In the TUMT group, 10% needed additional treatment versus 4.3% in the TURP arm. These data suggest that, at 5 years, clinical results obtained with PLFT-TUMT were comparable to those seen after TURP. It should be noted that most durability studies have a high attrition rate; in this study, less than half of the initial group of patients treated were analysed at 4-5 years. In addition, patients who remained in the study were likely to represent the best data (responders).

5.3.4  Tolerability and safety

Treatment is well tolerated, even though most patients experience perineal discomfort and urinary urgency and require pain medication prior to or during therapy. Pooled morbidity data of randomised studies comparing TUMT and TURP have been published (3,4,20). Catheterisation time, incidence of dysuria/urgency and urinary retention were significantly less with TURP, while the incidence of hospitalisation, haematuria, clot retention, transfusions, TUR syndrome, and urethral strictures were significantly less for TUMT. In a systematic review of randomised trials (3), the re-treatment rate due to strictures during follow-up was estimated and expressed as the number of events per person per year of follow-up. Transurethral resection of the prostate patients (5.85/100 person years) were more likely than TUMT patients (0.63/100 person years) to require surgical re-treatment for strictures (meatal, urethral, or bladder neck). Pooled data showed that TUMT had less impact.
on sexual function (ED, retrograde ejaculation) than TURP (3,4,20).

5.3.5 **Practical considerations**
Endoscopy is essential because it is important to identify the presence of an isolated enlarged middle lobe or an insufficient length of the prostatic urethra. Reported low morbidity and the absence of any need for anaesthesia (spinal or general) make TUMT a true outpatient procedure, providing an excellent option for older patients with co-morbidities at high operative risk and, therefore, unsuitable for invasive treatment (21). Independent baseline parameters predicting an unfavourable outcome include advanced age of the patient, small prostate volume, mild-to-moderate BOO and a low amount of energy delivered during treatment (22). However, it should be remembered that a predictive factor for a particular device cannot necessarily be applied to other devices.

### Table 18: Efficacy of TUMT. Absolute and relative changes compared to baseline are listed for symptoms (IPSS), maximum urinary flow rate \( (Q_{\text{max}}) \), post-void residual urine \( (PVR) \), and prostate volume \( (PVol) \)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Patients (n)</th>
<th>Change IPSS (absolute [%])</th>
<th>Change ( Q_{\text{max}} ) (mL/s, [%])</th>
<th>Change QoL (absolute [%])</th>
<th>Change PVR (absolute [%])</th>
<th>Change PVol (absolute [%])</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman et al. (2007)</td>
<td>52</td>
<td>322</td>
<td>-12.7(^a) (-65.0)</td>
<td>5.6(^a) (70.0)</td>
<td>-2.4(^a) (58.5)</td>
<td>NA</td>
<td>NA</td>
<td>1a</td>
</tr>
<tr>
<td>Gravas et al. (2005)</td>
<td>52</td>
<td>183</td>
<td>-14.5(^a) (-69.0)</td>
<td>8.4(^a) (109.0)</td>
<td>-2.97(^a) (70.9)</td>
<td>NA</td>
<td>-17.0(^a) (-33.0)</td>
<td>1b</td>
</tr>
<tr>
<td>Mattiasson et al. (2007)</td>
<td>260</td>
<td>100</td>
<td>-13.6(^a) (-61.5)</td>
<td>3.8(^a) (50.0)</td>
<td>-3.2(^a) (-74.4)</td>
<td>-36.0 (-34.0)</td>
<td>-4.0 (-8.1)</td>
<td>1b</td>
</tr>
<tr>
<td>Floratos et al. (15)</td>
<td>156</td>
<td>78</td>
<td>-8.0(^a) (-40.0)</td>
<td>2.7(^a) (29.3)</td>
<td>-2.0(^a) (-50.0)</td>
<td>NS</td>
<td>NA</td>
<td>1b</td>
</tr>
<tr>
<td>Thalmann et al. (2002)</td>
<td>104</td>
<td>200</td>
<td>-20.0(^a) (-87.0)</td>
<td>7.0(^a) (116.6)</td>
<td>-4.0(^a) (-80.0)</td>
<td>-143(^a) (-84.1)</td>
<td>-17.7(^a) (-30.7)</td>
<td>2b</td>
</tr>
<tr>
<td>Miller et al. (2003)</td>
<td>260</td>
<td>150</td>
<td>-10.6(^a) (-47.0)</td>
<td>2.4(^a) (37.0)</td>
<td>-2.3(^a) (-54.7)</td>
<td>NA</td>
<td>NA</td>
<td>2b</td>
</tr>
<tr>
<td>Trock et al. (2004)</td>
<td>208</td>
<td>541</td>
<td>-8.9(^a) (-42.7)</td>
<td>2.8(^a) (35.0)</td>
<td>-2.1(^a) (-50.1)</td>
<td>NA</td>
<td>NA</td>
<td>2b</td>
</tr>
</tbody>
</table>

\(^a\) = significant compared to baseline (indexed whenever evaluated); NS = not significant; NA = not available

5.3.6 **Recommendations**

| Transurethral microwave therapy achieves symptom improvement comparable to TURP, but is associated with decreased morbidity and lower flow improvements. | 1a | A |
| Durability is in favour of transurethral resection of the prostate with lower re-treatment rates compared to transurethral microwave therapy | 1a | A |

\(TURP = \text{transurethral resection of the prostate}\)
5.3.7 References


5.4 Transurethral Needle Ablation (TUNA™) of the prostate

5.4.1 Mechanism of action
The TUNA™ procedure works by inducing a coagulative necrosis within the transition zone of the prostate. As a result of scar maturation, there may be a reduction in transition zone volume and, therefore, a reduction of BPO. There may also be a poorly understood neuromodulatory effect.

5.4.2 Operative procedure
The TUNA™ device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the prostatic parenchyma. The needles are insulated, except at their tips, so that energy is only delivered into the prostatic parenchyma and not to the urethra. Needles are placed under direct vision using an attachment to the standard cystoscope. TUNA™ is carried out under anaesthetic (local or general) or sedation.

5.4.3 Efficacy
Several, non-randomised, clinical trials have documented the clinical efficacy of TUNA™ with a fairly consistent outcome (3-7). Symptomatic improvement has ranged from 40-70%. Improvements in Qmax vary widely from 26-121% in non-retention patients. A recent report with 5 years’ follow-up in 188 patients demonstrated symptomatic improvement in 58% and improved flow in 41%. However, 21.2% of patients required additional treatment (8).

5.4.3.1 Randomised clinical trials
TUNA™ has been compared with TURP in randomised studies (8-11) with varying follow-up. The studies found both TUNA™ and TURP produced symptomatic improvement. However, TURP produced greater symptom improvement and a better QoL than TUNA™, as well as a significant improvement in Qmax after TUNA™ (Table 19). More detailed comparisons between TUNA™ and TURP can be found in some very high-quality and comprehensive, systematic reviews and meta-analyses (12,13).

5.4.3.2 Impact on bladder outlet obstruction
Seven clinical studies on the impact of TUNA™ on BPO (14,15) have demonstrated a statistically significant decrease in maximum detrusor pressure or detrusor pressure at Qmax, even though a number of patients were still obstructed following TUNA™ therapy.
There is no convincing evidence that prostate size is significantly reduced following TUNA™ (6).

Recent reports have suggested that gadolinium-enhanced MRI can be used to assess TUNA™-related treatment effects (16).

5.4.3.3 Durability
Because most studies have been short-to-medium term, concerns have been risen about the durability of effects. Even short term (12 months), up to 20% of patients treated with TUNA™ need to be re-treated with TURP (1). A recent French report described a failure rate (incorporating re-treatment) of up to 50% over a 20-month period (17).

5.4.4 Tolerability and safety
TUNA™ is usually performed as an outpatient procedure under local anaesthesia, although intravenous sedation is sometimes required (1). Postoperative urinary retention is seen in 13.3-41.6% of patients and lasts for a mean of 1-3 days; within 1 week, 90-95% of patients are catheter-free (1). Irritative voiding symptoms up to 4-6 weeks are common (2). Continence status is not affected.

5.4.5 Practical considerations
Few selection criteria have been identified. However, TUNA™ is unsuitable for patients with prostate volumes > 75 mL or isolated bladder neck obstruction. Because TUNA™ cannot treat median lobes effectively it is not clear whether men with significant median lobes will experience the benefit in published studies. There is anecdotal evidence for TUNA™ in men receiving aspirin and anti-coagulants. TUNA™ can be performed as a day-case procedure and is associated with fewer side-effects compared to TURP (e.g. bleeding, ED, urinary incontinence). However, there remain concerns about the durability of the effects achieved by TUNA™.

5.4.6 Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

| Transurethral needle ablation™ is an alternative to transurethral resection of the prostate for patients who wish to defer/avoid (complications of) transurethral resection of the prostate, but patients should be aware of significant re-treatment rates and less improvement in symptoms and quality of life. |

Table 19: Summary of comparative level of evidence (LE) 1 data (TUNA™ vs TURP) (12)

<table>
<thead>
<tr>
<th>Symptoms (IPSS): mean (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (8,10)</td>
</tr>
<tr>
<td>1 year (9-11)</td>
</tr>
<tr>
<td>3 years (9,11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of life scores: mean (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (8,10)</td>
</tr>
<tr>
<td>1 year (9-11)</td>
</tr>
<tr>
<td>3 years (9,11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$Q_{max}$ (mL/s): mean (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (8,10)</td>
</tr>
<tr>
<td>1 year (9-11)</td>
</tr>
<tr>
<td>3 years (9,11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PVR (mL): mean (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year (10,11)</td>
</tr>
</tbody>
</table>

IPSS = International Prostate Symptom Score; $Q_{max}$ = maximum urinary flow rate; PVR = post-void residual. 
$a$ = TURP significantly better compared with TUNA™.
5.4.7 References


5.5 Laser treatments of the prostate

5.5.1 Holmium Laser Enucleation (HoLEP) and Holmium Laser Resection of the Prostate (HoLRP)

5.5.1.1 Mechanism of action

The holmium:yttrium-aluminum-garnet (Ho:YAG) laser (2140 nm) is a pulsed, solid-state laser that has been used in urology for a variety of endourological applications in soft tissues and for the disintegration of urinary calculi (1). The wavelength of the Ho:YAG laser is strongly absorbed by water. This means that the area of tissue coagulation and the resulting tissue necrosis is limited to 3-4 mm, which is enough to obtain adequate haemostasis (2). Peak power produces intense, non-thermal, localised, tissue destruction, resulting in precise and efficient cutting of prostatic tissue. Resection is usually performed when the prostate is smaller than 60 mL, while enucleation is used for larger glands.

5.5.1.2 Operative procedure

Instrumentation for this technique includes a 550 µm, end-firing, quartz fibre and an 80 W Ho:YAG laser. A continuous-flow resectoscope is required with a working element, while physiological saline solution is used as an irrigant. The basic principle of the HoLRP technique is retrograde resection of the prostate and fragmentation of resected tissue inside the bladder to allow its evacuation through the operating channel of the resectoscope (2,3). The introduction of holmium laser enucleation (HoLEP) has been a significant improvement. Mimicking open prostatectomy, the prostatic lobes are completely enucleated and pushed into the bladder, before being fragmented and aspirated afterwards by a morcellator (8).

5.5.1.3 Efficacy

Gilling et al. (4) has presented the results of a prospective RCT comparing TURP with HoLRP. To date, 120 patients have been enrolled with urodynamically-confirmed BPO (Schäfer grade > 2) and prostate sizes < 100 mL (Table 20). Preliminary analysis has revealed a significantly longer mean resection time (42.1 vs. 25.8 minutes) for HoLRP patients, while symptomatic and urodynamic improvement were equivalent in both treatment groups. In 2004, long-term results with a minimum follow-up of 4 years were published (7), which showed that there was no difference in urodynamic parameters between HoLRP and TURP after 48 months.

Gilling et al. (9) reported long-term data with a mean follow-up of 6.1 years, indicating that HoLEP results were durable and most patients remained satisfied with their procedure. Two meta-analyses, which analysed available RCTs comparing HoLEP and TURP (10,11), reported a significantly longer operation time with HoLEP (Table 20). Symptom improvements were comparable, but Q\text{max} at 12 months was significantly better with HoLEP (11). In prostates > 100 mL, HoLEP proved to be as effective as open prostatectomy for improving micturition, with equally low re-operation rates at 5-years’ follow-up (12).

5.5.1.4 Tolerability and safety

No major intra-operative complications have been described; however, the technique is a surgical procedure that requires relevant endoscopic skills. There are no specific limitations to the procedure. Patients taking anticoagulant medication and those with urinary retention can be treated safely (6). Dysuria was the most common peri-operative complication with an incidence of approximately 10% (2,4,5). Compared to TURP, HoLRP has a significantly shorter catheterisation time (20.0 vs. 37.2 hours), shorter hospitalisation time (26.4 vs. 47.4 hours) (4), and peri-operative morbidity (7). Potency, continence, symptom scores and major morbidity at 48 months were identical between HoLRP and TURP (7). Retrograde ejaculation occurred in 75-80% of patients; no postoperative impotence has been reported (2). Both meta-analyses found that HoLEP resulted in a significantly shorter catheterisation time and hospital stay, reduced blood loss and fewer blood transfusions, but had a longer operation time than TURP (10,11).

5.5.2 532 nm (‘Greenlight’) laser vaporisation of prostate

5.5.2.1 Mechanism of action

Vaporisation of prostatic tissue is achieved by a sudden increase in tissue temperature from 50°C to 100°C following the application of laser energy. A rapid increase in tissue temperature results in intracellular vacuoles (bubbles), followed by an increase in intracellular cell pressure. Once the cell pressure exceeds that compatible with cellular integrity, the vacuoles are released, as can be seen during the procedure. Because of the way in which tissue interacts with oxyhaemoglobin, laser vaporisation is increased within a wavelength range from 500-580 nm. Because of the green light emitted (λ=532 nm), this laser procedure is known as ‘Greenlight’ laser vaporisation.

It is important to include the wavelength or crystal used to produce the laser energy when describing the type of laser vaporisation used. This is because tissue interaction caused by laser energy varies according to the wavelength, applied energy, fibre architecture and tissue properties. This also means that the clinical results of different wavelengths are not comparable.
Table 20: Postoperative results of holmium resection (HoLRP) or enucleation (HoLEP) vs. transurethral resection of the prostate (TURP) open prostatectomy (OP) and ‘Greenlight’ laser vaporisation (KTP) vs. TURP. Absolute and relative changes compared to baseline, with regard to symptoms (AUA-SI/IPSS), maximum urinary flow rate ($Q_{\text{max}}$), post-void residual urine (PVR), and prostate volume.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration</th>
<th>Patients</th>
<th>Surgery</th>
<th>Change symptoms (IPSS)</th>
<th>Change $Q_{\text{max}}$ (mL/s)</th>
<th>Change PVR (mL)</th>
<th>Change prostate volume (mL)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(months)</td>
<td>(n)</td>
<td></td>
<td>absolute [%]</td>
<td>absolute [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le Duc et al. (1999) (1)</td>
<td>6</td>
<td>42</td>
<td>HoLRP</td>
<td>-18.4 [-84]</td>
<td>+15.1 [170]</td>
<td></td>
<td></td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43</td>
<td>TURP</td>
<td>-17.9 [-78]</td>
<td>+13.2 [145]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Westenberg et al. (2004) (7)</td>
<td>48</td>
<td>43</td>
<td>HoLRP</td>
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<td>-61.1 [a]†</td>
<td>-70 [a]†</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>TURP</td>
<td>-16.4 [-71] [a]</td>
<td>+9.4 [103] [a]</td>
<td>-50.4 [a]†</td>
<td>-60 [a]†</td>
<td></td>
</tr>
<tr>
<td>Fraundorfer et al. (1998) (8)</td>
<td>1</td>
<td>14</td>
<td>HoLEP</td>
<td>-14.0 [-66]</td>
<td>+18.2 [260]</td>
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</tr>
<tr>
<td>Gilling et al. (2008) (9)</td>
<td>72</td>
<td>38</td>
<td>HoLEP</td>
<td>-17.2 [-67]</td>
<td>+10.9 [135]</td>
<td>-71.7 [†]</td>
<td>-68 [†]</td>
<td></td>
</tr>
<tr>
<td>Tan et al. (2007) (10)</td>
<td>12</td>
<td>232</td>
<td>HoLRP</td>
<td>-17.5 to -21.7 [-81 to -83]</td>
<td>+13.4 to +23.0 [160 to +470]</td>
<td>-232.7 [-98]</td>
<td></td>
<td>1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>228</td>
<td>TURP</td>
<td>-17.7 to -18.0 [-76 to -82]</td>
<td>+10.1 to +21.8 [122 to +370]</td>
<td>-189.4 [-88]</td>
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<td></td>
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<tr>
<td>Lourenco et al. (2008) (11)</td>
<td>12</td>
<td>277</td>
<td>HoLRP</td>
<td>-17.7 to -21.7 [-82 to -92]</td>
<td>+13.4 to +23.0 [b] [160 to +470]</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>OP</td>
<td>-18.0 [-86]</td>
<td>+20.8 [578]</td>
<td>-286.7 [-98]</td>
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<td></td>
</tr>
<tr>
<td>Heinrich et al. (2007) (13)</td>
<td>6</td>
<td>140</td>
<td>KTP (80 W)</td>
<td>-10.9 [a] [-55]</td>
<td>+5.6 [43]</td>
<td>-65 [a]</td>
<td>-74 [a]</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td>48</td>
<td>KTP (80 W)</td>
<td>-10.9 [a] [-60]</td>
<td>+10.2 [a] [121]</td>
<td>-179 [a]</td>
<td>-86 [a]</td>
<td></td>
</tr>
</tbody>
</table>

† 6-month data; CG = control group; RUR = refractory urinary retention; OA = oral anticoagulation; NUR = no urinary retention

*a significant compared to baseline (indexed whenever evaluated)

b significant difference in favour of indicated treatment
<table>
<thead>
<tr>
<th>Study/Technique</th>
<th>Duration</th>
<th>Patients</th>
<th>Surgery</th>
<th>Change symptoms (IPSS)</th>
<th>Change Qmax (mL/s)</th>
<th>Change PVR (mL)</th>
<th>Change prostate volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Duc et al. (1999) (1)</td>
<td>6</td>
<td>42</td>
<td>HoLRP</td>
<td>-18.4</td>
<td>-84</td>
<td>+15.1</td>
<td>+170</td>
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<tr>
<td>Westenberg et al. (2004) (7)</td>
<td>48</td>
<td>43</td>
<td>HoLRP</td>
<td>-14.7</td>
<td>-67</td>
<td>+13.4</td>
<td>+151</td>
</tr>
<tr>
<td>Fraundorfer et al. (1998) (8)</td>
<td>1</td>
<td>14</td>
<td>HoLEP</td>
<td>-14.0</td>
<td>-66</td>
<td>+18.2</td>
<td>+260</td>
</tr>
<tr>
<td>Gilling et al. (2008) (9)</td>
<td>72</td>
<td>38</td>
<td>HoLEP</td>
<td>-17.2</td>
<td>-67</td>
<td>+10.9</td>
<td>+135</td>
</tr>
<tr>
<td>Tan et al. (2007) (10)</td>
<td>12</td>
<td>232</td>
<td>HoLRP</td>
<td>-17.5 to -21.7</td>
<td>-81 to -83</td>
<td>+13.4 to +23.0</td>
<td>+160 to +470</td>
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<tr>
<td>Lourenco et al. (2008) (11)</td>
<td>12</td>
<td>277</td>
<td>HoLRP</td>
<td>-17.7 to -21.7</td>
<td>-82 to -92</td>
<td>+13.4 to +23.0</td>
<td>+160 to +470</td>
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<tr>
<td>Kuntz et al. (2008) (12)</td>
<td>60</td>
<td>42</td>
<td>HoLEP</td>
<td>-19.1</td>
<td>-86</td>
<td>+ 20.5</td>
<td>+540</td>
</tr>
<tr>
<td>OP</td>
<td></td>
<td>32</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Heinrich et al. (2007) (13)</td>
<td>6</td>
<td>140</td>
<td>KTP</td>
<td>-10.9</td>
<td>-55</td>
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<td>+ 43</td>
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<tr>
<td>Ruszat et al. (2007) (17)</td>
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<td>116</td>
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<td>-70</td>
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<td>+140</td>
</tr>
<tr>
<td>KTP (80 W) CG</td>
<td>92</td>
<td></td>
<td></td>
<td>-12.7</td>
<td>-71</td>
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</tr>
<tr>
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<td>PVP RUR</td>
<td>-11.1</td>
<td>-72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVP NUR</td>
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<td></td>
<td></td>
<td>-12.1</td>
<td>-65</td>
<td>+16.2</td>
<td>+228</td>
</tr>
<tr>
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<tr>
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<td>KTP (80 W)</td>
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<td>-50,a</td>
<td>+12.0,a</td>
<td>+167,a</td>
</tr>
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<td></td>
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<td>-12.9,a</td>
<td>-50,a</td>
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<td>Bachmann et al. (2005) (21)</td>
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<td>+11.2,a</td>
<td>+162,a</td>
</tr>
<tr>
<td>TURP</td>
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<td></td>
<td></td>
<td>-12.5,a</td>
<td>-72,a</td>
<td>+12.2,a</td>
<td>+177,a</td>
</tr>
<tr>
<td>Bouchier-Hayes et al. (2008) (23)</td>
<td>12</td>
<td>46</td>
<td>KTP (80 W)</td>
<td>-16.4,a</td>
<td>-65,a</td>
<td>+9.8,a</td>
<td>+111,a</td>
</tr>
<tr>
<td>TURP</td>
<td>39</td>
<td></td>
<td></td>
<td>-14.5,a</td>
<td>-57,a</td>
<td>+10.5,a</td>
<td>+118,a</td>
</tr>
<tr>
<td>Horasanli et al. (2008) (24)</td>
<td>6</td>
<td>39</td>
<td>KTP (80 W)</td>
<td>-5.8</td>
<td>-31</td>
<td>+4.7</td>
<td>+156</td>
</tr>
<tr>
<td>TURP</td>
<td>37</td>
<td></td>
<td></td>
<td>-13.8,b</td>
<td>-68,b</td>
<td>+11.5,b</td>
<td>+225,b</td>
</tr>
</tbody>
</table>

† 6-month data; CG = control group; RUR = refractory urinary retention; OA = oral anticoagulation; NUR = no urinary retention

*a* significant compared to baseline (indexed whenever evaluated)

*b* significant difference in favour of indicated treatment
5.5.2.2  Operative procedure
Laser vaporisation of the prostate using an 80 W, 532 nm laser is performed by using a 600 µm side-firing laser fibre with a 70°-deflecting laser beam and a 30°-deflecting laser cystoscope. Cold sterile saline or water can be used for irrigation during the procedure. Under direct vision, vaporisation is performed with a fibre-sweeping technique, usually starting at the bladder neck and continuing with the lateral lobes and the apex (13). The visible, side-fired, laser beam leads to an immediate and apparent tissue ablation.

5.5.2.3  Efficacy
Numerous studies, predominantly with 80 W lasers, have been published in recent years (Table 20). The lack of long-term data means it is not yet possible to make final conclusions about the duration of improvement. A significant improvement in symptoms and voiding parameters and a re-operation rate comparable to TURP was reported in a 5-year follow-up study of 500 patients (14). Despite ongoing oral anticoagulation in 45% of the patients (n = 225), no severe intra-operative complications were observed. The mean catheterisation and post-operative hospitalisation time was 1.8 (0-10) and 3.7 (0-35) days, respectively.

Three years after photolaser vaporisation in men with mean vapourised prostate volumes of 28 ± 42 mL, the mean IPSS was 8.0, QoL score was 1.3, and Q_{max} was 18.4 mL/s. The re-treatment rate was 6.8%. Urethral and bladder neck strictures were observed in 4.4% and 3.6% of patients, respectively. However, follow-up was available only in a few patients. Significant improvements in voiding parameters at a follow-up of 12 months were demonstrated with urodynamic investigation (15). At 12 months' follow-up, the mean urethral opening pressure (Pdetopen; 76.2 vs. 37.4 cm H_{2}O) and detrusor pressure at Q_{max} (Pdetmax; 75 vs. 36.6 cm H_{2}O) were significantly reduced compared to baseline. The Q_{max} improved by 113% (mean 18.6 mL/s) compared to pre-operative Q_{max} (mean 7.9 mL/s).

To date, only two prospective RCTs and three non-randomised trials have been published. The longest available follow-up of an RCT is only 12 months; this trial indicated that 532 nm laser vapourisation was equivalent to TURP in symptom improvement (20). Both groups showed a significant increase in Q_{max} from baseline. In the TURP group, flow increased from 8.7 to 17.9 mL/s (149%) and in the laser vaporisation group from 8.5 to 20.6 mL/s (167%). The IPSS decreased from 25.4 to 12.4 (50%) in the TURP group and from 26 to 12 (50%) in the laser vaporisation group. Laser vaporisation also resulted in significant decreases (averaging 119 mL pre-operatively in the TURP group and 147 mL in the laser vaporisation group), with reductions to 37 and 27 mL, respectively. Similar trends were seen concerning bother and quality of life scores.

5.5.2.4  Tolerability and safety
Safety was shown in various, prospective, non-randomised trials in patients with oral anticoagulation, urinary retention, or prostates > 80 mL (16-19). Regarding intra-operative safety, 532 nm laser vapourisation was reported to be superior to TURP in non-randomised trials (21,22). It is also an effective technique when compared to TURP, producing equivalent improvements in flow rates and IPSS with the advantages of markedly reduced length of hospital stay, duration of catheterisation, and adverse events in a randomised trial. The duration of catheterisation was significantly less in the laser vapourisation than the TURP group, with a mean (range) of 13 (0–24) hours vs. 44.7 (6–192) hours. Additionally, the length of hospital stay was significantly shorter with laser vapourisation, with a mean (range) of 1.09 (1-2) and 3.6 (3-9) days in the laser vapourisation and TURP groups, respectively (23).

5.5.2.5  Practical considerations
Despite the efficacy of TURP in terms of tissue removal and reduction of BPO, a higher rate of peri-operative complications has resulted in an ongoing search for less invasive and safer surgical techniques. Based on the wavelength and power, laser can be used either for coagulation, vaporisation, or cutting (‘enucleation’). Non-thermal effects, also known as ‘ablation’, also result in tissue destruction. Functional results will therefore differ in terms of peri-operative handling of different laser devices, including learning curve, debulking issue, durability of results, and type of complications. The treatment choice how to reduce BPO is dependent on the availability of the armamentarium, patient’s choice, concomitant morbidity or drug use, and experience of the surgeon.

Several types of new generation lasers for prostate surgery have emerged during the last decade, including the holmium:YAG, potassium titanyl phosphate:yttrium aluminium garnet (KTP:YAG), thulium:yttrium aluminium garnet (thulium:YAG), light blue optics:yttrium aluminium garnet (LBO:YAG) and the diode lasers. Energy can be transmitted through a bare, right-angle or interstitial fibre. Each laser has wavelength-specified energy–tissue interaction. Prostatic tissue destruction results from both thermal and non-thermal effects. In 2009, published data were only available for HoLEP, 80 W Greenlight PV (photoselective vapourisation), and thulium:YAG laser prostatectomy. Only a few articles have been published on thulium:YAG prostatectomy, which may be used as a vapourising, coagulating, or cutting laser. The lack of published data means that firm conclusions are not yet possible with regard to the different laser treatments.
5.5.2.6 Recommendations

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoLEP and 532 nm laser vaporisation of the prostate are minimally-invasive alternatives to TURP in men with LUTS secondary to BPO which lead to immediate, objective and subjective improvements comparable to TURP.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>With regard to intra-operative safety, 532 nm laser vaporisation is superior to TURP and should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>With regard to long-term complication rates, results are only available for HoLEP, and are comparable to TURP.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

TURP = transurethral resection of the prostate; LUTS = lower urinary tract symptoms; BPO = benign prostatic obstruction

5.5.3 References

Prostate stents

5.6.1 Mechanism of action

The use of an endoprosthesis to preserve luminal patency is a well-established concept, while in 1980 Fabian first describing stenting of the prostatic urethra to relieve BPO (1). Prostatic stents were primarily designed as an alternative to an indwelling catheter in patients unfit for surgery because of co-morbidity. However, prostatic stents have also been assessed by several studies as a primary treatment option in patients without significant co-morbidities (2,3).

A prostatic stent requires a functioning detrusor, so that the bladder still has the ability to empty itself. This is in contrast to an indwelling catheter, which drains the bladder passively (4). Stents can be temporary or permanent. Permanent stents are biocompatible, allowing epithelialisation, so that eventually they become embedded in the urethra. Temporary stents do not epithelialise and may be either biostable or biodegradable. Temporary stents can provide short-term relief from BPO in patients temporarily unfit for surgery or after minimally invasive treatment (MIT) (4).

5.6.2 Operative procedure

Stent insertion is mostly performed in an outpatient setting under local anaesthesia. Prior to stent insertion, the length of the prostatic urethra is measured to determine the stent length. After the patient has been placed in the lithotomy position, the stent is advanced through the urethra until the tip of the prostatic urethral segment is positioned in the bladder. It is important that the stent is not positioned inside the external urethral sphincter as it may cause stress urinary incontinence. To confirm proper positioning, abdominal ultrasound or cystoscopy is performed. Removal of a temporary stent is achieved by pulling the retrieval suture, until the stent is completely retracted, or by using graspers under endoscopic guidance. It can be difficult to remove permanent stents in cases of stent migration, stent encrustation or epithelial in-growth, and general anaesthesia is usually needed. In general, antibiotic prophylaxis is not necessary unless there has been a positive urine culture.
5.6.3  Efficacy
There have been several small case studies on a range of stents of different designs and materials, which have provided a low level of evidence for their use. Table 21 describes the most important studies (2,5-9). All studies during follow-up have observed a significant attrition rate. There is only one RCT that has compared two versions of a blind-placement prostatic stent (BPS) for BPO (10), and there have been no studies comparing stents with sham or other treatment modalities. The BPS system is a temporary stent consisting of a soft silicone stent, retrieval line, and delivery device, with the difference between BPS-1 and BPS-2 being an additional 2-cm bulbular segment. This bulbular segment results in a significantly lower migration rate with BPS-2 (5%) compared with BPS-1 (85%), but the bulbular segment also caused significant discomfort (10). BPS-2 also has better symptom scores and voiding function than BPS-1, but only Q\text{max} reached statistical significance. The results from this study appear to indicate that stent design has a critical role in the efficacy and safety of prostatic stents (10).

5.6.3.1 Permanent stents (UroLume endourethral prosthesis)
The main representative of the permanent stents is the UroLume endourethral prosthesis. A recent systematic review identified 20 case series, with a total of 990 patients who received the UroLume stent (11). The 10 studies that reported symptom scores demonstrated improved symptoms following stent insertion, although the timing of assessment varied between studies. The reported decrease in Madsen-Iversen scores ranged from 7.9 to 14.3 points, while the IPSS decreased by 10-12.4 points (11). Additionally, the mean Q\text{max} increased between 4.2 and 13.1 mL/s following stent insertion. The pooled data from studies with patients using permanent transurethral catheters showed that 84% of patients (148/176) regained the ability to void spontaneously after UroLume treatment, with the mean Q\text{max} ranging from 8.8 to 20 mL/s. At 12 years of follow-up, the mean IPSS, Q\text{max}, and PVR were 10.82, 11.5 mL/s and 80 mL, respectively (12).

5.6.3.2 Non-epitheliasing (temporary) prostatic stent (Memokath)
The best data on non-epitheliasing prostatic stent are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent (13). In total, 14 case series with 839 patients were reviewed. Analysis of the seven studies reporting symptom scores found that Memokath insertion was associated with a reduction of 11-19 points in the IPSS and a reduction of 9 points in the Madsen-Iversen score. However, it is important to note that the assessment was made at different times after stent placement. Similarly, stent insertion resulted in a Q\text{max} increase of 3 to 11 mL/s, although again the time of assessment was variable after placement (13).

5.6.4 Tolerability and safety
In general, stents are subject to misplacement, migration, poor tolerability because of exacerbation of LUTS, and encrustation (4). The main adverse events immediately following stent placement include perineal pain or irritative voiding symptoms in most patients.

The systematic review of the UroLume reported a 16% failure rate (104/666) within 12 months of insertion, mainly due to stent misplacement or migration (37%) or recurrent obstructive or irritative voiding symptoms (14%). The overall failure rate at 5 years was 27% (50/188 stents), although many patients were lost to follow-up or died with the stent in situ (11). In the study with the longest follow-up, 18% of the patient population (11 men) completed 12 years of follow-up with the Urolume stent in situ, whereas 29 stents were removed (failure rate, 47%) and 22 patients (34%) died of diseases non related to male LUTS.

5.6.5 Practical considerations
In search for the ideal prostatic stent, a range of different stent types has been developed and undergone clinical study. Because of the side effects and high migration rate, prostatic stents have a limited role in the treatment of BPO. Prostatic stents remain an alternative to transurethral catheterisation for men who have (recurrent) urinary retention and are at high risk for surgery.

5.6.6 Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

Prostatic stents are an alternative to catheterisation for men unfit for surgery. Stents may have a role in the temporary relief of benign prostatic obstruction after minimally invasive treatment.
### Table 21: Efficacy of stents: key studies

<table>
<thead>
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<th>Stent</th>
<th>n</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Failure rate (follow-up in months)</th>
<th>LE</th>
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<td>Urolume (P) (2)</td>
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<td>14.1</td>
<td>4.7</td>
<td>9.3</td>
<td>17.1</td>
<td>Overall</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>R</td>
<td>4.6</td>
<td>R</td>
<td>13.7</td>
<td>15.5% (18 mos)</td>
<td></td>
</tr>
<tr>
<td>Memotherm (P) (5)</td>
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<td>24.0</td>
<td>6.1*</td>
<td>7.4</td>
<td>16.1*</td>
<td>4% (48 mos)</td>
<td>3</td>
</tr>
<tr>
<td>TITAN (P) (6)</td>
<td>85</td>
<td>15.9ª</td>
<td>9.331</td>
<td>8.59*</td>
<td>11.431</td>
<td>Overall</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>18.0</td>
<td>5.21</td>
<td>R</td>
<td>11.34</td>
<td>19% (24 mos)</td>
<td></td>
</tr>
<tr>
<td>Spanner (T) (7)</td>
<td>30</td>
<td>22.3</td>
<td>7.1</td>
<td>8.2</td>
<td>11.6</td>
<td>0% (2 mos)</td>
<td>3</td>
</tr>
<tr>
<td>Memokath (T-P) (8)</td>
<td>211</td>
<td>20.3</td>
<td>8.22</td>
<td>NA</td>
<td>NA</td>
<td>23% (7 y)</td>
<td>3</td>
</tr>
<tr>
<td>Horizon Bell-shaped (T) (9)</td>
<td></td>
<td>108</td>
<td>22.0</td>
<td>15.0</td>
<td>9.1</td>
<td>9.6</td>
<td>46% (3 mos)</td>
</tr>
</tbody>
</table>

Q\textsubscript{max} = maximum urinary flow rate (free uroflowmetry); (P) = permanent stent; R = retention; (T) = temporary stent; NA = not available

* Immediately after insertion; "ª Madsen score; "1 at 2 years; "2 at 3 months

### References


5.7 Emerging operations

5.7.1 Intra-prostatic ethanol injections

5.7.1.1 Mechanism of action
Absolute (dehydrated, 95-98%) ethanol is injected into the prostatic parenchyma for the treatment of LUTS secondary to BPO. The precise mechanism of action in both humans and animals remains unclear. The use of ethanol was investigated in the canine model and demonstrated the ability of ethanol to cause inflammation, coagulative necrosis with protein denaturation and cell membrane lysis, and, finally, atrophy and ablation of prostatic tissue resulting in cavity formation (1-4). Tissue necrosis was typically wedge-shaped (4). The volume of injected ethanol correlated only moderately with the size of tissue necrosis (4). Intra-prostatic cavity formation appeared in the canine model after 7 days (3).

5.7.1.2 Operative procedure
Liquid dehydrated ethanol or ethanol gel is injected into the prostatic parenchyma with a 20-22 gauge needle either transurethrally, transperineally, or transrectally. The transurethral approach (TEAP or TUEIP) has been used more frequently (5-14) than the transperineal (11,15,16) or transrectal approaches (11).

Specific devices have been developed for the transurethral delivery of ethanol (InecTx™ in the USA and Prostaject™ in Europe) (17). There is no consensus on the number of injection sites or injection volumes, which depend on total prostate volume, urethral length and/or presence of a prostate median lobe, and have ranged from 2 mL to 25 mL of ethanol per patient in different studies (with the injection volume being up to 42% of the volume of the prostate).

Local anaesthesia supplemented by conscious sedation may be considered, although regional or general anaesthesia were chosen by most patients. The procedure is usually completed within approximately 30 minutes. The majority of patients need an indwelling catheter after the procedure.

5.7.1.3 Efficacy
So far, 12 trials (5-16) have been published (Table 22), with the majority having investigated men refractory to medical treatment. Only one trial investigated patients with urinary retention (10). None of these trials was randomised against TURP or other minimally invasive procedures for BPH-LUTS or BPO. Mean follow-up varied among studies from 12 to 208 weeks (3-48 months).

The majority of trials demonstrated a significant reduction in symptoms (IPSS -41% to -71%) and PVR (-6% to -99%) as well as a significant improvement in the maximum urinary flow rate ($Q_{\text{max}} +35\%$ to $+155\%$) and QoL (IPSS-QoL -47% to -60%). Prostate volume decreased significantly in approximately half the trials (-4% to -45%). After an initial strong reduction in prostate volume, 1-2 years postoperatively prostate size increased again, although LUTS and peak urinary flow remained significantly improved (8). No predictive efficacy parameter or dose-response relationship has been found (8,12).

Several trials demonstrated a considerable number of retreatments within the first year after the procedure (usually treated by a second ethanol injection, TURP, or open prostatectomy). Little is known about the durability of clinical effects later than 1 year after the operation; one trial with a mean follow-up of 3 years showed a retreatment rate of 41% (8).
Table 22: Results of intra-prostatic ethanol injections for treating BPH-LUTS or BPO in men refractory to medical treatment or in urinary retention

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Patients (n)</th>
<th>Change in symptoms (IPSS)</th>
<th>Change in Qmax (ml/s)</th>
<th>Change in PVR (ml)</th>
<th>Change in prostate volume</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goya et al. 1999 (5)</td>
<td>12</td>
<td>10</td>
<td>-10.9a -47</td>
<td>+5.1a +64</td>
<td>-79.8a -62</td>
<td>-2.1 -4</td>
<td>3</td>
</tr>
<tr>
<td>Savoca et al. 2001 (15)</td>
<td>24</td>
<td>8</td>
<td>-11a -52</td>
<td>+5a +46</td>
<td>-103a -79</td>
<td>n/a n/a</td>
<td>3</td>
</tr>
<tr>
<td>Ditrolio et al. 2002 (6)</td>
<td>52</td>
<td>15</td>
<td>-1.65 -74</td>
<td>+6.2 +109</td>
<td>n/a n/a</td>
<td>-21.6 -45</td>
<td>3</td>
</tr>
<tr>
<td>Plante et al. 2002 (7)</td>
<td>52</td>
<td>5</td>
<td>-9.6a -41</td>
<td>+3.2 +32</td>
<td>-7.6 -6.4</td>
<td>-15.8a -30</td>
<td>2b</td>
</tr>
<tr>
<td>Chiang et al. 2003 (16)</td>
<td>12</td>
<td>11</td>
<td>-9.2a -52</td>
<td>+8.2a +155</td>
<td>-203.2a -88</td>
<td>-2.2 -5</td>
<td>3</td>
</tr>
<tr>
<td>Goya et al. 2004 (8)</td>
<td>156</td>
<td>34</td>
<td>-8.7a -40</td>
<td>+4.4a +65</td>
<td>-65a -70</td>
<td>+2.1 +4</td>
<td>3</td>
</tr>
<tr>
<td>Grise et al. 2004 (9)</td>
<td>52</td>
<td>115 (94)</td>
<td>-10.3a -50</td>
<td>+3.5a +35</td>
<td>n/a n/a</td>
<td>-7.4a -16</td>
<td>2b</td>
</tr>
<tr>
<td>Mutaguchi et al. 2006 (10)†</td>
<td>64</td>
<td>16</td>
<td>Spontaneous voiding in 87.5%</td>
<td>Mean PVR 60 mL</td>
<td>-19.7a -34</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Larson et al. 2006 (11)</td>
<td>52</td>
<td>65</td>
<td>-9.4a -44</td>
<td>+2.8a +33</td>
<td>n/a n/a</td>
<td>n/a n/a</td>
<td>3</td>
</tr>
<tr>
<td>Plante et al. 2007 (12)*</td>
<td>24</td>
<td>79</td>
<td>-10.6a -47</td>
<td>+3.2 to +8.1a</td>
<td>-1.2 to -27.3a</td>
<td>-1 to -11.2 to -25</td>
<td>2b</td>
</tr>
<tr>
<td>Magno et al. 2008 (13)</td>
<td>52</td>
<td>36</td>
<td>-13.3a -55</td>
<td>+9.2a +154</td>
<td>-286.4a -99</td>
<td>-12.7 -19</td>
<td>3</td>
</tr>
<tr>
<td>Sakr et al. 2009 (14)</td>
<td>208</td>
<td>35</td>
<td>-12.1a -55</td>
<td>+11a +186</td>
<td>-32.6a -47</td>
<td>-2.8a -5</td>
<td>3</td>
</tr>
</tbody>
</table>

Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Qmax), post-void residual (PVR), and prostate volume. a = significant compared with baseline (indexed whenever evaluated); † = patients with urinary retention; * = three study arms comparing transurethral, transrectal and transperineal injections.

5.7.1.4 Tolerability and safety

Frequently reported adverse events included:
- perineal or abdominal discomfort/pain;
- bladder storage symptoms (< 40%);
- haematuria (< 40%);
- UTI or epididymitis;
- urinary retention.

Less frequently reported (< 5%) adverse events included:
- decreased libido;
- retrograde ejaculation;
- urge urinary incontinence;
- urethral stenosis;
- ED.

Animal studies revealed a high percentage of urethral sphincter damage and stress urinary incontinence when ethanol was injected via the perineal route (1), but these complications have not been reported in humans (15,16). One man developed a big bladder stone six months after treatment, most probably due to calcification of sloshed necrotic prostatic masses (18). Two cases of severe complications after ethanol injections have been reported; bladder necrosis required cystectomy and urinary diversion (9).
5.7.1.5 **Practical considerations**

Intra-prostatic ethanol injections are considered to be a minimally invasive treatment option for patients with LUTS secondary to BPO. However, the mechanism of action, patient selection and application of ethanol (the number of injection sites and the injection volume) have not been well investigated, severe adverse events occurred in some patients, and long-term results are sparse. Intra-prostatic ethanol injections are therefore still regarded as experimental and should be used only in trials.

Randomised-controlled trials with long-term follow-up comparing ethanol injections with TURP, other minimally invasive procedures, or drugs are needed to be able to judge adequately the value of this treatment modality.

5.7.1.6 **Recommendations**

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-prostatic ethanol injections for LUTS due to BPO are still experimental.</td>
<td>3</td>
</tr>
<tr>
<td>Intra-prostatic ethanol injections should be performed only in clinical trials.</td>
<td>C</td>
</tr>
</tbody>
</table>

*LUTS = lower urinary tract symptoms; BPO = benign prostatic obstruction.*

5.7.1.7 **References**


5.7.2 Intra-prostatic botulinum toxin injections

5.7.2.1 Mechanism of action
BTX is the exotoxin of the bacterium Clostridium botulinum. This 150 kDa toxin is the most potent neurotoxin known in humans, and causes botulism (food-borne, wound or infant). Seven subtypes of BTX are known (types A-G), of which subtypes A and B have been manufactured for use in humans.

Experience with intra-prostatic injections for the treatment of LUTS/BPO exists only for BTX-A. The precise mechanism of action has been evaluated in experimental animals but is not fully understood. BTX-A blocks the release of neurotransmitters (e.g. acetylcholine or norepinephrine) from pre-synaptic nerves (1). BTX-A directly or indirectly reduces LUTS by induction of apoptoses of prostatic (epithelial) cells leading to tissue atrophy and prostate size reduction (2-4), inhibition of sensory neurons in the prostate and reduction of afferent signals to the central nervous system (3), and/or relaxation of smooth muscle cells in the prostatic parenchyma and reduction of BPO (4-6). Down-regulation of 1A adrenergic receptors in the prostate may contribute to smooth muscle cell relaxation (3). The latter two mechanisms are summarised as chemical denervation that possibly has a negative influence on prostate growth.

5.7.2.2 Operative procedure
Under ultrasound visualisation, BTX-A can be injected into the prostatic parenchyma transperineally, transurethrally or transrectally, using a 21-23 gauge needle. The transperineal approach has been described most frequently (7-13); the transurethral (5) and transrectal routes (14,15) have also been used but applied less often. Botox™ (Allergan, Irving, CA, USA) was employed in all but one study (13).

Different therapeutic doses (100-300 units Botox™ or 300-600 units Dysport™) and dilutions (25-50 units Botox™/mL or 75 units Dysport™/mL) were used in various studies, but doses and dilutions have not been systematically tested. Doses of 100 units Botox™ have been suggested for prostate sizes < 30 mL, 200 units for sizes between 30 mL and 60 mL, and 300 units for sizes > 60 mL (9). For Dysport™, 300 units were used for prostate sizes < 30 mL, and 600 units for sizes > 30 mL were used (13). The majority of patients were treated without anaesthesia, local anaesthesia, or sedation.

5.7.2.3 Efficacy
So far, 11 trials have been published (Table 23 investigating intra-prostatic BTX-A injections in patients with BPH/LUTS who required or were resistant to medical therapy, or patients with an indwelling urethral catheter due to acute or chronic urinary retention (5,14,15). Only two trials were randomised, one against injection of saline solution (7), the other against α1-blocker therapy (12).

The majority of patients in the published trials received only a single injection of BTX-A and mean follow-up ranged between 12 and 120 weeks (3 to 30 months). All trials reported significant improvements with regard to symptoms (IPSS -39% to -79%) and urinary flow rate ($Q_{\text{max}} +27\%$ to $+122\%$), or a decrease of prostate volume (-11% to -61%). Post-void residual urine decreased in all studies, but reduction was significant in only approximately half of the trials. BTX-A injection therapy was significantly superior to saline injection in the randomised-controlled trial with regard to symptom and $Q_{\text{max}}$ improvement as well as PVR and prostate volume reduction; all parameters were significantly different compared with baseline or saline solution within the first treatment month (7).
In patients with urinary retention before BTX-A injections, 80-100% of men could void spontaneously within one month of the operation, and maintained voiding throughout the follow-up period. Little is known about the long-term effects and durability of the treatment; prostate volume seems to increase again after 6-12 months (11,14) despite stable improvements in symptoms, $Q_{\text{max}}$ and PVR. Retreatment rates with BTX-A were as high as 29% (11).

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Patients (n)</th>
<th>Change in symptoms (IPSS)</th>
<th>Change in $Q_{\text{max}}$</th>
<th>Change in PVR</th>
<th>Change in prostate volume</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria et al. 2003 (7)*</td>
<td>52</td>
<td>30</td>
<td>-14.4a,b</td>
<td>+6.9a,b</td>
<td>-102a,b</td>
<td>-32a,b</td>
<td>1b</td>
</tr>
<tr>
<td>Chuang et al. 2005 (8)*</td>
<td>40</td>
<td>16</td>
<td>-9.8a</td>
<td>+5.3a</td>
<td>-41</td>
<td>-3a</td>
<td>3</td>
</tr>
<tr>
<td>Kuo 2005 (5)†</td>
<td>24</td>
<td>10</td>
<td>Spontaneous voiding in 100% of patients</td>
<td>+4.0a</td>
<td>-206a</td>
<td>-17a</td>
<td>24</td>
</tr>
<tr>
<td>Chuang et al. 2006 (9)*</td>
<td>52</td>
<td>41</td>
<td>-11a</td>
<td>+4.1a</td>
<td>-68</td>
<td>-7a</td>
<td>3</td>
</tr>
<tr>
<td>Park et al. 2006 (10)*</td>
<td>24</td>
<td>23</td>
<td>-9.3a</td>
<td>+2.0a</td>
<td>-49a</td>
<td>-7a</td>
<td>3</td>
</tr>
<tr>
<td>Chuang et al. 2006 (4)</td>
<td>12</td>
<td>8</td>
<td>-15a</td>
<td>+6.5a</td>
<td>-155.5</td>
<td>-12.1a</td>
<td>3</td>
</tr>
<tr>
<td>Silva et al. 2008 (14)**</td>
<td>12 (24)</td>
<td>21 (10)</td>
<td>Spontaneous voiding in 80% of patients</td>
<td>+11.4</td>
<td>Mean PVR 66 mL</td>
<td>-20a</td>
<td>-29</td>
</tr>
<tr>
<td>Brisinda et al. 2009 (11)#</td>
<td>120</td>
<td>77</td>
<td>-13a</td>
<td>+5.9a</td>
<td>-65a</td>
<td>-27.2a</td>
<td>3</td>
</tr>
<tr>
<td>Kuo and Liu 2009 (12)*</td>
<td>52</td>
<td>30</td>
<td>-7.1a</td>
<td>+2.3a</td>
<td>+21</td>
<td>-13a</td>
<td>1b</td>
</tr>
<tr>
<td>Silva et al. 2009 (15)†</td>
<td>72</td>
<td>11</td>
<td>Spontaneous voiding in 100% of patients</td>
<td>+10.5</td>
<td>Mean PVR 58 mL</td>
<td>-9.2a</td>
<td>-11</td>
</tr>
<tr>
<td>Nikoobakht et al. 2010 (13)‡</td>
<td>52</td>
<td>72</td>
<td>-11.3a</td>
<td>+7.7a</td>
<td>-34a</td>
<td>n/a</td>
<td>3</td>
</tr>
</tbody>
</table>

Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate ($Q_{\text{max}}$), post-void residual (PVR), and prostate volume. a = significant compared with baseline (indexed whenever evaluated); b = significant compared with placebo (saline solution) or $\alpha$1-blockers; † = patients with acute or chronic urinary retention; * = Botox™; ‡ = Dysport™

5.7.2.4 Tolerability and safety
BTX-A injections were well tolerated in all studies, and no systemic adverse events have yet been reported to have arisen from BTX-A. There was no need for postoperative analgesia. Adverse events were dysuria in ≤ 19%, haematuria in ≤ 14%, and acute prostatitis in one patient (2%). Urinary retention occurred in ≤ 6%, but many patients received a transurethral catheter or performed clean intermittent catheterisation during the early postoperative period (one week to one month) (8,14).

5.7.2.5 Practical considerations
BTX-A injections into the prostatic parenchyma seem to be a promising and quick minimally invasive treatment modality with low morbidity for patients who are refractory to medical treatment or in urinary retention. However, despite the excellent and homogeneous outcomes in published trials, BTX-A has been injected into only a few patients, and all trials have a limited follow-up. Only two randomised-controlled trials have been published so far. Trials with a larger number of patients, randomisation against saline injections, drugs, TURP, or other minimally invasive treatments, and long-term follow-up are therefore necessary to judge adequately the value of intra-prostatic BTX-A injections in the context of other available medical or surgical treatments of LUTS/BPO.
5.7.2.6 Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-prostatic botulinum toxin injections for lower urinary tract symptoms due to benign prostatic obstruction or urinary retention are still experimental.</td>
<td>3</td>
</tr>
<tr>
<td>Intra-prostatic botulinum toxin injections should be performed only in clinical trials.</td>
<td>C</td>
</tr>
</tbody>
</table>

5.7.2.7 References


5.8 Summary treatment

The choice of treatment depends on:
- findings assessed during evaluation;
- treatment preferences of the individual patient;
- ability of the treatment modality to change assessed findings;
- expectations to be met in terms of speed of onset, efficacy, side-effects, quality of life, and disease progression.

Table 24 provides differential information about conservative, medical and surgical treatment options described in the EAU Guidelines on Male LUTS, including BPO. Note that treatment modalities may be combined leading to different effects.

Table 24: Speed of onset and influence on basic parameters with conservative or surgical treatment modalities for the management of non-neurogenic male LUTS. Note that the drug treatment studies have typically used data after a run-in phase as baseline, whereas those of interventional treatments did not.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Onset</th>
<th>LUTS</th>
<th>Uroflowmetry ($Q_{max}$)</th>
<th>Prostate size</th>
<th>PVR</th>
<th>Disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watchful waiting, behavioural treatment</td>
<td>months</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>α-adrenoceptor antagonists</td>
<td>days</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>/ +</td>
</tr>
<tr>
<td>5α-reductase inhibitors</td>
<td>months</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Muscarinic receptor antagonists</td>
<td>weeks</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(increase)</td>
</tr>
<tr>
<td>Plant extracts</td>
<td>weeks</td>
<td>+</td>
<td>-</td>
<td>/ +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>α-adrenoceptor antagonists + 5α-reductase inhibitors</td>
<td>days</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>/ +</td>
</tr>
<tr>
<td>α-adrenoceptor antagonists + muscarinic receptor antagonists</td>
<td>days</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>/ +</td>
</tr>
<tr>
<td>PDE5Is</td>
<td>weeks</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Surgical treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURP–TUIP</td>
<td>hours</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Open prostatectomy</td>
<td>hours</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>TUMT</td>
<td>weeks</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>TUNA</td>
<td>weeks</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HoLEP</td>
<td>hours</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>KTP</td>
<td>days</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Prostate stents</td>
<td>hours</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Ethanol injections prostate</td>
<td>weeks</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Botulinum toxin injections prostate</td>
<td>weeks</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

LUTS = Lower Urinary Tract Symptoms; $Q_{max}$ = maximum urinary flow rate; PVR = post-void residual urine
Key to Table:
- no influence
+ mild influence
++ moderate influence
+++ strong influence
++++ very strong influence
? unknown

Behavioural with or without medical treatments are usually the first choice of therapy. A flowchart illustrating conservative and medical treatment choices according to evidence-based medicine and patients’ profiles is provided in Figure 3.

Figure 3: Treatment algorithm of male lower urinary tract symptoms (LUTS) using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation (◊). Minus (−) indicate the absence and plus (+) the presence of the condition.

Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery). Additionally, surgery is usually needed when patients have had insufficient relief in LUTS or PVR after conservative or medical treatments (relative operation indications). The choice of the surgical technique depends primarily on prostate size, co-morbidities of the patient, and the ability to have anaesthesia but also on patients’ preferences, willingness to accept surgery-associated side effects, availability of the surgical armamentarium, and experience of the surgeon with these operation techniques. A flowchart illustrating surgical treatment choices according to evidence-based medicine and patients’ profiles is provided in Figure 4.
6. FOLLOW-UP

6.1 Watchful waiting – behavioural
Patients who elect to pursue a WW policy should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits:

- I-PSS
- Uroflowmetry and PVR urine volume.

6.2 Medical treatment
Patients receiving α-blockers, muscarinic receptor antagonists, or the combination of α-blockers with 5α-reductase inhibitors or muscarinic receptor antagonists should be reviewed 4 to 6 weeks after drug initiation in order to determine treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued.

Patients should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following tests are recommended at follow-up visits:
Patients receiving 5α-reductase inhibitors should be reviewed after 12 weeks and 6 months to determine their response and adverse events. Follow-up visits are similar to the above mentioned drugs. The following are recommended at follow-up visits:

- I-PSS;
- Uroflowmetry and PVR urine volume.

Patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month and, if serum sodium concentration has remained normal, every 3 months subsequently. The following tests are recommended at follow-up visits:

- Serum-sodium concentration;
- Frequency-volume chart.

After dose adjustment, follow-up should be repeated likewise.

6.3 Surgical treatment

Patients after prostate surgery should be reviewed 4 to 6 weeks after catheter removal in order to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events no further re-assessment is necessary. The following tests are recommended at follow-up visit after 4 to 6 weeks:

- I-PSS;
- Uroflowmetry and PVR urine volume.

6.4 Recommendations

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Follow-up for all conservative or operative treatment modalities is based on empirical data or theoretical considerations but not on evidence based studies.
7. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AVP     arginine vasopressin
BOO     bladder outlet obstruction
BOO(I)  bladder outlet obstruction (index)
BPE     benign prostatic enlargement
BPH     benign prostatic hyperplasia
BPO     benign prostatic obstruction
cGMP    cyclic guanosine monophosphate
CombAT  combination of avodart® and tamsulosin
DHT     dihydrotestosterone
EBM     evidence-based medicine
ED      erectile dysfunction
eNOS    endothelial
ER      extended release
GITS    gastrointestinal therapeutic system
IFIS    intra-operative floppy iris syndrome
IPSS    international prostate symptom score
IR      immediate release
LUTS    lower urinary tract symptoms
MR      modified release
MTOPS   medical therapy of prostatic symptoms
NAION   non-arteritic anterior ischemic optic neuropathy
NO      Nitric oxide
NOS     NO synthases
nNOS    neuronal
n.s.    not significant
OCAS    oral controlled absorption system
PDE     phosphodiesterase
PSA     prostate specific antigen
PVR     post-void residual
Qmax    maximum urinary flow rate during free uroflowmetry
QoL     quality of life
RR      relative risk
SHBG    sexual hormone binding globulin
SR      sustained release
tmax    time to maximum plasma concentration
t½      elimination half-life
TUIP    transurethral incision of the prostate
TUMT    transurethral microwave therapy
TUNATM  transurethral needle ablation
TURP    transurethral resection of the prostate
UTI     urinary tract infection
WW      watchful waiting

Conflict of interest
All members of the Male LUTS Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Male Sexual Dysfunction:
Erectile dysfunction and premature ejaculation

E. Wespes (chair), I. Eardley, F. Giuliano, D. Hatzichristou, K. Hatzimouratidis (vice-chair), I. Moncada, A. Salonia, Y. Vardi

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6. ABBREVIATIONS USED IN THE TEXT
1. BACKGROUND

1.1 Introduction
Erectile dysfunction (ED) and premature ejaculation (PE) are the two main complaints in male sexual medicine (1,2). New oral therapies have completely changed the diagnostic and therapeutic approach to ED and the Guidelines Office of the European Association of Urology (EAU) has appointed an Expert Panel to update previously published EAU guidelines for ED or impotence (3,4).

1.2 Methodology
The update is based on a systemic literature search performed by the panel members. The MedLine database was searched using the major Medical Subject Headings (MeSH) terms “erectile dysfunction”, “sexual dysfunction” “ejaculation”. MedLine search was supplemented by the term “premature ejaculation” in all search fields. All articles published between January 2009 (previous update) and January 2013 were considered for review. The Expert Panel has also identified critical problems and knowledge gaps, setting priorities for future clinical research.

1.3 Level of evidence and grade of recommendation
References in the text have been assessed according to their level of scientific evidence (LE), and guideline recommendations have been graded follow the listings in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (5). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from (5).

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results. Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (4-6).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.

Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
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<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from (5).
1.4  **Publication History**

The first European Association of Urology (EAU) Guidelines on Erectile Dysfunction were published in 2000 (6) with subsequent updates in 2001, 2002, 2004, 2005 and 2009. In particular the 2009 document presented a significant update of the previous publication with the inclusion of the topic “Premature Ejaculation” and the text was renamed to “EAU Guidelines on Male Sexual Dysfunction” (7). In 2011 the expert panel decided to develop separate guidelines addressing Penile Curvature, which resulted in a publication in 2012 (8).

Several scientific summaries have been published in the EAU scientific journal, European Urology (9-12). Quick reference documents (pocket guidelines) are available presenting the main findings of both the Male Sexual Dysfunction Guidelines and the Penile Curvature Guidelines. These documents follow the updating cycle of the underlying large texts. All material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of translations and republications produced by national urological associations: [http://www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/online-guidelines/).

The chapters on Erectile Dysfunction were peer-reviewed prior to publication.

1.5  **Potential conflict of interest statement**

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: [http://www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/online-guidelines/).

1.6  **References**


2. ERECTILE DYSFUNCTION

2.1 Epidemiology and risk factors

Erection is a neuro-vasculo-tissular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism (1,2).

Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners (3). There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease; thus, ED should not be regarded only as a QoL issue but also as a potential warning sign of cardiovascular disease (4-8).

2.1.1 Epidemiology

Epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large, community-based study of ED was the Massachusetts Male Aging Study (MMAS) (3). The study reported an overall prevalence of 52% ED in non-institutionalised 40-70-year-old men in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% (9). In the National Health and Social Life Survey (NHSLS), the prevalence of sexual dysfunction in males (not specific ED) was 31% (10). The incidence rate of ED (new cases per 1,000 men annually) was 26 in the MMAS study (11), 65.6 (mean follow-up of 2 years) in a Brazilian study (12), and 19.2 (mean follow-up of 4.2 years) in a Dutch study (13). In Taiwan, the prevalence of ED was 27% among all patients investigated and 29% among those aged ≥ 40 years (14). In Ghana, the overall prevalence of ED is 59.6% and there are positive correlations between ED, dissatisfaction, age and other sexual dysfunctions (15). Differences between these studies can be explained by differences in methodology and in the ages, socioeconomic and cultural status of the populations studied.

Data from epidemiological studies have demonstrated consistent and compelling evidence for an association between lower urinary tract symptoms (LUTS)/benign prostatic hypertrophy (BPH) and sexual dysfunction in aging men that is independent of the effects of age, other comorbidities, and various lifestyle factors (16). The Massachusetts Male Aging (MSAM-7) study systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. It was performed in the US and six European countries (France, Germany, Italy, Netherlands, Spain, and UK). Eighty-three percent of men considered themselves sexually active, and 71% reported at least one episode of sexual activity in the past 4 weeks. The overall prevalence of LUTS was 90%. Only 19% of men had sought medical help for LUTS and only 11% were medically treated. The overall prevalence of ED was 49%, and 10% of patients reported complete absence of erection. The overall prevalence of ejaculation disorders was 46% and 5% reported anejaculation (17).

2.1.2 Risk factors

Erectile dysfunction shares common risk factors with cardiovascular disease (e.g., lack of exercise, obesity, smoking, hypercholesterolaemia, and metabolic syndrome); some of which can be modified. Moreover, men with mild ED have similar risk factors to those of a general ED clinical trial population. Thus, mild ED is an important indicator of risk for associated underlying disease. Men complaining of mild ED should be evaluated adequately (for underlying cardiovascular risk) (18).

In the MMAS, men who began exercising in midlife had a 70% reduced risk for ED compared to sedentary men and a significantly lower incidence over an 8-year follow-up period of regular exercise (19). A multicentre, randomised, open-label study in obese men with moderate ED compared 2 years of intensive exercise and weight loss with a control group given general information about healthy food choices and exercise (20). Significant improvements in body mass index (BMI) and physical activity scores, as well as erectile function, were observed in the lifestyle intervention group. These changes were highly correlated with both weight loss and activity levels.

Some studies have shown some evidence that lifestyle modification and pharmacotherapy for cardiovascular risk factors are effective in improving sexual function in men with ED. However, it should be emphasized that more controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED (6).

2.1.3 Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localised prostate cancer and a life expectancy of at least 10 years. This procedure may lead to treatment-specific sequelae affecting health-related QoL. This outcome has become increasingly
important with the more frequent diagnosis of prostate cancer in younger patients (21-22). Research has shown that 25-75% of men experience postoperative ED (23). A systematic review has shown that incidence of potency recovery after robotic prostatectomy is influenced by numerous factors. It reported, for the first time, a significant advantage in favor of robotic laparoscopic radical prostatectomy in comparison with retropubic radical prostatectomy in terms of 12-month potency rates (24). However, there was no significant difference between laparoscopic RP and robot-assisted laparoscopic RP. Today, we do not have enough evidence-based data to consider that robot-assisted laparoscopic RP has any advantageous effect on functional outcome. Experience of the surgeon seems to be the main factor besides preservation of neurovascular bundles and patient age.

Post-RP ED is multifactorial. Cavernosal nerve injury induces proapoptotic (loss of smooth muscle) and profibrotic (increase in collagen) factors within the corpora cavernosa. These changes may also be caused by poor oxygenation due to changes in the blood supply to the cavernosa because of possible arterial damage during the surgical procedure.

Preoperative potency is a major factor associated with the recovery of erectile function after surgery, therefore, patients being considered for nerve-sparing radical prostatectomy (NSRP) should ideally be potent preoperatively (24-29). It is also clear that cavernosal nerves must be preserved to ensure erectile function recovers after RP. In addition, the role of vascular insufficiency is of increasing interest in postoperative ED (30,31).

ED is also a common sequela after external beam radiotherapy and brachytherapy for prostate cancer. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue (32,33). Alternative treatments for prostate cancer including cryotherapy and high-intensity focused ultrasound are associated with equivalent or worsened rates of ED compared to surgery or radiation therapy (34,35).

2.1.4 Managing ED: implications for everyday clinical practice

Advances in basic and clinical research in ED during the past 15 years have led to the development of a variety of new treatment options, including pharmacological agents for intracavernous, intraurethral, and oral use (36-38). Reconstructive vascular surgery is reserved for select cases of arterial insufficiency, with no current indications for venous ligation procedures, given the poor overall outcomes (39,40).

An increasing number of men are currently seeking help for ED due to the growing public awareness of the condition and the availability of effective, safe and user-friendly oral drug therapy. However, not all physicians evaluating and treating ED have appropriate background knowledge and clinical experience in sexual medicine. Thus, men with ED may receive little or no evaluation before treatment and will therefore not receive treatment for any underlying disease that may be causing their ED. Other men without ED may be requesting treatment simply to enhance their sexual performance.

2.1.5 Conclusions on the epidemiology of ED

<table>
<thead>
<tr>
<th>LE</th>
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<tr>
<td>2b</td>
<td>Erection is a neuro-vasculo-tissular phenomenon under hormonal control.</td>
</tr>
<tr>
<td>2b</td>
<td>ED is common worldwide.</td>
</tr>
<tr>
<td>2b</td>
<td>ED shares risk factors with cardiovascular disease.</td>
</tr>
<tr>
<td>1b</td>
<td>Lifestyle modification (intensive exercise and decrease in BMI) can improve erectile function.</td>
</tr>
<tr>
<td>4</td>
<td>ED is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.</td>
</tr>
<tr>
<td>2b</td>
<td>ED is common after radical prostatectomy, irrespective of the surgical technique used.</td>
</tr>
<tr>
<td>2b</td>
<td>ED is common after external radiotherapy and brachytherapy.</td>
</tr>
</tbody>
</table>

2.1.6 References


2.2 Diagnostic evaluation

2.2.1 Basic work-up

The first step in evaluating ED is always a detailed medical and sexological history of patients and partners when available (1,2). Often it is not possible to include the partner on the patient’s first visit, but an effort should be made to include the partner at the second visit. The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 3) (3). Taking a comprehensive medical history may reveal one of the many common disorders associated with ED.

It is important to establish a relaxed atmosphere during history-taking. This will make it easier to ask questions about erectile function and other aspects of sexual history. A relaxed atmosphere will also make it easier to explain the diagnosis and therapeutic approach to the patient and his partner.

Table 3: Pathophysiology of ED

<table>
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<tr>
<th>Vasculogenic</th>
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<td>Cardiovascular disease</td>
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<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Major surgery (RP) or radiotherapy (pelvis or retroperitoneum)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Central causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative disorders (multiple sclerosis, Parkinson’s disease, multiple atrophy etc.)</td>
<td></td>
</tr>
<tr>
<td>Spinal cord trauma or diseases</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Central nervous system tumours</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Peripheral causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 and 2 diabetes mellitus</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Surgery (pelvis or retroperitoneum, radical prostatectomy, colorectal surgery, etc.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomical or structural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypospadias, epispadias</td>
</tr>
<tr>
<td>Micropenis</td>
</tr>
<tr>
<td>Congenital curvature of the penis</td>
</tr>
<tr>
<td>La Peyronie’s disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormonal</th>
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</thead>
<tbody>
<tr>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Hyper- and hypothyroidism</td>
</tr>
<tr>
<td>Hyper- and hypocortisolism (Cushing’s disease etc)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives (diuretics are the most common medication causing ED)</td>
</tr>
<tr>
<td>Antidepressants (selective serotonin reuptake inhibitors, tricyclics)</td>
</tr>
<tr>
<td>Antipsychotics (incl. neuroleptics)</td>
</tr>
<tr>
<td>Antiandrogens; GnRH analogues and antagonists</td>
</tr>
<tr>
<td>Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised type (e.g., lack of arousability and disorders of sexual intimacy)</td>
</tr>
<tr>
<td>Situational type (e.g., partner-related, performance-related issues or due to distress)</td>
</tr>
</tbody>
</table>
2.2.1.1 Sexual history

The sexual history must include (when available) information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually stimulated and morning erections and of problems with arousal, ejaculation, and orgasm. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) (4), help to assess the different sexual function domains (i.e., sexual desire, erectile function, orgasmic function, ejaculation, intercourse, and overall satisfaction), as well as the impact of a specific treatment modality. Psychometric analysis also supports the use of erectile hardness score as a simple, reliable and valid tool for the assessment of penile rigidity in practice and in clinical trials research (5).

In cases of clinical depression, the use of a 2-question scale for depression is recommended: “During the past month have you often been bothered by feeling down, depressed or hopeless? During the past month have you often been bothered by little interest or pleasure, doing things?” (6). Patients should be screened for symptoms of possible of possible hypogonadism, including decreased energy, libido, fatigue, and cognitive impairment, as well as for symptomatic lower urinary tract symptoms. Where indicated, screening questionnaires, such as the International Prostate Symptom Score may be utilised.

2.2.1.2 Physical examination

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems (1). A physical examination may reveal unsuspected diagnoses, such as La Peyronie’s disease, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics etc.) (2). A rectal examination should be performed in every patient older than 40 years. Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months. Particular attention must be given to patients with cardiovascular disease (Section 2.2.2).

2.2.1.3 Laboratory testing

Laboratory testing must be tailored to the patient’s complaints and risk factors. Patients may need a fasting glucose or HbA1c and lipid profile if not recently assessed. Hormonal tests include a morning sample of total testosterone. If indicated bioavailable or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone to maintain ED is low and ED is usually a symptom of more severe cases of hypogonadism (7). For levels > 8 nmol/l the relationship between circulating testosterone and sexual function is very low (7,8).

Additional laboratory tests may be considered in selected patients, for example, prostate-specific antigen (PSA) for detection, or suspicion, of prostate cancer (9). Additional hormonal tests, for example, prolactin, and luteinizing hormone, are performed when low testosterone levels are detected. If any abnormality is observed, referral to an endocrinologist may be indicated (10,11).

Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, these opportunities to identify critical comorbid conditions should not be missed (12).

Figure 1 gives the minimal diagnostic evaluation (basic work-up) in patients with ED.
2.2.2 **Cardiovascular system and sexual activity: the patient at risk**

Patients who seek treatment for sexual dysfunction have a high prevalence of cardiovascular disease. The cardiac risks associated with sexual activity are well established. Epidemiological surveys have emphasised the association between cardiovascular and metabolic risk factors and sexual dysfunction in men and women (13). ED can improve the sensitivity of screening for asymptomatic cardiovascular disease in men with diabetes (14,15). ED significantly increases the risk of cardiovascular disease, coronary heart disease, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors (16).

There has been an extensive investigation of the pharmacological properties of phosphodiesterase 5 inhibitors (PDE5Is), including their effects on cardiac smooth muscle activity and overall cardiovascular safety. The EAU Guidelines recommendations given here for treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk (17-19). The Princeton Consensus (Expert Panel) Conference is dedicated to optimizing sexual function and preserving cardiovascular health. A total of three consensus papers have been published (17-19). The Third Princeton Consensus had two primary objectives. The first focused on evaluation and management of cardiovascular risk in men with ED and no known cardiovascular disease, with particular emphasis on identification of men with ED who may require additional cardiological work-up. The second objective focused on re-evaluation and modification of previous recommendations for evaluation of cardiac risk associated with sexual activity in men with known cardiovascular disease. The recommendations built on those developed during the first and second Princeton Consensus Conferences; first, emphasising the use of exercise ability and stress testing to ensure that each man’s cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED; and second, highlighting the link between ED and...
cardiovascular disease, which may be asymptomatic and benefit from cardiovascular risk reduction (19). Patients with ED can be stratified into three cardiovascular risk categories (Table 4), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient’s history.

Table 4: Cardiac risk stratification (based on 2nd Princeton Consensus) (18)

<table>
<thead>
<tr>
<th>Low-risk category</th>
<th>Intermediate-risk category</th>
<th>High-risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, &lt; 3 risk factors for CAD (excluding sex)</td>
<td>≥ 3 risk factors for CAD (excluding sex)</td>
<td>High-risk arrhythmias</td>
</tr>
<tr>
<td>Mild, stable angina (evaluated and/or being treated)</td>
<td>Moderate, stable angina</td>
<td>Unstable or refractory angina</td>
</tr>
<tr>
<td>Uncomplicated previous MI</td>
<td>Recent MI (≥ 3, &lt; 6 weeks)</td>
<td>Recent MI (&lt; 2 weeks)</td>
</tr>
<tr>
<td>LVD/CHF (NYHA class I)</td>
<td>LVD/CHF (NYHA class II)</td>
<td>LVD/CHF (NYHA class III/IV)</td>
</tr>
<tr>
<td>Post-successful coronary revascularisation</td>
<td>Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)</td>
<td>Hypertrophic obstructive and other cardiomyopathies</td>
</tr>
<tr>
<td>Controlled hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild valvular disease</td>
<td></td>
<td>Moderate-to-severe valvular disease</td>
</tr>
</tbody>
</table>

| CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 2: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) (19)

- Sexual inquiry of all men
- ED confirmed
- Exercise ability
- Low risk
- Intermediate risk
- High risk
- Stress test
- Pass
- Fail
- Advice, treat ED
- Cardiologist

*Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing two flights of stairs in 10 s.

**Sexual activity is equivalent to 4 min of the Bruce treadmill protocol.
2.2.2.1 Low-risk category
The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low risk is typically implied by the ability to perform exercise of modest intensity, which is defined as ≥ 6 “metabolic equivalents of energy expenditure in the resting state” (METs) without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

2.2.2.2 Intermediate- or indeterminate-risk category
The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

2.2.2.3 High-risk category
High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient’s cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

2.2.3 Specialised diagnostic tests
Most patients with ED can be managed within the sexual care setting, conversely, some patients may need specific diagnostic tests (Tables 5 and 6).

2.2.3.1 Nocturnal penile tumescence and rigidity test
The nocturnal penile tumescence and rigidity (NPTR) assessment should be done on at least two nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ≥ 10 min (20).

2.2.3.2 Intracavernous injection test
The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min (21). This response indicates a functional, but not necessarily normal, erection, and the erection may coexist with arterial insufficiency and/or veno-occlusive dysfunction (22). A positive test shows that a patient will respond to the intracavernous injection programme. The test is inconclusive as a diagnostic procedure and duplex Doppler study of the penis should be requested, if clinically warranted.

2.2.3.3 Duplex ultrasound of the penis
A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal (21). Further vascular investigation is unnecessary when a Duplex examination is normal.

2.2.3.4 Arteriography and dynamic infusion cavernosometry or cavernosography
Arteriography and dynamic infusion cavernosometry or cavernosography (DICC) should be performed only in patients who are being considered for vascular reconstructive surgery (23).

2.2.3.5 Psychiatric assessment
Patients with psychiatric disorders must be referred to a psychiatrist who is particularly interested in ED. In younger patients (< 40 years) with long-term primary ED, psychiatric assessment may be helpful before any organic assessment is carried out.

2.2.3.6 Penile abnormalities
Surgical correction may be needed for patients with ED due to penile abnormalities, e.g. hypospadias, congenital curvature, or Peyronie’s disease with preserved rigidity.

2.2.4 Patient education - consultation and referrals
Consultation with the patient should include a discussion of the expectations and needs of both the patient and his stable sexual partner, if available. It should also review both the patient’s and partner’s understanding
of ED, the results of diagnostic tests, and provide a rational selection of treatment options. Patient and partner education is an essential part of ED management (24,25).

Table 5: Indications for specific diagnostic tests

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ED (not caused by organic disease or psychogenic disorder).</td>
</tr>
<tr>
<td>Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery.</td>
</tr>
<tr>
<td>Patients with penile deformities that might require surgical correction, e.g., Peyronie’s disease, congenital curvature.</td>
</tr>
<tr>
<td>Patients with complex psychiatric or psychosexual disorders.</td>
</tr>
<tr>
<td>Patients with complex endocrine disorders.</td>
</tr>
<tr>
<td>Specific tests may be indicated at the request of the patient or his partner.</td>
</tr>
<tr>
<td>Medicolegal reasons, e.g., implantation of penile prosthesis, sexual abuse.</td>
</tr>
</tbody>
</table>

Table 6: Specific diagnostic tests

<table>
<thead>
<tr>
<th>Specific diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTTR using Rigiscan</td>
</tr>
<tr>
<td>Vascular studies</td>
</tr>
<tr>
<td>- Intracavernous vasoactive drug injection</td>
</tr>
<tr>
<td>- Duplex Doppler study of the penis</td>
</tr>
<tr>
<td>- Dynamic Infusion Cavernosometry and Cavernosography (DICC)</td>
</tr>
<tr>
<td>- Internal pudendal arteriography</td>
</tr>
<tr>
<td>Neurological studies, e.g., bulbocavernosus reflex latency, nerve conduction studies</td>
</tr>
<tr>
<td>Endocrinological studies</td>
</tr>
<tr>
<td>Specialised psychodiagnostic evaluation</td>
</tr>
</tbody>
</table>

2.2.5 Guidelines for the diagnostic evaluation of ED

| Clinical use of validated questionnaire related to ED may help to assess all sexual function domains and the effect of a specific treatment modality. |
|-------------------------------------------------------------------------------------------------------------------------------------|----|---|
| Physical examination is needed in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED. | 3  | B |
| Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and lifestyle factors that can be modified. | 4  | B |
| Specific diagnostic tests are indicated by only a few conditions.                                                                      | 4  | B |

2.2.6 References


3. TREATMENT OF ERECTILE DYSFUNCTION

3.1 Treatment options
The primary goal in the management strategy of a patient with ED is to determine its etiology and treat it when possible, and not to treat the symptom alone. ED may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors. These factors may be modified either before, or at the same time as, specific therapies are used.

As a rule, ED can be treated successfully with current treatment options, but cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism and hyperprolactinaemia), which potentially can be cured with specific treatment.

Most men with ED will be treated with therapeutic options that are not cause specific. This results in a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as well as patient preference (1). To properly counsel patients with ED, physicians must be fully informed of all available treatment options. In this context, physician-patient (partner) dialogue is essential throughout the management of ED.

The assessment of treatment options must consider patient and partner satisfaction and other QoL factors as well as efficacy and safety. A treatment algorithm for ED is given in Figure 3.
3.2 Lifestyle management in ED with concomitant risk factors

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany any pharmacological treatment.

The potential benefits of lifestyle changes may be particularly important in individuals with ED and specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension (2–4). Besides
improving erectile function, aggressive lifestyle changes may also benefit overall cardiovascular and metabolic health, with recent studies supporting the potential of lifestyle intervention to benefit both ED and overall health (5,6).

Although further studies are needed to clarify the role of lifestyle changes in management of ED and related cardiovascular disease, lifestyle changes can be recommended alone or combined with PDE5 therapy. Some studies have suggested that the therapeutic effects of PDE5Is may be enhanced when other comorbidities or risk factors are aggressively managed (7). A significant improvement can be expected as soon as after 3 months of initiating lifestyle changes (8).

However, these results have yet to be confirmed in well-controlled, long-term studies. As a result of the success of pharmacological therapy for ED, clinicians need to provide specific evidence for the benefits of lifestyle change, and hopefully, future research will show this.

3.3 Erectile dysfunction after radical prostatectomy

Use of proerectile drugs following RP is important in achieving postoperative erectile function. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Early compared with delayed erectile rehabilitation brings forward the natural healing time of potency (9).

Historically, the treatment options for postoperative ED have included intracavernous injections (10), urethral microsuppository (11), vacuum device therapy (12), and penile implants (13). Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral compounds are not adequately effective or contraindicated for postoperative patients (Sections 3.6 and 3.7). The management of post-RP ED has been revolutionised by the advent of PDE5Is, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. Overall, it must be emphasized that post-RP ED patients are poor responders to PDE5Is. However, PDE5Is are the first-line choice of oral pharmacotherapy for post-RP ED in patients who have undergone nerve-sparing (NS) surgery. The choice of PDE5Is as first-line treatment is controversial because the experience (surgical volume) of the surgeon is a key factor in preserving postoperative erectile function, in addition to patient age and NS technique (14–16). In fact, PDE5Is are most effective in patients who have undergone a rigorous NS procedure, which is more commonly performed by large-volume surgeons (14,15).

Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa (17). Daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery (18,19). The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP (18-21).

Effectiveness of tadalafil and vardenafil as on-demand treatment has been evaluated in post-RP ED.

• A large multicentre trial in Europe and USA has studied tadalafil in patients with ED following bilateral NS surgery. Erectile function was improved in 71% of patients treated with 20 mg tadalafil versus 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil versus 26% with placebo (22).

• Similarly, vardenafil has been tested in patients with ED following either unilateral or bilateral NS surgery in a randomised, multicentre, prospective, placebo-controlled study in North America (23). Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same patients undergoing NSRP has underlined the benefit of vardenafil compared to placebo regarding intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience (24).

A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP. In patients whose IIEF erectile function domain (IIEF-EF) score was ≥ 26 before surgery, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED (25). A prospective, randomised, open label, multicentre American study in men with normal erection who underwent bilateral NSRP showed that oral and intraurethral treatment has the same benefit for penile recovery within the first year after surgery (26).

Patients who do not respond to oral PDE5Is after NSRP may be treated with prophylactic intracorporeal alprostadil (27,28). Penile prosthesis remains a satisfactory approach for patients who do not respond to either oral or intracavernous pharmacotherapy or to a vacuum device (29).
3.4 Causes of ED that can be potentially treated with a curative intent

3.4.1 Hormonal causes

The advice of an endocrinologist may be beneficial for managing patients with hormonal abnormalities. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes, including a functional pituitary tumour resulting in hyperprolactinaemia.

Testosterone replacement therapy (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded (30). Testosterone replacement is controversial in men with a history of prostate carcinoma (LE: 4) (31). There is limited evidence suggesting that such treatment may not pose an undue risk of prostate cancer recurrence or progression (32). Before initiating testosterone replacement, digital rectal examination, serum PSA test, hematocrit, liver function tests and lipid profile should be performed (33). Patients given androgen therapy should be monitored for clinical response, elevated hematocrit and development of hepatic or prostatic disease. Testosterone therapy is contraindicated in patients with untreated prostate cancer or unstable cardiac disease.

3.4.2 Post-traumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate (34). The lesion must be demonstrated by duplex Doppler study of the penis and confirmed by penile pharmacoarteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by DICC. Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results (35).

3.4.3 Psychosexual counselling and therapy

For patients with a significant psychological problem, psychosexual therapy may be given either alone or with another therapeutic approach. Psychosexual therapy requires ongoing follow-up and has had variable results (36).

3.5 First-line therapy

3.5.1 Oral pharmacotherapy

PDE5 hydrolysates cGMP in the cavernosum tissue. Inhibition of PDE5 results in smooth muscle relaxation with increased arterial blood flow, leading to compression of the subtunical venous plexus and penile erection (37).

Three potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED. They are not initiators of erection and require sexual stimulation to facilitate an erection.

3.5.1.1 Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration. Sildenafil is effective from 30-60 min after administration. Its efficacy is reduced after a heavy, fatty meal due to prolonged absorption. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient’s response and side effects. Efficacy may be maintained for up to 12 h (38). The pharmacokinetic data of sildenafil are presented in Table 7. Adverse events (Table 8) are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to that with placebo (39).

After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo (40). Sildenafil significantly improves patient scores in IIEF, sexual encounter profile (SEP)2, SEP3, and general assessment question (GAQ) and treatment satisfaction.

The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. In patients with diabetes, 66.6% reported improved erections (GAQ) and 63% successful intercourse attempts compared to 28.6% and 33% of men taking placebo, respectively (41).

3.5.1.2 Tadalafil

Tadalafil was licenced for treatment of ED in February 2003 and is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h (42) and is not affected by food. Ten and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient’s response and side effects. Pharmacokinetic data of tadalafil are presented in Table 7. Adverse events (Table 8) are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to that with placebo (43).

In premarketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group (43). Tadalafil significantly improves patient scores in IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. These results have been confirmed in
postmarketing studies (44).

Tadalafil also improves erections in difficult-to-treat subgroups. In patients with diabetes, 64% reported improved erections (i.e., improved GAQ) versus 25% of patients in the control group, and the change in the final score for IIEF-EF was 7.3 compared to 0.1 for placebo (45). Nevertheless diabetic patients remain poor responders to tadalafil on demand, with a successful intercourse rates increasing from 21.8% with placebo to 45.4 and 49.9% with 10 and 20 mg of tadalafil on demand respectively (46).

3.5.1.3 Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 min after administration. Its effect is reduced by a heavy, fatty meal (> 57% fat). Five, 10 and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient’s response and side effects. In vitro, it is 10-fold more potent than sildenafil, although this does not necessarily mean greater clinical efficacy (47). Pharmacokinetic data of vardenafil are presented in Table 7. Adverse events (Table 8) are generally mild in nature and self-limited by continuous use, with a drop-out rate similar to that with placebo (48).

After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo (49). Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in postmarketing studies (50).

Vardenafil improves erections in difficult-to-treat subgroups. In patients with diabetes, the final IIEF-EF score was 19 compared to 12.6 for placebo (51). Nevertheless, again, diabetic patients remain poor responders to vardenafil on demand with a successful intercourse rates increasing from 23% with placebo to 49% and 54% with 10 and 20 mg of vardenafil on demand, respectively (51).

Recently, a new formulation of vardenafil has been released, in the form of an orodispersible tablet (ODT). ODT formulations offer improved convenience over film-coated formulations and may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bioavailability compared to film-coated tablets (52). The efficacy of vardenafil ODT has been demonstrated in several randomised controlled trials and did not seem to differ from the regular formulation (53-56).

3.5.1.4 Choice or preference between the different PDEs inhibitors

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil, and vardenafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient’s personal experience.

Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it.

3.5.1.5 On-demand or chronic use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5Is improves or prevents significantly the intracavernous structure alterations due to age, diabetes, or surgical damage (57-62). No data exists for a human population.

In humans, a randomised study (n = 145) has shown that daily tadalafil led to a significantly higher IIEF-EF score and higher completion of successful intercourse attempts compared to on-demand tadalafil (63). Two major randomised double-blind studies, using 5 and 10 mg/day tadalafil for 12 weeks (n = 268) (64) and 2.5 and 5 mg/day tadalafil for 24 weeks (n = 268) (65), have shown that daily dosing was well tolerated and significantly improved erectile function. However, these studies lacked a comparative on-demand treatment arm. An open-label extension was carried out for both studies in 234 patients for 1 year and 238 patients for 2 years. Tadalafil, 5 mg once daily, was shown to be well tolerated and effective (66). Tadalafil, 5 mg once daily, therefore provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. Nevertheless, in the 1-year open-label 5 mg tadalafil extension study followed by 4 weeks wash-out, erectile function was not maintained after discontinuation of therapy in most patients (about 75%).

In 2007, tadalafil 2.5 and 5 mg have been approved by the European Medicines Agency (EMA) for daily treatment of ED. According to EMA, patients who anticipate a frequent use of tadalafil (i.e., at least twice weekly) a once daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician’s judgement. In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability. The appropriateness of the continuous use of a daily regimen should be reassessed periodically.

A double-blind, placebo-controlled, multicentre, parallel-group study was conducted in 236 men with mild-to-moderate ED randomised to receive 10 mg vardenafil once daily plus on-demand placebo for 12 or 24 weeks, or once-daily placebo plus on-demand 10 mg vardenafil for 24 weeks, followed by 4 weeks wash-out.
Despite preclinical evidence, the results suggested that once-daily dosing of 10 mg vardenafil does not offer any sustainable effect after cessation of treatment compared to on-demand administration in patients with mild-to-moderate ED. Other studies (open-label, randomised, crossover studies with limited patient numbers) have shown that chronic, but not on-demand, tadalafil treatment improves endothelial function with a sustained effect after its discontinuation (68, 69). This has been confirmed in another study of chronic sildenafil in men with type 2 diabetes (70).

Recently, in a double-blind, placebo-controlled study of 298 men with diabetes and ED, 2.5 and 5 mg tadalafil once daily for 12 weeks was efficacious and well tolerated. This regimen provides an alternative to on-demand treatment for some men with diabetes (71).

Table 7: Summary of the key pharmacokinetic data for the three PDE5 inhibitors used to treat ED

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil, 100 mg</th>
<th>Tadalafil, 20 mg</th>
<th>Vardenafil, 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>560 μg/L</td>
<td>378 μg/L</td>
<td>18.7 μg/L</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.8-1 h</td>
<td>2 h</td>
<td>0.9 h</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>2.6-3.7 h</td>
<td>17.5 h</td>
<td>3.9 h</td>
</tr>
<tr>
<td>AUC</td>
<td>1685 μg.h/L</td>
<td>8066 μg.h/L</td>
<td>56.8 μg.h/L</td>
</tr>
<tr>
<td>Protein binding</td>
<td>96%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>41%</td>
<td>NA</td>
<td>15%</td>
</tr>
</tbody>
</table>

C<sub>max</sub>: maximal concentration; T<sub>max</sub>: time-to-maximum plasma concentration; T<sub>1/2</sub>: plasma elimination halflife; AUC: area under curve or serum concentration time curve.

Table 8: Common adverse events of the three PDE5 inhibitors used to treat ED

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12.8%</td>
<td>14.5%</td>
<td>16%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10.4%</td>
<td>4.1%</td>
<td>12%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4.6%</td>
<td>12.3%</td>
<td>4%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1.1%</td>
<td>4.3%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2%</td>
<td>2.3%</td>
<td>2%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>1.9%</td>
<td>&lt; 2%</td>
<td>&lt; 2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from EMA statements on product characteristics.


3.5.1.6 Safety issues for PDE5 inhibitors

3.5.1.6.1 Cardiovascular safety

Clinical trial results and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either double-blind, placebo-controlled trials or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is had an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina (72, 73). In fact, they may even improve exercise tests. Sildenafil does not alter cardiac contractility, cardiac output or myocardial oxygen consumption according to available evidence. Chronic or on-demand use is well tolerated with a similar safety profile.

3.5.1.6.2 Nitrates are contraindicated with PDE5 inhibitors

Organic nitrates (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) and other nitrates preparations used to treat angina, as well as amyl nitrite or amyl nitrate (“poppers” used for recreation), are absolute contraindications for the use of PDE5Is. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used.
If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) is used (half-life, 4 h), and for at least 48 h if tadalafil is used (half-life, 17.5 h).

If a patient develops angina while taking a PDE5I, other agents may be given instead of nitroglycerine until the appropriate time has passed. If nitroglycerine must be reintroduced following administration of a PDEI, the patient should receive it only after an appropriate interval has elapsed, as described above, and under close medical observation.

3.5.1.6.3 Antihypertensive drugs
Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5I is not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

3.5.1.6.4 α-Blocker interactions
All PDE5Is show some interaction with α-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling currently advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α-blocker (especially doxazosin). Hypotension is more likely to occur within 4 h following treatment with an α-blocker. A starting dose of 25 mg is recommended.
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy.
- Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension (74).
- Tadalafil is not recommended in patients taking doxazosin but this is not the case for tamsulosin, 0.4 mg (75).

These interactions are more pronounced when PDE5Is are given to healthy volunteers not previously taking α-blockers. Therefore, patients should be stable on α-blocker therapy prior to initiating combined treatment, and that the lowest dose should be started initially of PDE5Is. Further research is needed into the interaction between other PDE5Is and other α-blockers (e.g., alfuzosin, once-daily), or mixed α/β-blockers (e.g., carvedilol and labetalol).

3.5.1.6.5 Dosage adjustment
Drugs that inhibit the CYP34A pathway will inhibit the metabolic breakdown of PDE5Is. They include ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (ritonavir and saquinavir). Such agents may increase blood levels of PDE5Is, so that lower doses of PDE5Is are necessary.

However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP34A and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3.5.1.7 Management of non-responders to PDE5 inhibitors
The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. The management of non-responders depends upon identifying the underlying cause.

3.5.1.7.1 Check that the patient has been using a licensed medication
There is a large black market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

3.6.1.7.2 Check that the medication has been properly prescribed and correctly used
The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The main ways in which a drug may be incorrectly used are:

- failure to use adequate sexual stimulation;
- failure to use an adequate dose;
- failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Lack of adequate sexual stimulation: PDE5Is depend for their action upon the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual
stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work.

Oral PDE5Is take different times to reach maximal plasma concentrations (76,77). Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all three drugs have an onset of action in some patients within 30 min of oral ingestion, most patients require a longer delay between taking the medication, with at least 60 min being required for men using sildenafil and vardenafil, and up to 2 h being required for men using tadalafil (78-80).

Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal (81). Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse (77).

It is possible to wait too long after taking medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about 4 h, suggesting that the normal window of efficacy is 6-8 h following drug ingestion, although responses following this time period are well recognised. Tadalafil has a longer half-life of ~17.5 h, so the window of efficacy is much longer at ~36 h.

For financial reasons, some physicians may prescribe only lower doses of a drug. It is important to check that the patient has had an adequate trial of the maximal dose of the drug. Data suggest an adequate trial involves at least six attempts with a particular drug (82).

Data from uncontrolled studies suggests patient education can help salvage an apparent non-responder to a PDE5I. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I (83-85).

One study (84) went further, and in those patients who still did not respond to the PDE5I, a second-line adjustment was instituted. Patients taking tadalafil were advised to wait at least 2 h between oral ingestion and attempting intercourse. Patients taking vardenafil were advised to use the drug only after a fast. In both patient groups, further apparent non-responders were salvaged. No patients using sildenafil were included in this study.

3.5.1.7.3 Possible manoeuvres in patients correctly using a PDE5 inhibitor

When the patient is using an adequate dose of the drug properly and the response is still inadequate, there are several changes that may improve drug efficacy, although the evidence supporting these interventions is limited.

Erectile dysfunction is typically a symptom of an underlying condition, such as diabetes, hypertension, or dyslipidaemia. There is evidence suggesting that, in patients with hypogonadism, normalisation of serum testosterone might improve response to a PDE5I (86). Modification of other risk factors may be also be beneficial as discussed in section 3.2.

A randomised trial has suggested that vardenafil benefits non-responders to sildenafil (87), but because of poor study design, the results are considered to overstate the benefits of switching PDE5Is. However, a randomised, open-label, crossover trial comparing sildenafil and tadalafil has indicated that some patients might respond better to one PDE5I than to another (88). According to the IIEF-EF score, 17% of patients had a better response (≥ 5 points) to tadalafil than to sildenafil, while 14% had a better response to sildenafil than tadalafil.

Although these differences might be explained by variation in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful.

Two non-randomized trials have suggested that daily dosing with a PDE5I might salvage some non-responders to intermittent dosing. In one trial (89), some men benefited from regular dosing with either vardenafil or tadalafil, while in the other trial (84) daily dosing with tadalafil salvaged some men who had failed to respond to intermittent dosing with a PDE5I.

Currently, there are no randomised trials to support this intervention. Although tadalafil is licensed for daily dosing at 2.5 and 5 mg, neither sildenafil nor vardenafil are licensed for use in this way.

If drug treatment fails, then patients should be offered an alternative therapy such as intracavernosal injection therapy or use of a vacuum erection device.

3.5.2 Vacuum erection devices

Vacuum erection devices (VEDs) provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. Thus, erections with these devices are not normal because they do not use physiological erection pathways. Efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% (90). Men with a motivated, interested, and understanding partner report the highest satisfaction rates. Long-term use of VEDs decreases to 50-64% after 2 years (91). Most men who discontinue use of VEDs do so within 3 months.

The commonest adverse events include pain, inability to ejaculate, petechiae, bruising, and
numbness, which occur in < 30% of patients (92). Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 min. VEDs are contraindicated in patients with bleeding disorders or on anticoagulant therapy.

VEDs may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED (90).

3.5.3 Shockwave therapy
Recently, the use of low-intensity extracorporeal shock wave therapy was proposed as a novel treatment for ED (93). In the first randomised, double-blind, sham-controlled study, it was demonstrated that low-intensity extracorporeal shock wave therapy had a positive short-term clinical and physiological effect on the erectile function of men who respond to oral PDE5Is (94). Moreover, there are preliminary data showing improvement in penile hemodynamics and endothelial function, as well as IIEF-EF domain score in severe ED patients who are poor responders to PDE5Is (95). The feasibility and tolerability of this treatment, coupled with its potential rehabilitative characteristics, make it an attractive new therapeutic option for men with ED. However, current data are limited and clear recommendations cannot be given. Data regarding the mechanism of action of this procedure are still lacking. In a diabetic rat model, low-intensity extracorporeal shock wave therapy ameliorated diabetes mellitus associated ED by promoting regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis. These beneficial effects appear to be mediated by recruitment of endogenous mesenchymal stem cells (MSCs) (96).

3.6 Second-line therapy
Patients not responding to oral drugs may be offered intracavernous injections. Success rate is high (85%) (97,98). Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago (99).

3.6.1 Intracavernous injections
3.6.1.1 Alprostadil
Alprostadil (CaverjectTM, Edex/ViridalTM) was the first and only drug approved for intracavernous treatment of ED (99). Intracavernous alprostadil is most efficacious as monotherapy at a dose of 5-40 μg; although the 40 μg dose is not registered in every European country. The erection appears after 5-15 min and lasts according to the dose injected. An office-training programme (one or two visits) is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners. The use of an automatic special pen that avoids a view of the needle can resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of > 70% have been found in general ED populations, as well as in patient subgroups (e.g., diabetes or cardiovascular disease), with reported sexual activity after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners (100-102).

Complications of intracavernous alprostadil include penile pain (50% of patients reported pain but pain reported only after 11% of total injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) (103). Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia (104,105). Cavernosal fibrosis (from a small hematoma) usually clears within a few months after temporary discontinuation of the injection program. However, tunical fibrosis suggests early onset of La Peyronie’s disease and may indicate stopping intracavernosal injections indefinitely. Systemic side effects are uncommon. The most common is mild hypotension, especially when using higher doses.

Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders.

Despite these favourable data, intracavernous pharmacotherapy is associated with high drop-out rates and limited compliance. Drop-out rates of 41-68% have been described (106-108), with most drop outs occurring within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection programme (109).

Today, intracavernous pharmacotherapy is considered a second-line treatment. Patients not responding to oral drugs may be offered intracavernous injections with a high success rate of 85%. Most long-term injection users can switch to sildenafil despite underlying pathophysiology (110-112). However, almost one-third of long-term intracavernous injections users who subsequently also responded to sildenafil preferred to continue with an intracavernous injection programme (112,113).
3.6.1.2 Combination therapy

Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating side effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy today due to its high incidence of side effects as monotherapy.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide (CGRP), usually combined with the main drugs (114,115). Most combinations are not standardised and some drugs have limited availability worldwide.
- Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 μg), have been widely used with improved efficacy rates, although they have never been licensed for ED (116-118). The triple combination regimen of papaverine, phentolamine and alprostadil has the highest efficacy rates, reaching 92%; this combination has similar side effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose). In addition, mild hepatotoxicity has been reported with papaverine (119).

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone (120). However, combination therapy is associated with an incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant.

3.6.1.3 Intraurethral alprostadil

A specific formulation of alprostadil (125-1000 μg) in a medicated pellet (MUSE™) has been approved for use in ED (121). A vascular interaction between the urethra and the corpora cavernosa enables drug transfer between these structures (121). Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 μg) have been used with low consistency response rates (121-123). The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy (123,124).

The most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration.

Efficacy rates are significantly lower than intracavernous pharmacotherapy (125). Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-eficacious treatment.

3.7 Third-line therapy (penile prostheses)

The surgical implantation of a penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. The two currently available classes of penile implants include inflatable (2- and 3-piece) and malleable devices (126-129).

Most patients prefer the three-piece inflatable devices due to the more “natural” erections obtained. The three-piece inflatable penile include a separate reservoir placed in the abdominal cavity. Three-piece devices provide the best rigidity and the best flaccidity because they will fill every part of the corporal bodies. However, the two-piece inflatable prosthesis can be a viable option among patients who are deemed high risk of complications with reservoir placements. Malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state (126-129).

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic (126-129). The penoscrotal approach provides an excellent exposure, it affords proximal crural exposure if necessary, avoids dorsal nerve injury and permits direct visualisation of pump placement. However, with this approach the reservoir is blindly placed into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy). The infrapubic approach has the advantage of reservoir placement under direct vision but the implantation of the pump may be more challenging, and patients are at a slightly increased risk of dorsal nerve injury. Revision surgery is associated with decreased outcomes and may be more challenging.

3.7.1 Efficacy and satisfaction rates

Prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED based on appropriate consultation (130-137). Mulhall and colleagues
have used the IIEF and the Erectile Dysfunction Index for Treatment Satisfaction (EDITS) at 3-month intervals following implantation of inflatable penile prostheses. There was a continued improvement in scores for the IIEF and EDITS stabilised 9-12 months following surgery. All variables, including erection, ejaculation, orgasm, and overall sexual satisfaction, improved above baseline values at 1 year after surgery. However, at 3 months following surgery, the results were less satisfactory, suggesting that postoperative counselling and encouragement of patients is important to obtain ultimate satisfaction and positive outcomes at 9-12 months (134).

In a long-term multicentre study of the AMS 700CX three-piece inflatable prosthesis, with a median follow-up of 48 months, 79% of patients were using their device at least twice monthly and 88% would recommend the prosthesis to a friend or relative (135). In another multicentre study with 59 months follow-up, at almost 5 years after surgery, 92.5% of patients were using their prosthesis an average of 1.7 times weekly and excellent or satisfactory results were reported by patients and their partners (132).

Increasingly, in patients with favourable prognosis after RP for prostate cancer, the presence of urinary incontinence and sexual dysfunction (primarily ED and orgasmic dysfunction) is leading doctors to the need for global management of both conditions. Based on appropriate clinical and diagnostic assessments of severity of adverse outcomes depending on patient preference, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established, definitive role to address this problem (138).

3.7.2 Complications
The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prosthesis (AMS 700CX/CXR™ and Coloplast Alpha I™) resulted in mechanical failure rates of < 5% after 5 years follow-up (135,139). Careful surgical technique with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2-3% with primary implantation in low-risk patients. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast itan™) (140-143).

Higher risk populations include patients undergoing revision surgery, those with impaired host defenses (immunosuppresson, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis (126-129). Although diabetes is considered to be one of the main risk factors for infection, this is not supported by current data (126-129). Infections, as well as erosions, are significantly higher (9%) in patients with spinal cord injuries (9%) (126-129). Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a washout protocol with successful salvages achieved in > 80% of cases (144,145). The majority of revisions are secondary to mechanical failure and combined erosion or infection. Overall, 93% of cases are successfully revised, providing functioning penile prosthesis.

3.7.3 Conclusions
Penile implants are an attractive solution for patients who do not respond to more conservative therapies. There is enough evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates.
3.8 Guidelines for the treatment of ED

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Lifestyle changes and risk factor modification must precede or accompany ED treatment.</td>
<td>1a</td>
</tr>
<tr>
<td>Pro-erectile treatments have to be given at the earliest opportunity after RP.</td>
<td>1b</td>
</tr>
<tr>
<td>When a curable cause of ED is found, it must be treated first.</td>
<td>1b</td>
</tr>
<tr>
<td>PDE5Is are first-line therapy.</td>
<td>1a</td>
</tr>
<tr>
<td>Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5Is.</td>
<td>3</td>
</tr>
<tr>
<td>A VED can be used in patients with a stable relationship.</td>
<td>4</td>
</tr>
<tr>
<td>Intracavernous injection is second-line therapy.</td>
<td>1b</td>
</tr>
<tr>
<td>Penile implant is third-line therapy.</td>
<td>4</td>
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</tbody>
</table>

3.9 References


http://www.ncbi.nlm.nih.gov/pubmed/11402580


4. PREMATURE EJACULATION

4.1 Introduction
Although premature ejaculation is a very common male sexual dysfunction, it is poorly understood. Patients are often unwilling to discuss their symptoms and many physicians do not know about effective treatments. As a result, patients may be misdiagnosed or mistreated (1). In addition, there is currently no registered pharmacological treatment for PE.

These guidelines provide an evidence-based analysis (2) of published data on definition, clinical evaluation and treatment. It provides recommendations to clinicians on the diagnosis and treatment of PE, without preempting physician judgement on individual cases.

4.2 Definition of PE
4.2.1 Overview
There have previously been two official definitions of PE, neither of which were universally accepted:

• In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), PE is defined as a ‘persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity’ (3).

• In the World Health Organization’s International Classification of Diseases-10 (ICD-10), PE is defined as ‘the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity’ (4).

Recently, two more definitions have been proposed:

• The Second International Consultation on Sexual and Erectile Dysfunction defined PE as ‘ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control’ (5).

• The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition, ‘Premature ejaculation is a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy’. It must be noted that this definition is limited to men with lifelong PE who engage in vaginal intercourse since there are insufficient objective data to propose an evidence-based definition for acquired PE (6).

All four definitions have taken into account the time to ejaculation, the inability to control or delay ejaculation, and negative consequences (bother/distress) from PE. However, the major point of debate is quantifying the time to ejaculation, which is usually described by intravaginal ejaculatory latency time (IELT). Several proposals for updating the definition of PE in the forthcoming DSM-V and ICD-11 have been presented (7-11).

4.2.2 Classifications
Premature ejaculation is classified as ‘lifelong’ (primary) or ‘acquired’ (secondary) (12). Lifelong PE is characterised by onset from the first sexual experience, remains so during life and ejaculation occurs too fast (before vaginal penetration or < 1-2 min after). Acquired PE is characterised by a gradual or sudden onset following normal ejaculation experiences before onset and time to ejaculation is short (usually not as short as in lifelong PE).

Recently, two more PE syndromes have been proposed (11):

• ‘Natural variable PE’ is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.

• ‘Premature-like ejaculatory dysfunction’ is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new types may aid patient stratification, diagnosis and treatment, but their exact role remains to be defined (13).
4.3 Epidemiology

4.3.1 Prevalence

The major problem in assessing the prevalence of PE is the lack of an accurate (validated) definition at the time the surveys were conducted (14). However, epidemiological research has consistently shown that PE, at least according to the DSM-IV definition, is the most common male sexual dysfunction, with prevalence rates of 20-30% (15-17).

The highest prevalence rate of 31% (men aged 18-59 years) was found by the USA NHLS study (16). Prevalence rates from 18 to 29 years, 30 to 39 years, 40 to 49 years and 50 to 59 years were 30%, 32%, 28% and 55%, respectively. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower. A British mailed questionnaire survey estimated that the prevalence rate of PE was between 14% (3 months) and 31% (life-time) (18). A French telephone survey of men aged 18 to 69 years estimated the life-time prevalence of early ejaculation at 15%, including 5% who often had experienced ejaculation prior to penetration and 10% who often had ejaculated too rapidly after vaginal intromission (19). A Swedish interview reported an overall prevalence rate of 9% in men aged 18 to 74 years (20), with prevalence by age being 4% for 18-24 years, 7% for 25-34 years, 8% for 35-49 years, 8% for 50-65 years and 14% for 66-74 years. A Danish study about sexual problems using a questionnaire (12 questions) and an interview (23 questions) reported the prevalence rate for PE to be 14% in men aged 51 years (21). An Italian questionnaire survey recorded a prevalence rate of 21% (22). Finally, in a self-administered questionnaire survey in the Netherlands, the prevalence rate was 13% in men aged 50-78 years (23).

The prevalence of PE in the Premature Ejaculation Prevalence and Attitudes (PEPA) survey (a multinational, internet-based survey) was 22.7% (24.0% in the USA, 20.3% in Germany, and 20.0% in Italy) (17). The Global Study of Sexual Attitudes and Behaviors (GSSAB) survey was conducted in men between 40 and 80 years old in 29 different countries using personal and telephone interviews and self-completed mailed questionnaires; it confirmed that the worldwide prevalence of PE was almost 30%. Except for a low reported rate of PE in Middle Eastern countries (10-15%), prevalence was relatively similar throughout the rest of the world (15). Finally, the prevalence rate of PE was 18% in a five-country European Observational study using the IELT and the Premature Ejaculation Profile (PEP) (24), comparable to those obtained in a similarly designed USA observational study (25).

Further research is needed on the prevalence of lifelong and acquired PE. Limited data suggests that the prevalence of lifelong PE, defined as IELT < 1-2 min, is about 2-5% (20, 25). These results are supported by the moderate genetic influence on PE (26) and low prevalence rates of IELT < 1 min (27).

4.3.2 Pathophysiology and risk factors

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety, penile hypersensitivity, and 5-HT receptor dysfunction (5). In addition, the pathophysiology of PE is largely unknown. In contrast to ED, there is no impairment of the physiological events leading up to the forceful expulsion of sperm at the urethral meatus.

A significant proportion of men with ED also experience PE (15). High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED.

According to the NHLS, the prevalence of PE is not affected by age (16,17), unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status (16). However, PE is more common in blacks, Hispanic men and men from Islamic backgrounds (28,29) and may be higher in men with a lower educational level (15,16). Other risk factors may include a genetic predisposition (30), poor overall health status and obesity (16), prostate inflammation (31,32), thyroid hormone disorders (33), emotional problems and stress (16,34), and traumatic sexual experiences (15,16).

In the only published study on risk modification/prevention strategies (35), successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in IELT and ejaculatory control compared to untreated patients.

4.4 Impact on quality of life

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse (36,37). However, the negative impact of PE extends beyond sexual dysfunction. PE has a detrimental effect on self-confidence and the relationship with the partner, and may cause mental distress, anxiety, embarrassment and depression (36,38). Sexual drive and overall interest in sex does not appear to be affected by PE (39). However, the partner’s satisfaction with the sexual relationship decreased with increasing severity of the man’s condition (40).

Despite the serious psychological and QoL consequences of PE, few men seek treatment. In the GSSAB survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems (15), with men more likely to seek treatment for ED than for PE (15). In the PEPA survey,
only 9% of men with self-reported PE consulted a doctor (17). The main reasons for not discussing PE with their physician are patient embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE (41,42). Physicians need to encourage patients to talk about PE.

4.5 Diagnosis
Diagnosis of PE is based on the patient’s medical and sexual history (43,44). History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED.

Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection (45). Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE (46).

There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis (47).

Table 9: Common factors in different definitions of ED

<table>
<thead>
<tr>
<th>Time to ejaculation assessed by IELT</th>
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<tr>
<td>Perceived control</td>
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<tr>
<td>Distress</td>
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<tr>
<td>Interpersonal difficulty related to the ejaculatory dysfunction</td>
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4.5.1 Intravaginal ejaculatory latency time (IELT)
The use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE (24,25). Moreover, IELT has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse (48). In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation).

In everyday clinical practice, self-estimated IELT is sufficient. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity (49). Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all to 4 = extremely). However, stopwatch-measured IELT is necessary in clinical trials.

4.5.2 PE assessment questionnaires
The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs (47). Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT: five-item questionnaire based on focus groups and interviews from the USA, Germany and Spain. Assesses control, frequency, minimal stimulation, distress and interpersonal difficulty (50,51).
- Arabic Index of Premature Ejaculation (AIPE): seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction for the patient and partner, anxiety or depression (52).

These tools are a significant step in simplifying the methodology of PE drug studies, though further cross-cultural validation is needed (53).

Other questionnaires used to characterise PE and determine treatment effects include the PEP (25), Index of Premature Ejaculation (IPE), (54) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) (55). Currently, their role is optional in everyday clinical practice.

4.5.3 Physical examination and investigations
Physical examination is part of the initial assessment of men with PE. It includes a brief examination of the vascular, endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as chronic illness, endocrinopathy, autonomic neuropathy, Peyronie’s disease,
urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended (44).

4.6 Recommendations on the diagnosis of PE

<table>
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<tr>
<td>Diagnosis and classification of PE is based on medical and sexual history. It should be multidimensional and assess IELT, perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.</td>
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<tr>
<td>Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials.</td>
<td>2a</td>
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<tr>
<td>Patient-reported outcomes (PROs) have the potential to identify men with PE. Further research is needed before PROs can be recommended for clinical use.</td>
<td>3</td>
</tr>
<tr>
<td>Physical examination may be necessary in initial assessment of PE to identify underlying medical conditions that may be associated with PE or other sexual dysfunctions, particularly ED.</td>
<td>3</td>
</tr>
<tr>
<td>Routine laboratory or neurophysiological tests are not recommended. They should only be directed by specific findings from history or physical examination.</td>
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4.7 References


http://www.ncbi.nlm.nih.gov/pubmed/16409229


4.8 Treatment

In many relationships, PE causes few, if any, problems. In such cases, treatment should be limited to psychosexual counselling. Before beginning treatment, it is essential to discuss patient expectations thoroughly. Erectile dysfunction, in particular, or other sexual dysfunction or genitourinary infection (e.g. prostatitis), should be treated first or at the same time as PE.

Various behavioural techniques have demonstrated benefit in treating PE and are indicated for patients uncomfortable with pharmacological therapy. In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner and can be difficult to do. In addition, long-term outcomes of behavioural techniques for PE are unknown.

Pharmacotherapy is the basis of treatment in lifelong PE. Since no drug for PE has been approved by the EMEA or FDA, all medical treatments are off-label indications. Only chronic selective serotonin reuptake inhibitors (SSRIs) and on-demand topical anaesthetic agents have consistently shown efficacy in PE. Again, long-term outcomes for pharmacological treatments are unknown.

An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grade of recommendation are provided and a treatment algorithm is presented (Figure 3).

4.8.1 Psychological/behavioural strategies

Behavioural strategies mainly include the ‘stop-start’ programme developed by Semans (1) and its modification, the ‘squeeze’ technique, proposed by Masters and Johnson.

- In the ‘stop-start’ programme, the partner stimulates the penis until the patient feels the urge to ejaculate. At this point, he instructs his partner to stop, waits for the sensation to pass and then stimulation is resumed.
- The ‘squeeze’ technique is similar but the partner applies manual pressure to the glans just before ejaculation until the patient loses his urge.

Both these procedures are typically applied in a cycle of three pauses before proceeding to orgasm. Behavioural strategies are based on the hypothesis that PE occurs because the man fails to appreciate the sensations of heightened arousal and to recognise the feelings of ejaculatory inevitability. Re-training may attenuate stimulus-response connections by gradually exposing the patient to progressively more intense and more prolonged stimulation, while maintaining the intensity and duration of the stimulus just below the threshold for triggering the response. There are several modifications of these techniques making comparison difficult.

Masturbation before anticipation of sexual intercourse is a technique used by many younger men. Following masturbation, the penis is desensitised resulting in greater ejaculatory delay after the refractory period is over. In a different approach, the man learns to recognise the signs of increased sexual arousal and how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex. Efficacy is similar to the ‘start-stop’ programme (2).

Overall, success rates of 50-60% have been reported short term (3,4). However, there is no controlled research to support the efficacy of behavioural techniques, while a double-blind, randomised, crossover study showed that pharmacological treatment (chlomipramine, sertraline, paroxetine and sildenafil) resulted in greater
IELT prolongation than behavioural therapy (5). Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long term (6,7).

4.8.1.1 Recommendation on the psychological/behavioural treatment of PE

<table>
<thead>
<tr>
<th>Psychological/behavioural therapies may be attempted but no clinical data exists supporting prolonged effect.</th>
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4.8.2 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE (8).

4.8.2.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from 1 min in the placebo group to 6.7 min in the treatment group (11). In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 min while no difference was recorded in the placebo group (1.67 to 1.95 min) (12). Lidocaine-prilocaine cream (5%) is applied for 20 to 30 min prior to intercourse. Prolonged application of topical anaesthetic (30 to 45 min) may result in loss of erection due to numbness of the penis in a significant percentage of men (11). A condom is required to avoid diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner. Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Although no significant side-effects have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any component of the product.

An aerosol formulation of lidocaine 7.5 mg plus prilocaine 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation, TEMPE (13) has been evaluated in a phase II study (14). Intravaginal ejaculatory latency time increased from a baseline of 1 min to 4.9 min in the TEMPE-treated group compared to an increase from baseline of 0.9 min to 1.6 min (p < 0.01) in the placebo-treated group. It has been suggested that lidocaine-prilocaine can penetrate the glans within 5–10 min, but penetrates intact keratinised skin less easily, reducing penile numbness and ED (14,15).

Finally, in a randomised, double-blind, placebo-controlled, parallel-group study, lidocaine-prilocaine cream showed similar efficacy to combination with sildenafil (50 mg before coitus) and significantly better efficacy than sildenafil alone (16). However, no specific data on estimated IELT were provided.

4.8.2.2 SS-cream

SS-cream is a topical anaesthetic agent made from the extracts of nine herbs. It is applied to the glans penis 1 h before and washed off immediately prior to coitus. SS-cream increased the vibratory threshold in a dose-dependent fashion, as well as the latency and amplitude of somatosensory-evoked potentials measured at the glans penis (17,18). In a double-blind, randomised, placebo-controlled study (19), application of 0.2 g SS-cream improved IELT from 1.37 min to 10.92 min in the treatment group versus 2.45 min in the placebo group. Sexual satisfaction improved by 82% in the treatment group versus 20% in the placebo group. Mild local burning and mild pain were reported by 18.5% of patients. No adverse effects on sexual function or partner or systemic side-effects were observed.

4.8.2.3 Recommendations on the topical therapy for PE

| Lidocaine-prilocaine cream. | LE | GR |
| SS-cream. | 1B | A |

4.8.3 Selective serotonin reuptake inhibitors

Ejaculation is mediated by a spinal ejaculation generator (20, 21) and by descending supraspinal modulation from several brain regions. The neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) is also involved in ejaculatory control. The retarding effect of 5-HT on ejaculation is probably due to central activation (i.e. spinally and supraspinally) of 5-HT1B and 5-HT2C receptors, while stimulation of 5-HT1A receptors precipitates ejaculation.

Selective serotonin reuptake inhibitors (SSRIs) are used to treat mood disorders, but can delay
ejaculation and are therefore widely used ‘off-label’ for PE. As in depression, SSRIs must be given for 1 to 2 weeks to be effective in PE (22). Chronic SSRI administration causes prolonged increases in synaptic cleft serotonin, which desensitise the 5-HT1A and 5-HT1B receptors (23). Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment (24). Selective serotonin reuptake inhibitors have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 (25). Today, daily treatment with SSRIs has become the first choice of treatment in PE. Commonly used SSRIs include citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar pharmacological mechanism of action.

A systematic review and meta-analysis of all drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE (26). Open-design studies and studies using subjective reporting or questionnaires showed greater variation in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch.

Based on this meta-analysis, SSRIs were expected to increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective (27,28).

 Ejaculation delay may start a few days after drug intake, but it is more evident after 1 to 2 weeks since receptor desensitisation requires time to occur. While efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6 to 12 months (24).

Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhea and perspiration; they are usually mild and gradually improve after 2 to 3 weeks (24). Decreased libido, anorgasmia, anejaculation and ED have also been reported.

In one controlled trial, on-demand use of clomipramine (but not paroxetine), 3 to 5 h before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug (29). However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects (30,31).

4.8.3.1 Dapoxetine

Dapoxetine is a potent SSRI, which has been designed as an on-demand oral treatment for PE. It is quickly absorbed with a Tmax of 1.5 h and is rapidly cleared, avoiding accumulation.

An integrated analysis of two, double-blind, randomised, controlled trials (1,958 patients) with dapoxetine was published (32). Dapoxetine, 30 and 60 mg, was administered 1 to 3 h before intercourse. Intravaginal ejaculatory latency time improved from a baseline of 0.9 min to 1.75 min, 2.78 min and 3.32 min in the patient groups treated with placebo, 30 mg dapoxetine, and 60 mg dapoxetine, respectively. Improved ejaculation control was reported by 51% and 58% of patients in the 30 mg and 60 mg groups, respectively. Both dapoxetine doses were effective on the first dose. Common adverse events for 30 mg and 60 mg doses of dapoxetine, respectively, were nausea (8.7%, 20.1%), diarrhea (3.9%, 6.8%), headache (5.9%, 6.8%), and dizziness (3.0%, 6.2%).

In a subanalysis of these two studies (33), 32% of men reported a two-category (from a 5-point scale, ‘very poor’ to ‘very good’) or greater increase in control and satisfaction with sexual intercourse after treatment. More than 95% of those men rated their PE as ‘slightly better’, ‘better’, or ‘much better’ on the global impression of change (7-point scale, ‘much worse’ to ‘much better’) while 67.1% gave ratings of ‘better’ or ‘much better.’ They also had greater improvements in IELT than men with less than a two-category increase in control, with a mean (SD) change from baseline of 3.7 (4.3) vs 0.77 (1.8) min, respectively. The proportions of men with a two-category or greater increase in control with dapoxetine 30 and 60 mg were 36.3% and 44.5%, respectively (vs 15% with placebo).

In another randomised, double-blind, parallel-group, placebo-controlled, phase II trial including 1,162 men in 22 countries (34), mean average IELT increased from 0.9 min at baseline (all groups) to 1.9 min, 3.2 min, and 3.5 min with placebo and dapoxetine 30 mg and dapoxetine 60 mg, respectively, at study end point. The geometric mean IELT increased from 0.7 min at baseline to 1.1 min, 1.8 min, and 2.3 min, respectively, at study end point. All PEP measures and IELTs improved significantly with dapoxetine versus placebo at week 12 and week 24 (p < 0.001 for all). The most common adverse effects were nausea, dizziness, diarrhea, and headache. Adverse effects led to discontinuation in 1.3%, 3.9%, and 8.2% of subjects with placebo and dapoxetine 30 mg. Finally, in a randomised, double-blind, placebo controlled, phase III trial (1,238 men in USA and Canada), dapoxetine reduced the personal distress and interpersonal difficulty associated with PE (35).
Dapoxetine has been approved (December 2008) for the on-demand treatment of PE in seven European countries (Sweden, Austria, Finland, Germany, Spain, Italy and Portugal). This is currently the first and only drug approved for such an indication.

### 4.8.3.2 Recommendation on the treatment of PE

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### 4.8.4 Phosphodiesterase type 5 inhibitors

Several recent studies have supported the therapeutic role of PDE5 inhibitors in PE. They may reduce performance anxiety due to better erections and may down-regulate the erectile threshold to a lower level of arousal so that greater arousal is required to achieve the ejaculation threshold. However, many of the mechanisms involved remain speculative (33,36-38).

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo (39). Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation.

In another randomised, double-blind, placebo-controlled study, lidocaine-prilocaine had similar efficacy to combination with sildenafil (50 mg before intercourse), while the efficacy of sildenafil was similar to placebo (no IELT data provided) (16). In contrast, in a randomised, double-blind, parallel group study, sildenafil significantly improved IELT and satisfaction and reduced overall anxiety compared to several SSRIs and the ‘pause-squeeze’ technique. From a baseline of IELT at 1 min, IELT improved to 15 min with sildenafil, 4 min with clomipramine, 3 min with sertraline, 4 min with paroxetine and 3 min with the ‘pause-squeeze’ technique (5).

Finally, several open-label studies showed that sildenafil combined with an SSRI is superior to SSRI monotherapy. Sildenafil combined with paroxetine improved IELT significantly and satisfaction versus paroxetine alone (40). Sildenafil combined with sertraline improved IELT and satisfaction significantly versus sertraline alone (41). Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed (42). Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction versus behavioural therapy alone (43).

There are limited data on the efficacy in PE of other PDE5 inhibitors (tadalafil and vardenafil) (37, 38). Overall, the role of PDE5 inhibitors in PE patients without ED is not established, with only minimal double-blind placebo controlled data are available.

### 4.8.4.1 Recommendation on the use of PDE5 inhibitors for the treatment of PE

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### 4.8.5 Other drugs

Adrenergic blockade for PE aims to decrease the sympathetic tone of the seminal tract and therefore delay ejaculation (44). Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline.

Research suggests that the alpha-1 adrenergic antagonists, terazosin and alfuzosin (45,46), and tramadol (47,48) may have some efficacy in PE. However, further research is needed to investigate their role fully. Currently they are not recommended in clinical practice (49).

### 4.8.6 Recommendations on the treatment of PE

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</table>
Daily SSRIs are first-line, off-label, pharmacological treatment for PE. The pharmacokinetic profile of SSRIs is not amenable to pm dosing.

Dapoxetine, a short-acting SSRI, has already been approved for the on-demand treatment of PE in seven European Countries.

Topical anaesthetic agents provide viable alternatives to SSRIs (off-label).

Recurrence is likely after treatment cessation.

Behavioural therapy may augment pharmacotherapy to enhance relapse prevention.

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ED = erectile dysfunction; PE = premature ejaculation; SSRI = selective serotonin reuptake inhibitor; pm = on-demand administration.
Clinical diagnosis of premature ejaculation based on patient/partner history
- Time to ejaculation (IELT)
- Perceived degree of ejaculatory control
- Degree of bother/distress
- Onset and duration of PE
- Psychosocial/Relationship issues
- Medical history

Treatment of premature ejaculation
- Patient counselling
- Discussion of treatment options
- If PE is secondary to ED, treat ED first or concomitantly

Lifelong PE
- Pharmacotherapy
- Relationship counselling
- Behavioural therapy
- Combination treatment

Acquired PE
- Behavioural therapy
- Pharmacotherapy
- Relationship counselling
- Combination treatment

Attempt graduated withdrawal of Drug therapy after 6-8 weeks
- Behavioural therapy includes stop/start technique, squeeze and sensate focus
- Pharmacotherapy (off label) includes SSRIs (daily use) and topical anaesthetics; it is recommended as first-line treatment option in lifelong PE
- Consider dapoxetine for on-demand use (the only approved drug for PE)

* Adapted from Lue et al. 2004 (49).

ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time;
SSRI = selective serotonin receptor inhibitor.
4.9 References


   Marital Ther 1997 Spring;23(1):3-23.

5. Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmaceutical therapy 


   24(6):665-75. [no abstract available]

   ejaculation. BJU Int 2007 Sep;100(3):493-501.

9. Sachs BD, Liu YC. Maintenance of erection of penile glans, but not penile body, after transection of 

10. Wieder JA, Brackett NL, Lynne CM, et al. Anesthetic block of the dorsal penile nerve inhibits vibratory- 


12. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, 


    (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. 


    EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. Urology 2006 Feb; 
    67(2):388-91.

17. Xin ZC, Choi YD, Seong DH, et al. Sensory evoked potential and effect of SS-cream in premature 

18. Xin ZC, Choi YD, Lee WH, et al. Penile vibratory threshold changes with various doses of SS-cream in 


5. CONCLUSION

Modern treatment of ED has been revolutionised by the worldwide availability of three PDE5Is for oral use – sildenafil, tadalafil and vardenafil. These drugs have high efficacy and safety rates, even in difficult-to-treat populations, such as patients with diabetes mellitus or who have undergone RP. Patients should be encouraged to try all three PDE5Is. Patients should make up their own minds about which compound has the best efficacy, while also considering other factors, such as time of onset, duration of action, window of opportunity and how side-effects affect them individually.

Treatment options for patients who do not respond to oral drugs, or for whom drugs are contraindicated, include intracavernous injections, intraurethral alprostadil, vacuum constriction devices, or implantation of a penile prosthesis.

It is very important that the physician warns the patient that sexual intercourse is a vigorous physical activity, which increases heart rate as well as cardiac work. Physicians should assess the cardiac fitness of patients prior to treating ED.

Any successful pharmacological treatment for erectile failure demands a degree of integrity of the penile mechanisms of erection. Further studies of individual agents and synergistic activity of available substances are underway. The search for the ideal pharmacological therapy for erectile failure aims to fulfill the following characteristics: good efficacy, easy administration, freedom from toxicity and side-effects, with a rapid onset and a possible long-acting effect.

Premature ejaculation is another very common male sexual dysfunction, with prevalence rates of 20% to 30%. Four major definitions of PE are currently used and the most widely accepted classification of PE includes “lifelong” (primary) and “acquired” (secondary) forms (syndromes).

Diagnosis of PE in everyday clinical practice is based on medical and sexual history assessing IELT, perceived control, distress, and interpersonal difficulty related to the ejaculatory dysfunction. Physical examination and laboratory testing may be needed in selected patients only.

Pharmacotherapy is the basis of treatment in lifelong PE including daily dosing of SSRIs and topical anaesthetics. Behavioural techniques may be efficacious as a monotherapy or in combination with pharmacotherapy, but they can be difficult to perform. In every case, recurrence is likely to occur after treatment withdrawal.
6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

5-HT  5-hydroxytryptamine
AIPE  Arabic Index of Premature Ejaculation
AUC  area under curve - serum concentration time curve
BMI  body mass index
CAD  coronary artery disease
cGMP  cyclic guanosine monophosphate
CGRP  calcitonin gene-related peptide
CHF  congestive heart failure
Cmax  maximal concentration
DICC  dynamic infusion cavernosometry or cavernosography
DRE  digital rectal examination
DSM-IV-TR  Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision
EAU  European Association of Urology
ED  erectile dysfunction
EMEA  European Medicines Agency
FDA  (US) Food and Drug Administration
FSH  follicle-stimulating hormone
GAQ  General Assessment Question
GR  grade of recommendation
GSSAB  Global Study of Sexual Attitudes and Behaviors
ICD-10  International Classification of Diseases-10
IELT  intravaginal ejaculatory latency time
IIED  International Index for Erectile Function
IIED-EF  International Index for Erectile Function - erectile function domain
IPE  Index of Premature Ejaculation
ISSM  International Society for Sexual Medicine
LE  level of evidence
LH  luteinising hormone
LVD  left ventricular dysfunction
MET  metabolic equivalent of energy expenditure in the resting state
MI  myocardial infarction
MMAS  Massachusetts Male Aging Study
MSHQ-EjD  Male Sexual Health Questionnaire Ejaculatory Dysfunction
NHSLS  National Health and Social Life Survey
NS  nerve sparing
NO  nitric oxide
NPTR  nocturnal penile tumescence and rigidity
NSRP  nerve-sparing radical prostatectomy
NYHA  New York Heart Association
PCa  prostate cancer
PDE5Is  phosphodiesterase type 5 inhibitors
PE  premature ejaculation
PEDT  Premature Ejaculation Diagnostic Tool
PEP  Premature Ejaculation Profile
PEPA  Premature Ejaculation Prevalence and Attitudes
PRO  Patient reported outcome
PSA  prostate-specific antigen
QoL  quality of life
RP  radical prostatectomy
SEP  sexual encounter profile
SSRI  selective serotonin reuptake inhibitor
TEMPE  topical eutectic mixture for premature ejaculation
Tmax  time to maximum plasma concentration
VCD  vacuum constriction devices
VIP  vasointestinal peptide
Conflict of interest

All members of the Male Sexual Dysfunction Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. INTRODUCTION

Penile curvature can be congenital or acquired. Congenital curvature is discussed in these guidelines as a distinct pathology in the adult population without any other concomitant abnormality present (such as urethral abnormalities). For paediatric congenital penile curvature, please refer to the EAU Guidelines on Paediatric Urology, Chapter 7, Congenital Penile Curvature.

Acquired curvature is secondary due to La Peyronie’s disease (referred to as Peyronie’s disease in this text), which was named by a French physician, François Gigot de La Peyronie, in 1743 - although he was not the first one to describe this disease (1).

2. METHODOLOGY

A systematic literature search of the Medline database was performed by panel members. The controlled vocabulary of the Medical Subject Headings (MeSH) database uses the specific term ‘penile induration’ for Peyronie’s disease. There is no specific MeSH term for congenital penile curvature. In order to identify relevant articles, the search included the MeSH terms ‘congenital abnormalities’, ‘penis/*abnormalities’ and ‘male’ as well as the free text term ‘congenital penile curvature’. Since this is the first time guidelines on this topic are published, the search includes all relevant articles published up to January 2012. A total of 48 articles were identified for congenital penile curvature while this number was 1200 for Peyronie’s disease. The panel reviewed all these records and selected the articles with the highest evidence available. However, in several subtopics only articles with low levels of evidence were available and discussed accordingly.

2.1 Level of evidence and grade of recommendation

The level of evidence (LE) and grade of recommendation (GR) provided in these guidelines follow the listings in Tables 1 and 2. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (2).

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as ‘upgraded based on panel consensus’. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (3-5).

The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.
Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (2).

2.2 Publication history
The present Penile Curvature guidelines are a new publication that underwent a blinded peer-review process before publication. The standard procedure will be an annual assessment of newly published literature in this field, guiding future updates. An ultra-short reference document is being published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

3. CONGENITAL PENILE CURVATURE

3.1 Epidemiology and physiopathology
Congenital curvature is rare: one study reports an incidence of less than 1% (6) while another suggests it is more common with prevalence rates of 4-10% in the absence of hypospadias (7).

There is no evident cause of congenital penile curvature. A single study analysing the ultrastructure of the tunica albuginea has demonstrated widening and fragmentation of collagen fibres, with complete disappearance of striation and transformation into electron-dense, fibrous, granulated material and elastin accumulation (8).

3.2 Patient evaluation
Taking medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is only useful to document curvature and exclude other pathologies (9). Erectile function is normal but it can be compromised by excessive curvature.

3.3 Treatment
Only androgens have been tried for congenital penile curvature with no improvement in adults (10). Therefore, the treatment of this pathology is only surgical. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section) but can be performed at any time in adults. Notably, most operations for Peyronie's disease have been described first for congenital penile curvature (11). Plication techniques are used almost exclusively with high curvature correction rates (67-97%) (12-14). The use of grafting material in isolated congenital penile curvature is too limited to draw any meaningful conclusions (15).

<table>
<thead>
<tr>
<th>Conclusions on treatment</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is useful for documentation of the curvature and exclusion of other pathologies.</td>
<td>3</td>
</tr>
<tr>
<td>Surgery is the only treatment option which can be performed at any time in adult life. Plication techniques have been used almost exclusively in isolated penile curvature with high curvature correction rates.</td>
<td>3</td>
</tr>
</tbody>
</table>
4. PEYRONIE’S DISEASE

4.1 Epidemiology, physiopathology and natural history

Epidemiological data on Peyronie’s disease are limited. Prevalence rates of 0.4-9% have been published (16-22).

The aetiology of Peyronie’s disease is unknown. However, an insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease (23). Peyronie’s disease starts with an acute inflammatory process. The acute inflammation is characterised by increased proliferation of the tunical fibroblasts, some of which differentiate into myofibroblasts, with excessive deposition of collagen, persistence of fibrin and elastin fragmentation. A prolonged inflammatory response will result in the remodelling of connective tissue into a dense fibrotic plaque (23-25). Penile plaque formation can result in curvature which, if severe, may prevent vaginal intromission. The most commonly associated comorbidities and risk factors are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, erectile dysfunction, smoking, and excessive consumption of alcohol (21,22,26,27). Dupuytren’s contracture is more common in patients with Peyronie’s disease affecting 9-39% of patients (18,28-30) while 4% of patients with Dupuytren’s contracture reported Peyronie’s disease (28). However, it is still unclear if these factors contribute to the pathophysiology of Peyronie’s disease. While the pathogenesis has to be clarified, younger men and Caucasian men are at increased risk for Peyronie’s disease after radical pelvic surgery, e.g. radical prostatectomy (31).

Peyronie’s disease can be a chronic and progressive disease. Two phases of the disease can be distinguished (32). The first is the acute inflammatory phase, which may be associated with pain in the flaccid state or painful erections and manifestation of a ‘soft’ nodule/plaque and penile curvature. The second is the fibrotic phase with the formation of hard palpable plaques that can be calcified, which also result in disease stabilisation. With time, penile curvature is expected to worsen in 30-50% of patients or stabilise in 47-67% of patients, while spontaneous improvement has been reported by only 3-13% of patients (27,33,34). An improvement in penile curvature is more likely to occur in the early stage of the disease, rather than in a later phase when the plaque has been formed and has become densely calcified (35). Pain is present in 35-45% of patients during the early stages of the disease (36). Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease (33,34).

In addition to physiological and functional alteration of the penis, affected men also suffer significant distress. Validated mental health questionnaires have shown that 48% of men with Peyronie’s disease have mild or moderate depression, sufficient to warrant medical evaluation (37).

**Conclusions**

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peyronie’s disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity.</td>
<td>2</td>
</tr>
<tr>
<td>The contribution of associated comorbidities or risk factors (e.g. diabetes, hypertension, lipid abnormalities and Dupuytren’s contracture) to the pathophysiology of Peyronie’s disease is still unclear.</td>
<td>3</td>
</tr>
<tr>
<td>Two phases of the disease can be distinguished. The first phase is the acute inflammatory phase (painful erections, ‘soft’ nodule/plaque), and the second phase is the fibrotic/calcifying phase with formation of hard palpable plaques (disease stabilisation).</td>
<td>2</td>
</tr>
<tr>
<td>Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (30-50%) or stabilisation (47-67%). Pain is usually present during the early stages of the disease but tends to resolve with time in 90% of men.</td>
<td>2</td>
</tr>
</tbody>
</table>

4.2 Patient evaluation

The aim of the initial evaluation is to provide information on the presenting symptoms and their duration (erectile pain, palpable nodules, curvature, length, rigidity, and girth) and erectile function status. It is mandatory to obtain information on the distress provoked by the symptoms and the potential risk factors for erectile dysfunction and Peyronie’s disease. Although a disease-specific questionnaire has been designed to collect data, it is yet a validated instrument suitable for use in clinical practice (38).

Major attention should be given to whether the disease is still active, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have an active disease are those with short symptom
duration, pain during erection, or a recent change in penile curvature. It is often difficult to evaluate the end of the inflammatory phase, but resolution of pain and stability of the curvature for at least 3 months are well-accepted criteria of disease stabilisation and patients referral for surgical intervention when indicated (see Section 4.4.4 Surgical treatment of penile curvature) (33).

The examination should start with a routine genitourinary assessment, which is then extended to the hands and feet for detecting possible Dupuytren’s contracture or Ledderhose scarring of the plantar fascia (34). Penile examination consists generally of a palpable node or plaque. The whole of the penis should be examined. There is currently no standardised approach, but it is recommended to measure the penis dorsally from the base to the tip of the glans while at full stretch (34). Plaque size is measured in the erect penis. However, there is no correlation between plaque size and the degree of curvature (35). Measurement of length during erection is important because it impacts directly on treatment decisions (39). Girth-related changes are often self-reported by the patients.

Erectile function can be assessed using validated instruments such as the International Index of Erectile Function (IIEF) (40). However, it should be noted that IIEF has not been validated specifically in Peyronie’s disease patients. Erectile dysfunction is quite common (> 50%) in patients with Peyronie’s disease but it is important to define if pre-dated or post-dated Peyronie’s disease onset. It is mainly due to penile vascular disease (27,35). The presence of erectile dysfunction may impact on the treatment strategy (41).

Ultrasound (US) measurement of the plaque’s size is inaccurate and operator dependent and it is not recommended in everyday clinical practice (42). Doppler US may be required for the assessment of vascular parameters (41) (see also Section 2.5.3.3 and Table 3 in the EAU Guidelines on Male Sexual Dysfunction). An objective assessment of penile curvature with an erection is mandatory. This can be obtained by a home (self) photograph of a natural erection (preferably) or using a vacuum-assisted erection test or an intracavernosal injection using vasoactive agents (38).

<table>
<thead>
<tr>
<th>Recommendations on the evaluation of Peyronie’s disease</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical and sexual history in patients with Peyronie’s disease must include duration of the disease, penile pain, change of penile deformity, difficulty in vaginal intromission due to deformity, and erectile dysfunction.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Physical examination must include assessment of palpable nodules, penile length, extent of curvature (self-photograph, vacuum-assisted erection test or pharmacological-induced erection) and any other possibly related diseases (Dupuytren’s contracture, Ledderhose disease).</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>US measurement of the plaque’s size is inaccurate and operator dependent. It is not recommended in everyday clinical practice.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Doppler US is required to ascertain vascular parameters associated with erectile dysfunction.</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

### 4.3 Non-operative treatment

Conservative treatment of Peyronie’s disease is primarily focused on patients in the early stage of the disease, when symptoms are present and the plaque is not densely fibrotic or calcified (34,43). In this context, several options have been suggested, including oral pharmacotherapy, intralesion injection therapy and other topical treatments, which will be discussed in this section (Table 1). The role of conservative treatment in men with stable/chronic disease has not yet been adequately defined (32,44). No single drug has been approved by the European Medical Association for the treatment of Peyronie’s disease. Only potassium para-aminobenzoate (Potaba) has been classified as ‘possibly effective’ by the Food and Drug Administration (FDA) for the treatment of Peyronie’s disease.

The results of the studies on conservative treatment for Peyronie’s disease are often contradictory making it difficult to provide recommendations in the everyday, real-life setting. This fact is due to several methodological problems including uncontrolled studies, limited number of patients treated, short term follow-up and different outcome measures (44). Moreover, the efficacy of conservative treatment in distinct patient population in terms of early (inflammatory) or late (fibrotic) phases of the disease is not yet available.
Table 1: Non-operative treatments for Peyronie’s disease

<table>
<thead>
<tr>
<th>Oral treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
</tr>
<tr>
<td>Potassium para-aminobenzoate (Potaba)</td>
</tr>
<tr>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Acetyl esters of carnitine</td>
</tr>
<tr>
<td>Pentoxifylline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intralesional treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>Clostridial collagenase</td>
</tr>
<tr>
<td>Interferon</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Topical treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>Iontophoresis</td>
</tr>
<tr>
<td>Extracorporeal shock wave lithotripsy (SWL)</td>
</tr>
<tr>
<td>Traction devices</td>
</tr>
<tr>
<td>Vacuum devices</td>
</tr>
</tbody>
</table>

4.3.1 Oral treatment

4.3.1.1 Vitamin E
Vitamin E (tocopherol, a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in energy metabolism) is commonly prescribed by the majority of urologists at once or twice daily doses of 400 IU because of its wide availability, low cost and safety (45). Despite the fact that it has been suggested as a potential treatment option in patients with Peyronie’s disease (46), a double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size (47).

4.3.1.2 Potassium para-aminobenzoate (Potaba)
Potassium para-aminobenzoate is thought to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases (48). Its role in the treatment of Peyronie’s disease is due to preliminary studies that reported an improvement in penile curvature, penile plaque size, and penile pain during erection (49). In a prospective double-blinded controlled study in 41 patients with Peyronie’s disease, potassium para-aminobenzoate (12 g/day for 12 months) improved penile pain significantly, but not penile curvature or penile plaque size (50). In another prospective, randomised, double-blind, placebo-controlled in 103 patients with Peyronie’s disease, potassium para-aminobenzoate (4 x 3 g/day for 12 months) decreased penile plaque size significantly, but had no effect on penile curvature or penile pain (51). However, the pre-existing curvature under potassium para-aminobenzoate remained stable, suggesting a protective effect on the deterioration of penile curvature. Treatment-emergent adverse events are nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty in concentration, but no serious adverse events were reported.

4.3.1.3 Tamoxifen
Tamoxifen is a non-steroidal oestrogen receptor antagonist. Its proposed mechanism of action in Peyronie’s disease involves the modulation of TGFβ1 secretion by fibroblasts. Preliminary studies reported that tamoxifen (20 mg twice daily for 3 months) improved penile pain, penile curvature, and reduced the size of penile plaque (52). However, a placebo-controlled, randomised study (in only 25 patients, at late stage of the disease with a mean duration of 20 months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with Peyronie’s disease (53).

4.3.1.4 Colchicine
Colchicine is a medicine often used to treat acute attacks of gout. It has been introduced into the treatment
of Peyronie’s disease on the basis of its anti-inflammatory effect (54). Preliminary results in 24 men showed that half of the men given colchicine (0.6-1.2 mg daily for 3-5 months) found that painful erections and penile curvature improved, while penile plaque decreased or disappeared in 50% (55). In another study in 60 men (colchicine 0.5-1 mg daily for 3-5 months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% (54). Similar results have been reported in another uncontrolled retrospective study in 118 patients. The study concluded that lateral curvature is the most commonly altered deformity, which mostly shifts to the dorsal side of the penis after colchicine therapy (56). Reported treatment-emergent adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation (54).

The combination of vitamin E and colchicine (600 mg/day and 1 mg every 12 hours, respectively) for 6 months in patients with early-stage Peyronie’s disease resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for 6 months (57).

4.3.1.5 Acetyl esters of carnitine

Although the actual mechanism of action of acetyl esters of carnitine in patients with Peyronie’s disease is unknown, it has been suggested that it can reduce intracellular calcium levels in endothelial cells (58). This may eventually suppress fibroblast proliferation and collagen production, thus reducing penile fibrosis. In a randomised, double-blind study in 48 patients with early-stage Peyronie’s disease, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After 3 months, acetyl-L-carnitine was significantly more effective than tamoxifen in pain and curvature reduction and in inhibiting disease progression but not in penile plaque size reduction (both drugs significantly reduced plaque size) (59). Tamoxifen induced significantly more side-effects.

Finally, the combination of intralesional verapamil (10 mg weekly for 10 weeks) with propionyl-l-carnitine (2 g/day for 3 months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for 3 months (60).

4.3.1.6 Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down regulates TGFβ1 and increases fibrinolytic activity (61). Moreover, an increase of nitric oxide levels may be effective in preventing progression of Peyronie’s disease or reversing fibrosis (62). Preliminary data from a case report showed that pentoxifylline (400 mg three times daily for 6 months) improved penile curvature and the findings on US of the plaque (62). In another study in 62 patients with Peyronie’s disease, pentoxifylline treatment for 6 months appeared to stabilise or reduce calcium content in penile plaques (63).

4.3.1.7 Phosphodiesterase type 5 inhibitors

The rationale for the use of phosphodiesterase type 5 inhibitors (PDE5I) in Peyronie’s disease comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in the Peyronie’s disease-like plaque (64). In a retrospective controlled study, daily tadalafil (2.5 mg for 6 months) resulted in statistically significant (p < 0.05) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity (65). Therefore, no recommendation can be given for PDE5I in patients with Peyronie’s disease.

4.3.2 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure.

4.3.2.1 Steroids

Intralesional steroids are thought to act by opposing the inflammatory milieu responsible for Peyronie’s plaque progression via inhibition of phospholipase A2, suppression of the immune response and by decreasing collagen synthesis (66). In small, non-randomised studies, a decrease in penile plaque size and pain resolution was reported (67,68). In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistical significant changes in penile deformity, penile plaque size, and penile pain during erection were reported (69). Adverse effects include tissue atrophy, thinning of the skin and immune suppression (67).
4.3.2.2  Verapamil
The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie’s disease is based on in-vitro data that demonstrated transport of extracellular matrix molecules, which included collagen, fibronectin, and glycosaminoglycans as a calcium-dependent process, along with a concomitant increase in collagenase activity, a modification of the inflammatory response in the early phase of the disorder, and the inhibition of fibroblast proliferation in the plaques (70,71). A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume (72-76). These findings suggested that intralesional verapamil injections (multiple-puncture technique, 10 mg of verapamil diluted to 10 mL, distributed throughout the plaque every 2 weeks for a total of 12 consecutive sessions) could be advocated for the treatment of non-calcified acute phase or chronic plaques to stabilise disease progression or possibly reduce penile deformity, although large scale, placebo-controlled trials have not yet been conducted (72). Side effects are uncommon (4%). Minor side effects include nausea, light-headedness, penile pain, and ecchymosis (72). However, in the only randomised, placebo-controlled study, no statistical significant differences on plaque size, penile curvature, penile pain during erection or plaque ‘softening’ were reported (77). Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study (78).

4.3.2.3  Clostridial collagenase
Clostridial collagenase is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the Peyronie’s disease plaque (79-81). Conversely, clostridial collagenase injections received FDA approval for Dupuytren’s contracture, with a similar mechanism of action (82). In a prospective randomised, placebo-controlled, double-blind study, comparing the effects on plaque size and penile deformity of intralesional purified clostridial collagenase (6,000-14,000 units) and saline placebo, the overall response was 36% while in the placebo arm it was 4% (p < 0.007) (79). Follow-up was only 3 months. The response rates were even higher in patients with smaller plaques and curvature less than 60°. The efficacy of intralesional collagenase injections (three injections of clostridial collagenase 10,000 unit/0.25 cm3 per injection administered over 7-10 days and subsequently administered over 7-10 days at 3 months) has been assessed over a non-placebo-controlled, short-term follow-up study conducted in a small population of men with Peyronie’s disease (81). Although methodologically-biased, this study showed significant decreases from baseline in the deviation angle, in plaque width and in plaque length. The most commonly reported side effects were penile pain, contusions, and ecchymosis.

4.3.2.4  Interferon
Interferon α-2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improved the wound healing process from Peyronie’s disease plaques in-vitro (83). Intralesional injections (5 x 106 units of interferon α-2b in 10 mL saline, two times per week for 12 weeks) significantly improved penile curvature, plaque size and density, and pain compared to placebo (84,85). Side effects include myalgias, arthralgia, sinusitis, fever and flu-like symptoms. They can be effectively treated with non-steroidal anti-inflammatory drugs before interferon injection.

4.3.3  Topical treatments
4.3.3.1  Topical verapamil
In a small, randomised, placebo-controlled study, topical verapamil (gel 15% applied topically to the penile shaft twice daily) significantly improved penile curvature, plaque size, and penile pain (86). Moreover, treatment results significantly improved after 9 months compared to 3 months, showing that a prolonged treatment period may be important. However, there is lack of evidence that topical verapamil applied to the penile shaft results in adequate levels of the active compound within the tunica albuginea (87).

4.3.3.2  Iontophoresis
Iontophoresis (also known as transdermal electromotive drug administration or electromotive drug administration [EMDA]) has been introduced to try and overcome limitations on the local uptake of the drugs themselves. Uncontrolled studies showed promising results in terms of improvement in penile curvature, plaque size and penile pain during erection (88-90). In a randomised, double-blind, controlled study, iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in a statistically significant improvement in penile curvature and plaque size (91). However, in another randomised, double-blind, placebo-controlled study, penile curvature was not statistically improved after iontophoresis with verapamil 10 mg (92). The method is not associated with any significant adverse event.

4.3.3.3  Extracorporeal shock wave lithotripsy
The mechanism of action involved in shock wave lithotripsy (SWL) for Peyronie’s disease is still unclear,
but there are two hypotheses. In the first hypothesis, shock wave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, SWL increases the vascularity of the area by generating heat resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption (93). Most uncontrolled studies failed to show significant improvements in patients with Peyronie’s disease (94-96). In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of SWL, with each session consisting of 2000 focused shock waves, resulted in significant improvement only for penile pain (97).

4.3.3.4 Traction devices
The application of continuous traction in Dupuytren’s contracture increases the activity of degradative enzymes (98). This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen (98). This concept has been applied in an uncontrolled study, including 10 patients with Peyronie’s disease (the FastSize Penile Extender was applied as the only treatment for 2-8 hours/day for 6 months) (99). Penile curvature reduced in all men from 10° to 45°, with an average reduction of 33% (range: 51-34°). The stretched penile length increased to 0.5-2.0 cm. The erect girth increased to 0.5-1.0 cm, with a correction of hinge effect in four out of four men. There were no adverse events, including skin changes, ulcerations, hypoesthesia or diminished rigidity.

However, in another uncontrolled study in 15 patients with Peyronie’s disease and a curvature of less than 50° (the Andropenis Penile Extender was applied for at least 5 hours per day for 6 months). The decrease in penile curvature was minimal (4°, the effect size was not reached), while the mean stretched and flaccid penile length increased by 1.3 and 0.83 cm, respectively, at 6 months (100).

4.3.3.5 Vacuum devices
The application of vacuum devices follows the same principles as traction devices. Their efficacy has been assessed in an uncontrolled study (31 patients completed the study) (101). They used a vacuum device for 10 min twice daily over a 12 week period. Penile pain reduced significantly (p = 0.012). Stretched penile length also increased significantly (p = 0.029) with a mean of 0.5 cm. Reduction of the curvature was reported in 67% of patients while 10% of them had a worsening and 23% had no change. Half of them were satisfied with the outcome and the remaining had their curvature corrected surgically.

<table>
<thead>
<tr>
<th>Recommendations on non-operative treatment for Peyronie’s disease</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Conservative treatment for Peyronie’s disease is primarily aimed at treating patients in the early stage of disease. It is an option in patients not fit for surgery or when surgery is not acceptable to the patient.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.</td>
<td>1b</td>
<td>C</td>
</tr>
<tr>
<td>Intralesional treatment with clostridial collagenase showed significant decreases in the deviation angle, plaque width and plaque length.</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Topical verapamil gel 15% may improve penile curvature and plaque size.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Extracorporeal shock-wave treatment fails to improve penile curvature and plaque size, and should not be used with this intent but may be beneficial for penile pain.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Penile traction devices and vacuum devices may reduce penile deformity and increase penile length.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain. Therefore intralesional treatment with steroids cannot be recommended.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Oral treatment with vitamin E and tamoxifen are not associated with significant reduction in penile curvature, plaque size or penile pain thus should not be used with this intent.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Other oral treatments (acetyl esters of carnitine, pentoxifylline) are not recommended.</td>
<td>3</td>
<td>C</td>
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</table>
4.4 Surgical treatment
Although conservative treatment for Peyronie’s disease should resolve painful erections in most men, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct curvature and allow satisfactory intercourse (102). Surgery is indicated only in patients with stable disease for at least 3 months, although a 6-12 month period has also been suggested (103).

The potential aims and risks of surgery should be discussed with the patient so that he can make an informed decision. Specific issues that should be mentioned during this discussion are the risks of penile shortening, erectile dysfunction, penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery (32).

Two major types of repair may be considered for both congenital penile curvature and Peyronie’s disease: penile shortening and penile lengthening procedures (104). Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures (104). However, recent data suggest that circumcision is not always necessary. In cases where the foreskin is normal pre-operatively, circumcision is unnecessary (105). Finally, in patients with Peyronie’s disease and erectile dysfunction not responding to medical treatments, the surgical correction of the curvature with concomitant penile prosthesis implantation should be considered (106).

Choosing the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of erectile dysfunction (32). Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires for the evaluation of surgical outcomes (102). Data from well-designed prospective studies are scarce, with a low level of evidence. Most data are mainly based on retrospective studies, typically non-comparative and non-randomised, or on expert opinion (32,107).

4.4.1 Penile shortening procedures
In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature (11). Fourteen years later, this technique became a successful treatment option, also for Peyronie’s disease (108). This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature (104). The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients (109). Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of postoperative erectile dysfunction is minimal (104,110). Penile shortening is the most commonly reported outcome of the Nesbit procedure (110). However, shortening of only 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause for post-operative sexual dysfunction (108,111). Patients often perceive the loss of length as greater than it actually is (109,110). It is therefore advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used. Only one modification of the Nesbit procedure has been described (partial thickness shaving instead of conventional excision of a wedge of tunica albuginea) (112).

Plication procedures actually share the same principle as the Nesbit operation but are simpler to perform. Many of them have been described as Nesbit modifications in the older literature. They are based on single or multiple longitudinal incisions on the convex side of the penis closed in a horizontal way, applying the Heineke-Miculicz principle, or plication is performed without making an incision (113-118). Another modification has been described as the ‘16 dot’ technique with minimal tension under local anaesthesia (119). The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure (104). However, a lot of different modifications have been described and the level of evidence is not sufficient to recommend one method over the other.

4.4.2 Penile lengthening procedures
Tunical lengthening procedures entail an incision in the short (concave) side of the tunica to increase the length of this side, creating a tunical defect, which is covered by a graft. However, plaque removal may be associated with high rates of postoperative erectile dysfunction due to venous leak (120).

Devine and Horton introduced dermal grafting in 1974 (121). Since then, a variety of grafting materials and
techniques have been reported (Table 2) (122-136). Unfortunately, the ideal material for grafting has yet to be identified. In addition, grafting procedures are associated with erectile dysfunction rates as high as 25%. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17% re-operation rate (137).

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. Saphenous vein is the most common vein graft used, followed by dorsal penile vein (104). In the latter case, a secondary incision for graft harvesting is avoided. Postoperative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery (122-124). Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements (126).

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at 10 years (138). Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion by 30% (129). In a retrospective telephone interview, 44% of patients with pericardium grafting reported recurrent curvature, although most of them continued to have successful intercourse and were pleased with their outcomes (129,138).

Small intestinal submucosa (SIS, a collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine) has been shown to promote tissue-specific regeneration, and supports the growth of endothelial cells. Small intestinal submucosa acts as a scaffold to promote angiogenesis, host cell migration and differentiation, resulting in tissue structurally and functionally similar to the original. It has been used successfully to repair severe chordee and Peyronie’s disease, without significant contraction or histological alterations, but data are limited (133).

Tunical incision, preferably with grafting, offers an excellent surgical option for men with curvatures over 60º as well as patients with an hourglass deformity and good erectile function that are willing to risk a higher rate of postoperative erectile dysfunction (139). The presence of pre-operative erectile dysfunction, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for functional outcome after grafting surgery (106). Although the risk for penile shortening is significantly less compared to the Nesbit or plication procedures, it is still an issue and patients must be informed accordingly (104). The use of a penile extender device on an 8- to 12-hour daily regimen has been advocated as an effective and safe way to the loss of penile length in patients operated on for Peyronie’s disease (140).

**Table 2: Types of grafts used in Peyronie’s disease surgery**

<table>
<thead>
<tr>
<th>Autologous grafts</th>
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<tbody>
<tr>
<td>Dermis</td>
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<tr>
<td>Vein grafts</td>
</tr>
<tr>
<td>Tunica albuginea</td>
</tr>
<tr>
<td>Tunica vaginalis</td>
</tr>
<tr>
<td>Temporalis fascia</td>
</tr>
<tr>
<td>Buccal mucosa</td>
</tr>
<tr>
<td>Allografts</td>
</tr>
<tr>
<td>Cadaveric pericardium</td>
</tr>
<tr>
<td>Cadaveric fascia lata</td>
</tr>
<tr>
<td>Cadaveric dura matter</td>
</tr>
<tr>
<td>Cadaveric dermis</td>
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<tr>
<td>Xenografts</td>
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<tr>
<td>Porcine small intestinal submucosa</td>
</tr>
<tr>
<td>Bovine pericardium</td>
</tr>
<tr>
<td>Porcine dermis</td>
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<tr>
<td>Synthetic grafts</td>
</tr>
</tbody>
</table>
### 4.4.3 Penile prosthesis

Penile prosthesis implantation is typically reserved for the treatment of Peyronie's disease in patients with erectile dysfunction, especially when they are not responders to phosphodiesterase type 5 inhibitor (PDE5I) (104). Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients (141).

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. In cases of severe deformity, intra-operative ‘modelling’ of the penis over the inflated cylinders (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) has been introduced as an effective treatment (142,143). If there is a residual curvature of less than 30º, no further treatment is recommended, as the prosthesis will act as a tissue expander and will result in complete correction of curvature in a few months (142). While this technique is effective in most patients, a Nesbit/plication procedure or plaque excision/incision and grafting may be required in order to achieve adequate straightening (144-146).

The risk of complications (infection, malformation, etc.) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with ‘modelling’ over the inflated prosthesis (143).

#### Table 3: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) (108,110-136,138,139)

<table>
<thead>
<tr>
<th></th>
<th>Tunical shortening procedures</th>
<th>Tunical lengthening procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nesbit</td>
<td>Plication</td>
</tr>
<tr>
<td>Penile shortening</td>
<td>4.7-30.8%</td>
<td>41-90%</td>
</tr>
<tr>
<td>Penile straightening</td>
<td>79-100%</td>
<td>58-100%</td>
</tr>
<tr>
<td>Persistent or recurrent curvature</td>
<td>4-26.9%</td>
<td>7.7-10.6%</td>
</tr>
<tr>
<td>Post-operative erectile dysfunction</td>
<td>0-13%</td>
<td>0-22.9%</td>
</tr>
<tr>
<td>Penile hypoesthesia</td>
<td>2-21%</td>
<td>0-21.4%</td>
</tr>
<tr>
<td>Technical modifications</td>
<td>1</td>
<td>At least 3</td>
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</table>

#### 4.4.4 Treatment algorithm

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. If the degree of curvature is less than 60º, penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. This is typically the case for congenital penile curvature. If the degree of curvature is over 60º or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible. If there is erectile dysfunction, which is not responding to pharmacological treatment, the best option is the implantation of an inflatable penile prosthesis, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis). The treatment algorithm is presented in Figure 1.
The results of the different surgical approaches are presented in Table 3. It must be emphasised that there are no randomised controlled trials available addressing surgery in Peyronie’s disease. The risk of erectile dysfunction seems to be greater for penile lengthening procedures (32,104). Recurrent curvature implies either failure to wait until the disease has stabilised, a reactivation of the condition following the development of stable disease, or the use of re-absorbable sutures that lose their strength before fibrosis has resulted in acceptable strength of the repair (104). Accordingly, it is recommended that only non-absorbable sutures or slowly reabsorbed absorbable sutures be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, this issue seems to be alleviated by the use of slowly re-absorbed absorbable sutures (110). Penile numbness is a potential risk of any surgical procedure involving mobilisation of the dorsal neurovascular bundle. This will usually be a neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure for a dorsal deformity (104).

**ED = erectile dysfunction.**
8. Surgery is indicated when Peyronie’s disease is stable for at least 3 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms, and intercourse is compromised due to deformity.

9. Penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations must be assessed prior to surgery.

10. Tunical shortening procedures, especially plication techniques are the first treatment options for congenital penile curvature and for Peyronie’s disease with adequate penile length, curvature < 60° and absence of special deformities (hour-glass, hinge).

11. Grafting techniques are the preferred treatment option for patients with Peyronie’s disease with no adequate penile length, curvature > 60° and presence of special deformities (hour-glass, hinge).

12. Penile prosthesis implantation, with or without any additional procedure (modelling, plication or grafting), is recommended in Peyronie’s disease patients with erectile dysfunction not responding to pharmacotherapy.

5. REFERENCES


http://www.ncbi.nlm.nih.gov/pubmed/15017231


6. ABBREVIATIONS USED IN THE TEXT
This list is not comprehensive for the most common abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>ED</td>
<td>erectile dysfunction</td>
</tr>
<tr>
<td>EMDA</td>
<td>transdermal electromotive drug administration or electromotive drug administration</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
</tr>
<tr>
<td>IIEF</td>
<td>international index of erectile function</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
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<td>PDE5I</td>
<td>Phosphodiesterase type 5 inhibitors</td>
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<td>SWL</td>
<td>shock wave lithotripsy</td>
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Conflict of interest
All members of the Penile Curvature Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Male Infertility


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1. METHODOLOGY

1.1 Introduction
The European Association of Urology (EAU) Guidelines Panel on Male Infertility has prepared these guidelines to assist urologists and healthcare professionals from related specialties in the treatment of male infertility.

Urologists are usually the specialists who are initially responsible for assessing the male partner when male infertility is suspected. However, infertility can be a multifactorial condition requiring multidisciplinary involvement. The Male Infertility Guidelines Panel consists of urologists, endocrinologists and gynaecologists with special training in andrology and experience in the diagnosis and treatment of male infertility.

1.2 Data identification
The recommendations provided in the current guidelines are based on a systemic literature search performed by the panel members. MedLine, Embase, and Cochrane databases were searched to identify original and review articles. The controlled vocabulary of the MeSH database was used alongside a free-text protocol, combining “male infertility” with the terms “diagnosis”, “epidemiology”, “investigations”, “treatment”, “spermatogenic failure”, “genetic abnormalities”, “obstruction”, “hypogonadism”, “varicocele”, “cryptorchidism”, “testicular cancer”, “male accessory gland infection”, “idiopathic”, “contraception”, “ejaculatory dysfunction”, and “cryopreservation”.

All articles published between January 2011 (previous update) and October 2012 were considered for review. The expert panel reviewed these records and selected articles with the highest evidence.

1.3 Level of evidence and grade of recommendation
References in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from (1).

It should be noted that when recommendations are graded, the link between the level of evidence (LE) and grade of recommendation (GR) is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (2-4).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.
Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from (1).

1.4  Publication history

The EAU Male Infertility Guidelines were first published in 2001, followed by full-text updates in 2004, 2007, 2010 and 2012. For this 2013 publication, all sections have been revised and limited changes implemented. Starting in 2012, the expert panel instigated a new updating cycle. A quick reference guide presenting the main findings of the Male Infertility Guidelines is also available (Pocket Guidelines), as well as a number of scientific publications in the EAU journal European Urology (5-7). The Male Infertility panel published a separate scientific paper on Vasectomy in 2012 (7). All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/guidelines/online-guidelines/.

1.5  Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/.

1.6  Definition

“Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year”, World Health Organization (WHO) (8).

1.7  Epidemiology and aetiology

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child. Three percent of women remain involuntarily childless, while 6% of parous women are not able to have as many children as they would wish (9). Infertility affects both men and women. In 50% of involuntarily childless couples, a male-infertility-associated factor is found together with abnormal semen parameters. A fertile partner may compensate for the fertility problem of the man and thus infertility usually becomes manifest if both partners have reduced fertility (8). Male fertility can be reduced as a result of (8):

- congenital or acquired urogenital abnormalities;
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g. as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male-infertility-associated factor is found (idiopathic male infertility). These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine laboratory testing. However, semen analysis reveals a decreased number of spermatozoa (oligozoospermia), decreased sperm motility (asthenozoospermia), and many abnormal forms of sperm (teratozoospermia). These sperm abnormalities usually occur together and are called oligo-asthenoteratozoospermia (OAT) syndrome.

Table 3 summarises the main male-infertility-associated factors. Idiopathic male infertility is assumed to be caused by several factors, including endocrine disruption as a result of environmental pollution, reactive oxygen species, or genetic and epigenetic abnormalities.
Table 3: Male infertility causes and associated factors and percentage of distribution in 10,469 patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Unselected patients (n = 12,945)</th>
<th>Azoospermic patients (n = 1,446)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Infertility of known (possible) cause</td>
<td>42.6%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Maldescended testes</td>
<td>8.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Varicocele</td>
<td>14.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Sperm autoantibodies</td>
<td>3.9</td>
<td>-</td>
</tr>
<tr>
<td>Testicular tumour</td>
<td>1.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Others</td>
<td>5.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Idiopathic infertility</td>
<td>30.0</td>
<td>13.3</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>10.1</td>
<td>16.4</td>
</tr>
<tr>
<td>Klinefelter syndrome (47, XXY)</td>
<td>2.6</td>
<td>13.7</td>
</tr>
<tr>
<td>XX male</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Primary hypogonadism of unknown cause</td>
<td>2.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Secondary (hypogonadotrophic) hypogonadism</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Kallmann syndrome</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Idiopathic hypogonadotrophic hypogonadism</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Residual after pituitary surgery</td>
<td>&lt;0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Others</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Late-onset hypogonadism</td>
<td>2.2</td>
<td>-</td>
</tr>
<tr>
<td>Constitutional delay of puberty</td>
<td>1.4</td>
<td>-</td>
</tr>
<tr>
<td>General/systemic disease</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Cryopreservation due to malignant disease</td>
<td>7.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Testicular tumour</td>
<td>5.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>0.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Disturbance of erection/ejaculation</td>
<td>2.4</td>
<td>-</td>
</tr>
<tr>
<td>Obstruction</td>
<td>2.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Cystic fibrosis (CBAVD)</td>
<td>0.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Others</td>
<td>0.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

1.8 Prognostic factors

Prognostic factors for male infertility are:
- duration of infertility;
- primary or secondary infertility;
- results of semen analysis and
- age and fertility status of female partner.

The cumulative pregnancy rate is 27% in infertile couples with 2 years of follow-up and oligozoospermia as the primary cause of infertility (11). Female age is the most important single variable influencing outcome in assisted reproduction (12). Compared to a woman aged 25 years, the fertility potential of a woman aged 35 years is reduced to 50%, to 25% at 38 years, and less than 5% at over 40 years. In many Western countries, women postpone their first pregnancy until after their education and starting a career.
1.9 Recommendations on epidemiology and aetiology

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>To categorise infertility, both partners should be investigated simultaneously.</td>
<td>C</td>
</tr>
<tr>
<td>In the diagnosis and management of male subfertility, the fertility status of the female partner must also be considered, because this might determine the final outcome (9).</td>
<td>B</td>
</tr>
<tr>
<td>The urologist/andrologist should examine any man with fertility problems for urogenital abnormalities. This applies to all men diagnosed with reduced semen quality. A diagnosis is mandatory to start appropriate therapy (drugs, surgery, or assisted reproduction).</td>
<td>C</td>
</tr>
</tbody>
</table>

### References


2. INVESTIGATIONS

2.1 Semen analysis

A medical history and physical examination are standard assessments in all men, including semen analysis. A comprehensive andrological examination is indicated if semen analysis shows abnormalities compared with reference values (Table 4). Important treatment decisions are based on the results of semen analysis, therefore, it is essential that the complete laboratory work-up is standardised. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) (1). It is the consensus that modern spermatology must follow these guidelines.
Table 4: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower reference limit (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume (mL)</td>
<td>1.5 (1.4-1.7)</td>
</tr>
<tr>
<td>Total sperm number (10⁶/ejaculate)</td>
<td>39 (33-46)</td>
</tr>
<tr>
<td>Sperm concentration (10⁶/mL)</td>
<td>15 (12-16)</td>
</tr>
<tr>
<td>Total motility (PR + NP)</td>
<td>40 (38-42)</td>
</tr>
<tr>
<td>Progressive motility (PR, %)</td>
<td>32 (31-34)</td>
</tr>
<tr>
<td>Vitality (live spermatozoa, %)</td>
<td>58 (55-63)</td>
</tr>
<tr>
<td>Sperm morphology (normal forms, %)</td>
<td>4 (3.0-4.0)</td>
</tr>
<tr>
<td>Other consensus threshold values</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>&gt; 7.2</td>
</tr>
<tr>
<td>Peroxidase-positive leukocytes (10⁶/mL)</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Optional investigations</td>
<td></td>
</tr>
<tr>
<td><strong>MAR test (motile spermatozoa with bound particles, %)</strong></td>
<td>&lt; 50</td>
</tr>
<tr>
<td><strong>Immunobead test (motile spermatozoa with bound beads, %)</strong></td>
<td>&lt; 50</td>
</tr>
<tr>
<td><strong>Seminal zinc (μmol/ejaculate)</strong></td>
<td>≥ 2.4</td>
</tr>
<tr>
<td><strong>Seminal fructose (μmol/ejaculate)</strong></td>
<td>≥ 13</td>
</tr>
<tr>
<td><strong>Seminal neutral glucosidase (mU/ejaculate)</strong></td>
<td>≤ 20</td>
</tr>
</tbody>
</table>

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

2.1.1 Frequency of semen analysis

If the results of semen analysis are normal according to WHO criteria, one test is sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- **oligozoospermia**: spermatozoa < 15 million/mL;
- **asthenozoospermia**: < 32% motile spermatozoa;
- **teratozoospermia**: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as OAT syndrome. As in azoospermia, in extreme cases of oligozoospermia (spermatozoa < 1 million/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

2.2 Recommendations for investigations in male infertility

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests.</td>
<td>A</td>
</tr>
<tr>
<td>Assessment of andrological status must consider the suggestions made by WHO for the standardised investigation, diagnosis, and management of the infertile couple; this will result in implementation of evidence-based medicine in this interdisciplinary field of reproductive medicine.</td>
<td>C</td>
</tr>
<tr>
<td>Semen analysis must follow the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.). (1).</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus

2.3 References


3. TESTICULAR DEFICIENCY (PRIMARY SPERMATOGENIC FAILURE)

3.1 Definition
Testicular deficiency as a consequence of primary spermatogenic failure is caused by conditions other than hypothalamic-pituitary disease and obstruction of the male genital tract. It is the commonest form of reduced male fertility. Testicular deficiency may have different aetiologies and present clinically as severe OAT or non-obstructive azoospermia (NOA) (1).

3.2 Aetiology
The causes of testicular deficiency are summarised in Table 5.

Table 5: Causes of testicular deficiency

<table>
<thead>
<tr>
<th>Factors</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Anorchia</td>
</tr>
<tr>
<td></td>
<td>Testicular dysgenesis/cryptorchidism</td>
</tr>
<tr>
<td></td>
<td>Genetic abnormalities (karyotype, Y-chromosome deletions)</td>
</tr>
<tr>
<td>Acquired</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Testicular torsion</td>
</tr>
<tr>
<td></td>
<td>Post-inflammatory forms, particularly mumps orchitis</td>
</tr>
<tr>
<td></td>
<td>Exogenous factors (medications, cytotoxic or anabolic drugs, irradiation, heat)</td>
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<tr>
<td></td>
<td>Systemic diseases (liver cirrhosis, renal failure)</td>
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<td></td>
<td>Testicular tumour</td>
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<tr>
<td></td>
<td>Varicocele</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Surgery that may compromise vascularisation of the testes and lead to testicular atrophy</td>
</tr>
<tr>
<td></td>
<td>Unknown aetiology</td>
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<td></td>
<td>Unknown pathogenesis</td>
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</table>

3.3 Medical history and physical examination
Typical findings from the history and physical examination of a patient with testicular deficiency are:
- cryptorchidism;
- testicular torsion;
- genitourinary infection;
- testicular trauma;
- exposure to environmental toxins;
- gonadotoxic medication including anabolic drugs;
- exposure to radiation or cytotoxic agents;
- testicular cancer;
- absence of testes;
- abnormal secondary sexual characteristics;
- gynaecomastia;
- abnormal testicular volume and/or consistency;
- varicocele.

3.4 Investigations
Routine investigations include semen analysis and hormonal determinations. Other investigations may be required depending on the individual situation.

3.4.1 Semen analysis
In NOA, semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for 15 min and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically (2).

3.4.2 Hormonal determinations
In men with testicular deficiency, hypergonadotrophic hypogonadism is usually present, with high levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), and sometimes low levels of testosterone.
Generally, the levels of FSH correlate with the number of spermatogonia:
- when spermatogonia are absent or markedly diminished, FSH values are usually elevated;
- when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are within the normal range.

However, for an individual patient, FSH levels do not accurately predict the spermatogenesis status (3-5).

### Testicular biopsy

Testicular biopsy can be part of intracytoplasmic sperm injection (ICSI) treatment in patients with clinical evidence of NOA. Testicular sperm extraction (TESE) is the technique of choice and shows excellent repeatability (6-8). Spermatogenesis may be focal, which means that in about 50% of men with NOA, spermatozoa can be found and used for ICSI. Most authors therefore recommend taking several testicular samples (9,10). There is a good correlation between the histology found upon diagnostic biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI (7,11,12). However no threshold value has been found for FSH, inhibin B, or testicular volume and successful sperm harvesting. When there are complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is almost zero.

Microsurgical TESE may increase retrieval rates versus conventional TESE, even though comparative studies are not yet available (13-15). After opening the testis, an enlarged tubule is excised using microscissors or forceps. Then, tubules are minced using mechanical or enzymatic digestion to facilitate sperm search (16). Positive retrievals are reported even in conditions such as Sertoli cell only syndrome type II (1). Percutaneous epididymal sperm aspiration (PESA) results in lower retrieval rates than microsurgical TESE and does not allow histological examination to detect carcinoma in situ (CIS) and testicular malignancies (17,18). PESA may also result in more tubular and vascular damage than TESE (19).

The results of ICSI are worse when using sperm retrieved from men with NOA compared to sperm from ejaculated semen and from men with obstructive azoospermia (OA) (20-24). Birth rates are lower in NOA versus OA (19% vs 28%) (25).
- ICSI results in significantly lower fertilisation and implantation rates (26).
- Miscarriage rates are higher in NOA versus OA (11.5% vs 2.5%) (27).
- Neonatal health in terms of birth parameters, major anomalies and chromosomal aberrations in a large cohort of children born after use of non-ejaculated sperm are comparable to the outcome of children born after use of ejaculated sperm (28).

In OA, there were no significant differences in ICSI results between testicular and epididymal sperm (23). Also, no significant differences have been reported in ICSI results between the use of fresh and frozen-thawed sperm (23,25,26).

### Conclusions and recommendations for testicular deficiency

#### Conclusions

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>Impaired spermatogenesis is often associated with elevated FSH concentration.</td>
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<tr>
<td>Spermatozoa are found in about 50% of patients with NOA.</td>
<td>2a</td>
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<tr>
<td>Pregnancies and live births are eventually obtained in 30-50% of couples with NOA, when spermatozoa have been found in the testicular biopsy.</td>
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</table>

#### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Men who are candidates for sperm retrieval must receive appropriate genetic counselling.</td>
<td>A</td>
</tr>
<tr>
<td>Testicular biopsy is the best procedure to define the histological diagnosis and possibility of finding sperm. Spermatozoa should be cryopreserved for use in ICSI.</td>
<td>A</td>
</tr>
<tr>
<td>For patients with NOA who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.</td>
<td>A</td>
</tr>
<tr>
<td>Men with NOA can be offered TESE with cryopreservation of the spermatozoa to be used for ICSI (28).</td>
<td>A</td>
</tr>
<tr>
<td>To increase the chances of positive sperm retrieval in men with NOA, TESE (single, multiple or microsurgical) should be used rather than PESA.</td>
<td>B</td>
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</tbody>
</table>
3.6 References


4. GENETIC DISORDERS IN INFERTILITY

4.1 Introduction
All urologists working in andrology must have an understanding of genetic abnormalities associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with very low sperm counts can be offered a reasonable chance of paternity, using in vitro fertilisation (IVF), ICSI, and sperm harvesting from the epididymis or the testes in case of azoospermia. However, the spermatozoa of infertile men show an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples, however, screening of chromosomal anomalies in spermatozoa is also feasible and can be performed in selected cases (1,2).

4.2 Chromosomal abnormalities
Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations) (3). In a survey of pooled data from 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% (3). Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 newborn male infants, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities (3). The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with a spermatozoa count < 5 million/mL already show
Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) (5,7). If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

4.2.1 Sex chromosome abnormalities (Klinefelter’s syndrome and variants [47,XXY; 46,XY/47, XXY mosaicism])
Klinefelter’s syndrome is the most common sex chromosome abnormality (3,8). Adult men with Klinefelter’s syndrome have small firm testicles, devoid of germ cells. The phenotype varies from a normally virilised man to one with the stigmata of androgen deficiency, including female hair distribution, scant body hair, and long arms and legs due to late epiphyseal closure. Leydig cell function is commonly impaired in men with Klinefelter’s syndrome (9). Testosterone levels may be normal or low, oestradiol levels normal or elevated, and FSH levels increased. Libido is often normal despite low testosterone levels, but androgen replacement may be needed as the patient ages.

Germ cell presence and sperm production are variable in men with Klinefelter’s mosaicism, 46,XY/47,XXY. There is one case report of declining spermatogenesis in a man with Klinefelter’s syndrome, with the recommendation that early sperm retrieval should be considered (10). Based on sperm fluorescence in situ hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI (11).

The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter’s mosaicism (12,13) and in 1.36-25% of men with somatic karyotype 47,XXY (14-17). In patients with azoospermia, TESE or (micro-TESE) can be proposed as a therapeutic option since spermatozoa can be recovered in about 30% of cases. To date, 49 healthy children have been born using ICSI without preimplantation genetic diagnosis (PGD) and the conception of one 47,XXY foetus has been reported (8). However, a study of ICSI combined with PGD in 113 embryos reported a significant fall in the rate of normal embryos for couples with Klinefelter’s syndrome with respect to controls (54% vs 77.2%) (15). Due to the significant increase of sex chromosomal and autosomal abnormalities in the embryos of Klinefelter’s patients, PGD or amniocentesis analysis should be considered.

Follow-up (possibly every year) of men with Klinefelter’s syndrome is required and androgen replacement therapy should be started when testosterone level is in the range of hypoandrogenism.

4.2.2 Autosomal abnormalities
Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner is known or found to have an autosomal karyotype abnormality.

The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. As with Klinefelter’s syndrome, sperm FISH analysis provide a more accurate risk estimation of affected offspring, however, the diffusion of this genetic test is largely limited by the availability of laboratories able to perform this analysis.

When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed. Embryos with known unbalanced translocation should not be implanted.

4.2.3 Sperm chromosomal abnormalities
Sperm can be examined for their chromosomal constitution using multicolour FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis (3,18-20) and with translocations (21).

Florescence in situ hybridisation analysis of spermatozoa remains a research investigation, although it has been proposed for clinical use to assess spermatozoa from men with defined andrological conditions (18). Techniques are needed to separate populations of genetically abnormal sperm from normal sperm or to safely screen individual spermatozoa before IVF and ICSI.

4.3 Genetic defects
4.3.1 X-linked genetic disorders and male fertility
Each man has only one X-chromosome. An X-linked recessive disorder manifests in males. The defect will be transmitted to daughters, but not to sons.
4.3.2 **Kallmann syndrome**
The most common X-linked disorder in infertility practice is Kallmann syndrome due to mutation in the KALIG-1 gene on Xp22.3 (22). Several newly identified autosomal gene mutations can also cause Kallmann syndrome (23). Patients with Kallmann syndrome have hypogonadotrophic hypogonadism and anosmia, but may also have other clinical features, including facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes, and unilateral renal aplasia.

Spermatogenesis can be relatively easily induced by hormonal treatment (24), therefore, genetic screening prior to therapy is advisable although it is limited by the rarity of specialised genetic laboratories that can offer this genetic test. Treatment with gonadotropins allows natural conception in most cases, even for men with a relatively low sperm count. Thus, identification of the involved gene (X-linked, autosomal dominant or recessive) can help to provide more accurate genetic counselling, that is, risk estimation for transmission to the offspring.

4.3.3 **Mild androgen insensitivity syndrome**
The AR gene is located on the long arm of the X-chromosome. Mutations in the AR gene may result in mild to complete androgen insensitivity (25). The phenotypic features of complete androgen insensitivity syndrome are female external genitalia and absence of pubic hair (Morris syndrome). In partial androgen insensitivity syndrome, several different phenotypes are evident, ranging from predominantly female phenotype through ambiguous genitalia, to predominantly male phenotype with micropenis, perineal hypospadias, and cryptorchidism. The latter phenotype is also termed Reifenstein syndrome. In the above-mentioned severe forms of androgen resistance, there is no risk of transmission because affected men cannot generate their own biological children using the current technologies. Patients with mild androgen insensitivity syndrome have male infertility as their primary or even sole symptom. Disorders of the androgen receptor causing infertility in the absence of any genital abnormality are rare, and only a few mutations have been reported in infertile (26-29) or fertile (30) men.

4.3.4 **Other X-disorders**
An unexpectedly high number of genes with a testis-specific or enriched expression pattern have been identified on the X-chromosome, and in particular, premeiotic genes are over-represented on the X-chromosome compared with autosomal chromosomes (31,32). Nevertheless, to date only a few genes have been screened in relatively small populations and none of them appear relevant for male infertility (33,34). Two recent independent studies showed a significantly higher deletion load on the X-chromosome in men with spermatogenic failure with respect to normozoospermic controls (35,36).

4.4 **Y-chromosome and male infertility**

4.4.1 **Introduction**
The first association between azoospermia and microscopically detectable deletions of the long arm of the Y-chromosome was demonstrated in 1976 (37). With the advent of molecular genetic tools, microdeletions have been defined in three non-overlapping regions termed AZFa, AZFb and AZFc (38). With knowledge of the precise structure of the Y-chromosome in Yq11, it subsequently became clear that the AZFb and AZFc regions overlap and that there is no AZFd region (39). Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia (40). In each AFZ region, there are several spermatogenesis candidate genes (41). Deletions occur en bloc (i.e. removing more than one gene), thus, it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a “fine tuner” of sperm production, and its specific screening is not advised (42).

4.4.2 **Clinical implications of Y microdeletions**
The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure (43).
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men.
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%).
- AZFc deletions are most common (65-70%), followed by deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%).
- Complete removal of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete removal of the AZFb region is associated with spermatogenic rest.
Complete removal of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.

- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer (40).

The specificity and genotype/phenotype correlation reported above means that Y deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval (40).

4.4.2.1 Testing for Y microdeletions

Indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count $< 5 \text{ million/mL}$). Thanks to the European Academy of Andrology (EAA) guidelines (44) and EAA/EMQN (European Molecular Genetics Quality Network) external quality control programme (http://www.emqn.org/emqn/), Yq testing has become more homogeneous and reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting $> 95\%$ of clinically relevant deletions (44). The primers consist of two markers for each region and control markers from the Yp and X-chromosomes. The initial reports of large variability of deletion frequencies are more likely to have been caused by technical problems and unreliable markers rather than be an expression of true ethnic differences.

4.4.2.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted obligatorily to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son have the same microdeletion (45-48), but occasionally the son has a larger one (49). The extent of spermatogenic failure (still in the range of azoo-/oligozoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity for reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes (50,51), indicating a potential risk for any offspring to develop 45,X0 Turner’s syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia. The screening for Y-chromosome microdeletions in patients bearing a mosaic 46,XY/45,X0 karyotype with sexual ambiguity and/or Turner stigmata has shown a relatively high incidence of AZFc deletions (33%) (52). There are data to support the association of Yq microdeletions with an overall Y-chromosomal instability, which leads to the formation of 45,X0 cell lines (53,54). Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal (40,44). This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype.

When ICSI is used in the presence of a Y microdeletion, long-term follow up of any male children is needed with respect to their fertility status and cryopreservation of spermatozoa at a young age can be considered.

4.4.2.3 Y-chromosome: ‘gr/gr’ deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region (55). This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. There was an almost eightfold higher risk of developing oligozoospermia [odds ratio (OR) = 7.9, 95\% confidence interval (CI): 1.8-33.8; \( P < 0.001 \)] in gr/gr deletion carriers in the largest Caucasian study population published to date (56). The frequency of gr/gr deletion in oligozoospermic patients is $\sim 4\%$. According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production (57,58).

However, it is worth noticing that both the frequency of gr/gr deletion and its phenotypic expression vary between different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplogroups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is a still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multicentre study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours (59). However, these data need further confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noticing that partial AZFc deletions (gr/gr and b2/b3) may predispose to complete AZFc deletion in the next generation (60).
4.4.2.4 Conclusions and recommendations

**Conclusions**

<table>
<thead>
<tr>
<th>gr/gr deletion has been confirmed as a significant risk factor for impaired sperm production, whereas further evidence of the prognostic significance of gr/gr and development of a testicular germ cell tumour is needed.</th>
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</table>

A son who inherits a complete AZF deletion will have abnormal spermatogenesis because these deletions have not been reported in normozoospermic men.

<table>
<thead>
<tr>
<th>Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.</th>
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Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling (see below).

<table>
<thead>
<tr>
<th>If complete AZFa or AZFb microdeletions are detected, micro-TESE is not necessary because it is extremely unlikely that any sperm will be found.</th>
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<tr>
<th>If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.</th>
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**4.4.3 Autosomal defects with severe phenotypic abnormalities and infertility**

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (Table 6). Patients with these defects will be well known to doctors, often from childhood. A fertility problem must be managed in the context of the care of the man as a whole and considering the couple’s ability to care for a child.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Phenotype</th>
<th>Genetic basis</th>
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<tbody>
<tr>
<td>Prader-Willi syndrome</td>
<td>Obesity, mental retardation</td>
<td>Deletion of 15q12 on paternally inherited chromosome</td>
</tr>
<tr>
<td>Bardet-Biedle syndrome</td>
<td>Obesity, mental retardation, retinitis pigmentosa, polydactyly</td>
<td>Autosomal recessive 16q21</td>
</tr>
<tr>
<td>Cerebellar ataxia and hyponogonadotropic hypogonadism</td>
<td>Eunuchoidism, disturbances of gait and speech</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Noonan’s syndrome</td>
<td>Short stature, webbed neck, cardiac and pulmonary abnormalities, cryptorchidism</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Muscle wasting, cataract, testicular atrophy</td>
<td>Autosomal dominant 19q13.3</td>
</tr>
<tr>
<td>Dominant polycystic kidney disease</td>
<td>Renal cysts, obstruction from epididymal cysts</td>
<td>Autosomal dominant 16p13.3 and 4q</td>
</tr>
<tr>
<td>5α reductase deficiency</td>
<td>Perineal or scrotal hypospadias, vaginal pouch, immature female phenotype</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

**4.5 Cystic fibrosis mutations and male infertility**

Cystic fibrosis (CF) is a fatal autosomal-recessive disorder. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations and was found in ~2% of men with OA attending a clinic in Edinburgh, UK (61). The incidence in men with OA varies between different countries. The clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be very carefully examined to exclude CBAVD; particularly those with a semen volume < 1.5 mL and pH < 7.0. Approximately 1,500 mutations are listed on the CFTR database (http://www.genet.sickkids.on.ca/cftr/). Many studies have been published of men with CBAVD tested for varying numbers of
mutations. The most frequently found mutations are the ΔF508, R117H and W1282X but their frequency and the presence of other mutations largely depend on the ethnicity of the patient (62,63). Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR (63), it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CAVD patient.

As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a very low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community.

Given that this is a recessive disease, mutations should be found on both alleles of the CFTR gene; however, with the routine panel, in most men with CBAVD, mutation is found in only one copy. In these cases a second step analysis is advised which comprises the direct sequencing of the entire gene. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections).

When a man has CBAVD, it is important to test him and his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider very carefully whether to proceed with ICSI using the husband’s sperm, as the risk of a having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4%.

4.6  Unilateral or bilateral absence/abnormality of the vas and renal anomalies
Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation (64). Consequently, in these subjects CFTR mutation screening is not indicated. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. CFTR gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys.

An abdominal ultrasound should be undertaken both in unilateral and bilateral absence of vas deferens. Findings may range from unilateral absence of the vas with ipsilateral absence of the kidney, to bilateral vessel abnormalities and renal abnormalities, such as pelvic kidney (65).

4.7  Unknown genetic disorders
Considering the high predicted number of genes involved in male gametogenesis, it is likely that most idiopathic forms of spermatogenic disturbances are caused by mutations or polymorphisms in spermatogenesis candidate genes (34). However, despite an intensive search for new genetic factors, no clinically relevant gene mutations or polymorphisms (except those related to the Y-chromosome) have so far been identified (34, 66, 67, and references therein). The introduction of new analytical approaches is likely to provide major advances in this field (68,69).

Intracytoplasmic sperm injection is used to enable men with severely damaged spermatogenesis to father children in situations formerly considered hopeless and where very few spermatozoa can be obtained. This has led to concern that children may be born with a foetal abnormality, because ICSI may enable defective sperm to bypass the selective processes of the female genital tract and egg covering. Alternatively, eggs may be fertilised that would otherwise not be.

Intracytoplasmic sperm injection babies have a higher risk of de novo sex chromosomal aberrations (about a threefold increase compared with natural conceptions) and paternally inherited structural abnormalities. Treatment with assisted reproductive technology was associated with increased risks of cardiovascular, musculoskeletal, urogenital, and gastrointestinal defects and cerebral palsy (70-72).

4.8  DNA fragmentation in spermatozoa
There is increased DNA damage in spermatozoa from men with oligozoospermia. This increase is associated with reduced chances of natural conception and an increase of early pregnancy loss (73,74). DNA damage may improve after varicocele ligation (75,76).

4.9  Genetic counselling and ICSI
The best management is to agree treatment with the couple and provide them with full information on the genetic risks. Initially, the couple should be given full information about the risks to the child to help them decide whether to proceed with ICSI. Where there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy.

When both partners are known to carry defects (e.g., CFTR mutations), there is up to a 50% chance of the child developing a clinical condition. Many clinicians and infertility clinic personnel may consider it unethical to proceed because their duty of care to the future child and the interests of society outweigh the wishes of the individual couple. If there is a conflict that cannot be resolved by agreement, the interests of a future child probably take precedence over the interests of a couple. The couple also need to give
consideration to preimplantation diagnosis and replacement only of normal embryos.

4.10 Conclusions and recommendations for genetic disorders in male infertility

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>New insights into the genetic basis of infertility and the advent of ICSI require a good understanding of genetics by clinicians and the general public.</td>
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<tr>
<td>Diagnostic advances will allow us to identify the genetic basis of more disorders and diagnose known disorders at a lower cost. For some of these disorders, gene therapy might be practical in the future.</td>
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<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa &lt; 10 million/mL) who are seeking fertility treatment by IVF.</td>
<td>B</td>
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<tr>
<td>Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.</td>
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<tr>
<td>All men with Klinefelter’s syndrome need long-term endocrine follow-up and may require androgen replacement therapy.</td>
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</tr>
<tr>
<td>For men with severely damaged spermatogenesis (spermatozoa &lt; 5 million/mL), testing for Yq microdeletions is strongly advised.</td>
<td>A</td>
</tr>
<tr>
<td>When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.</td>
<td>A</td>
</tr>
</tbody>
</table>

4.11 References


34. Nuti F, Krausz C. Gene polymorphisms/mutations relevant to abnormal spermatogenesis. Reprod 
37. Tiepolo L, Zuffardi O. Localization of factors controlling spermatogenesis in the nonfluorescent portion 
   Sep;11:3049-61. 
42. Tyler-Smith C, Krausz C. The will-o'-the-wisp of genetics--hunting for the azoospermia factor gene. 
   Apr;26(2):70-5. 
44. Simoni M, Bakker E, Krausz C. EAA/EMQN best practice guidelines for molecular diagnosis of 
   capable of completing spermatogenesis: fertilization, normal embryonic development and pregnancy 
   occur when retrieved testicular spermatozoa are used for intracytoplasmic sperm injection. Hum 
   oligozoospermic men undergoing intracytoplasmic sperm injection after testicular sperm extraction. 
   the deleted in azoospermia (DAZ) and chromodomain (CDY1) genes from father to son through 
   deletions in the azoospermia factor (AZF) region of the Y-chromosome and the DAZ gene copy 


5. **OBSTRUCTIVE AZOOSPERMIA**

5.1 **Definition**
Obstructive azoospermia OA is the absence of spermatozoa and spermatogenetic cells in semen and post-ejaculate urine due to bilateral obstruction of the seminal ducts. OA is less common than NOA and occurs in 15-20% of men with azoospermia. Common causes of OA are summarised in Table 7.

Men with OA present with normal FSH, normal size testes, and epididymal enlargement. Sometimes, the vas deferens is absent due to congenital factors or previous inguinal or scrotal surgery. Obstruction in primary infertile men is often present at the epididymal level; other sites of obstruction are the ejaculatory ducts and the vas deferens. In 25% of men with a suspected obstruction, no spermatozoa are found in the epididymis during scrotal exploration, indicating an intratesticular obstruction or non-obstructive cause.

Table 7: Classification of OA, on the basis of ductal obstruction due to congenital and acquired causes

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epididymal obstruction</td>
<td>Idiopathic epididymal obstruction</td>
<td>Post-infective (epididymitis)</td>
</tr>
<tr>
<td></td>
<td>Epididymis detached from the tests (e.g., in some maldescended tests)</td>
<td>Post-surgical (epididymal cysts)</td>
</tr>
<tr>
<td>Vas deferens obstruction</td>
<td>Congenital absence of vas deferens</td>
<td>Post-vasectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-surgical (hernia, scrotal surgery)</td>
</tr>
<tr>
<td>Ejaculatory duct obstruction</td>
<td>Prostatic cysts (Mullerian cysts)</td>
<td>Post-surgical (bladder neck surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-infective</td>
</tr>
</tbody>
</table>
5.2 Classification

5.2.1 Intratesticular obstruction
Intratesticular obstruction occurs in 15% of men with OA (1). Congenital forms (dysjunction between rete testis and efferent ductules) are less common than acquired forms, that is, post-inflammatory or post-traumatic obstructions. Acquired forms are often associated with an obstruction of the epididymis and vas deferens.

5.2.2 Epididymal obstruction
Epididymal obstruction or disjunction is the most common cause of OA, affecting 30-67% of azoospermic men with serum FSH level less than twice the upper limit of normal (1-4).

Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases (5). This form is often accompanied by absence of the distal part of the epididymis and seminal vesicle agenesis (see Chapter 4). Other congenital forms of obstruction are rare, for example, disjunction between efferent ductules and the corpus epididymis; agenesis/atrophy of a short part of the epididymis.

Congenital forms of epididymal obstruction include chronic sinopulmonary infections (Young’s syndrome) (6), in which obstruction results from a mechanical blockage due to debris within the proximal epididymal lumen.

Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., chlamydial) epididymitis are most common (7,8) (see Chapter 11). Acute or chronic traumas can result in epididymal damage (9).

Azoospermia caused by surgery may occur after epididymal surgery, for example, cyst removal. Epididymal obstruction secondary to long-lasting distal obstruction must be considered when repairing seminal ducts (10).

5.2.3 Vas deferens obstruction
Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy for sterilisation, with possible subsequent germ cell impairment and fibrosis (11,12). Approximately 2-6% of these men request vasectomy reversal. Of those undergoing vasovasostomy, 5-10% have epididymal blockage as a result of tubule rupture, making epididymovasostomy mandatory (see Chapter 10). Vasal obstruction may also occur after herniotomy (13). Polypropylene mesh herniorrhaphy appears to be able to induce a fibroblastic response that can entrap or obliterate the vas deferens (14).

The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively (15) (see Chapter 4). Distal vas deferens obstruction includes CBAVD and accidental injury to the vas deferens during hernia surgery (16).

5.2.4 Ejaculatory duct obstruction
Ejaculatory duct obstruction is found in 1-3% of cases of OA (1) and is classified as either cystic or post-inflammatory.

Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are medially located in the prostate between the ejaculatory ducts. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst (17), while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst (18).

Paramedian or lateral intraprostatic cysts are Wolffian in origin and rare in clinical practice (19).

Post-inflammatory obstructions of the ejaculatory duct are usually secondary to acute, non-acute, or chronic urethroprostatitis (20).

Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose, and acid pH. The seminal vesicles are usually dilated (anterior-posterior diameter > 15 mm) (20,21).

5.2.5 Functional obstruction of the distal seminal ducts
Functional obstruction of the distal seminal ducts might be attributed to local neuropathy (22). This abnormality is often associated with urodynamic dysfunction because of the vasographic patterns of ampullo-vesicular atony or ejaculatory duct hypertony. Functional obstruction of the distal seminal ducts has been reported in juvenile diabetes and polycystic kidney disease (23); however, no relevant pathology has been found in most cases. Results of semen analysis vary between azoospermia, cryptozoospermia and severe OAT syndrome.

5.3 Diagnosis

5.3.1 Clinical history
Clinical history taking should follow the suggestions for investigation of infertile men (see Chapter 2).
Patients should be asked about:
- haematospermia;
- post-ejaculatory pain;
- previous or present urethritis or prostatitis;
- obstructive or irritative urinary symptoms;
- previous scrotal enlargement or pain or surgery;
- previous inguinal herniorrhaphy or trauma;
- chronic sinopulmonary infection.

5.3.2 Clinical examination
Clinical examination should follow suggestions for investigation of infertile men. The following findings indicate OA:
- at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with OA and concomitant partial testicular failure;
- enlarged and hardened epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas;
- signs of urethritis;
- prostatic abnormalities.

5.3.3 Semen analysis
At least two examinations must be carried out at an interval of 2-3 months, according to the WHO (see Chapter 2). Azoospermia means the inability to detect spermatozoa after centrifugation at ×400 magnification. Careful repeat observation of several smears after semen liquefaction is needed. If no spermatozoa are found in a wet preparation, then aliquots or the whole semen sample should be centrifuged at 3,000 g for 15 min. The pellet must be examined for spermatozoa.

Ejaculatory duct obstruction or CBAVD is suggested by a semen volume < 1.5 mL, acid pH, and low fructose level. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation, because their presence confirms an ejaculatory disorder. Absence of spermatozoa and immature germ cells in semen smears suggest complete proximal or distal seminal duct obstruction.

5.3.4 Hormone levels
Serum FSH levels may be normal, but do not exclude a testicular cause of azoospermia (e.g., spermatogenic arrest). FSH level is normal in 40% of men with primary spermatogenic failure. Inhibin B seems to have a higher predictive value for normal spermatogenesis (4).

5.3.5 Ultrasonography
Scrotal ultrasound is helpful in finding signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and associated CIS of the testis. For patients with a low seminal volume and in whom distal obstruction is suspected, transrectal ultrasound (TRUS) is essential. If possible, TRUS should be performed at high resolution and with high-frequency (> 7 MHz) biplane transducers. Seminal vesicle enlargement (anteroposterior diameter 15 mm) (21) and round, anechoic areas in the seminal vesicle (24) are TRUS anomalies more often associated with ejaculatory duct obstruction; especially when semen volume is < 1.5 mL. Mullerian duct or urogenital sinus/ejaculatory duct cysts (20) and ejaculatory duct calcifications (25) are other known anomalies in OA. TRUS may also be used to aspirate seminal vesicle fluid (26).

Invasive diagnosis, including testicular biopsy, scrotal exploration, and distal seminal duct evaluation, are indicated in patients with OA in whom an acquired obstruction of the seminal ducts is suspected. Explorative and recanalisation surgery should be carried out simultaneously.

5.3.6 Testicular biopsy
In selected cases, testicular biopsy may be indicated to exclude spermatogenic failure. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e., TESE) for cryopreservation and subsequent ICSI, when surgical recanalisation cannot be carried out or has failed. A scoring system for testicular biopsies is provided (e.g., Johnsen Score) (27).

5.4 Treatment
5.4.1 Intratesticular obstruction
Intratesticularly, seminal duct recanalisation is impossible. TESE allows sperm retrieval in nearly all OA patients.
and is therefore recommended. The spermatozoa retrieved may be used immediately for ICSI or should be cryopreserved.

5.4.2 **Epididymal obstruction**
Microsurgical epididymal sperm aspiration (MESA) (28) is indicated in men with CBAVD. TESE and PESA are also viable options for retrieving epididymal sperm from men with OA (29). Retrieved spermatozoa are used for ICSI. Usually, one MESA procedure provides sufficient material for several ICSI cycles (30) and it produces high pregnancy and fertilisation rates (31). In patients with azoospermia due to acquired epididymal obstruction, end-to-end or end-to-side microsurgical epididymovasostomy is recommended, with the preferred technique being microsurgical intussusception epididymovasostomy (32).

Reconstruction may be carried out unilaterally or bilaterally; patency and pregnancy rates are usually higher with bilateral reconstruction. Before microsurgery, it is important to check for full patency downstream of the epididymis. Anatomical recanalisation following surgery may require 3-18 months. Before microsurgery (and in all cases where recanalisation is impossible), epididymal spermatozoa should be aspirated and cryopreserved for use in ICSI in case of surgical failure (30).

Patency rates range between 60% and 87% (33-35) and cumulative pregnancy rates between 10% and 43%. Recanalisation success rates may be adversely affected by preoperative and intra-operative findings (e.g., concomitant abnormal testicular histology, absence of sperm in the spermatic fluid on sectioning the small epididymal tubules, or extensive fibrosis of the epididymis).

5.4.3 **Proximal vas obstruction**
Proximal vas obstruction after vasectomy requires microsurgical vasoepididymostomy (see Chapter 10). Vasoepididymostomy is also required in rare cases of proximal vasal obstructions (e.g., iatrogenic, post-traumatic, or post-inflammatory). The absence of spermatozoa in the intraoperative vas deferens fluid suggests the presence of a secondary epididymal obstruction; especially if the seminal fluid of the proximal vas has a thick “toothpaste” appearance. Microsurgical tubulovasostomy is then indicated.

5.4.4 **Distal vas deferens obstruction**
It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy (16). In these cases, proximal vas deferens sperm aspiration (37) or TESE/MESA can be used for cryopreservation for future ICSI. In large unilateral vas deferens defects associated with contralateral testicular atrophy, the vas deferens of the atrophic testis can be used for a crossover vasoepididymostomy or tubulovasostomy.

5.4.5 **Ejaculatory duct obstruction**
The treatment of ejaculatory duct obstruction depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) (20,38) can be used in large post-inflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst. Resection may remove part of the verumontanum.

In cases of obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst is required (20). Intraoperative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the vas deferens can help to document opening of the ducts. The limited success rate of surgical treatment of ejaculatory duct obstruction in terms of spontaneous pregnancies should be weighed against sperm aspiration and ICSI.

Complications following TURED include retrograde ejaculation due to bladder neck injury and urine reflux into the ejaculatory ducts, seminal vesicles, and vasa (causing poor sperm motility, semen acid pH, and epididymitis). The alternatives to TURED are MESA, TESE, proximal vas deferens sperm aspiration, seminal vesicle ultrasonically guided aspiration, and direct cyst aspiration.

In cases of functional obstruction of the distal seminal ducts, TURED often fails to improve sperm output. Spermatozoa can then be retrieved by antegrade seminal tract washout (38). Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.
5.5 Conclusions and recommendation for obstructive azoospermia

Conclusions

Obstructive lesions of the seminal tract should be suspected in azoospermic or severely oligozoospermic patients with normal-sized testes and normal endocrine parameters.

Recommendation

In azoospermia caused by epididymal obstruction, standard procedures include vasovasostomy and tubulovasostomy.

Sperm retrieval techniques, such as MESA, TESE, and PESA, can be used additionally. These methods should be used only when cryostorage of the material obtained is available.

In azoospermia caused by epididymal obstruction, scrotal exploration with microsurgical epididymal sperm aspiration and cryopreservation of spermatozoa should be performed. Microsurgical reconstruction should be performed, if applicable. Results of reconstructive microsurgery depend on the cause and location of the obstruction, and the surgeon’s expertise.

5.6 References


6. VARICOCELE

6.1 Introduction
Varicocele is a common abnormality (see Chapter 2) with the following andrological implications:
• failure of ipsilateral testicular growth and development;
• symptoms of pain and discomfort;
• male infertility.

6.2 Classification
The following classification of varicocele (1,2) is useful in clinical practice:
• subclinical: not palpable or visible at rest or during Valsava manoeuvre, but can be shown by special tests (Doppler ultrasound studies) (3);
• grade 1: palpable during Valsava manoeuvre, but not otherwise;
• grade 2: palpable at rest, but not visible;
• grade 3: visible and palpable at rest.

6.3 Diagnosis
The diagnosis of varicocele is made by clinical examination and should be confirmed by colour Doppler analysis (2). In centres where treatment is carried out by antegrade or retrograde sclerotherapy or embolisation, diagnosis is additionally confirmed by X-ray.

6.4 Basic considerations
6.4.1 Varicocele and fertility
Varicocele is a physical abnormality present in 11.7% of adult men and in 25.4% of men with abnormal semen analysis (4). The exact association between reduced male fertility and varicocele is unknown, but a recent meta-analysis showed that semen improvement is usually observed after surgical correction (5). Current information fits with the hypothesis that in some men the presence of varicocele is associated with progressive testicular damage from adolescence onwards, and consequent reduction in fertility. Varicocele is associated with increased sperm DNA damage, and this sperm pathology may be secondary to varicocele-mediated oxidative stress. Varicocelectomy can reverse this sperm DNA damage, as shown in several studies (6).

6.4.2 Varicocelectomy
Varicocele repair has been a subject of debate for several decades: controversy exists as to whether varicocele repair results in more spontaneous pregnancies as compared to observation. The 2009 Cochrane Database review concluded that there is no evidence that treatment of varicocele improves a couples’ chance of conception (7). This meta-analysis was criticised for including several heterogeneous studies, men with normal semen analysis, and men with a subclinical varicocele (8). In three RCTs repair of a subclinical varicocele was found to be ineffective (9-11). Also, studies of men with a varicocele and normal semen analysis have shown no clear benefit of treatment over observation (12,13).

The duration of infertility also seems to be important. In a recent study it was shown that couples with infertility of > 2 years duration had a significantly higher pregnancy rate after varicocelectomy compared to couples with an uncorrected varicocele. In couples with a shorter duration of infertility, such a difference was not observed (14).

In a recent meta-analysis of four RCTs of varicocelectomy in men with a clinical varicocele,
oligospermia and otherwise unexplained infertility, there was a trend in favour of surgical correction (15). The combined OR was 2.23 (95% CI, 0.86-5.78; \( P = 0.091 \)), indicating that varicocelectomy was moderately superior to observation, but the effect was not statistically significant.

There is a need for a large, properly conducted RCT of varicocele treatment in men with abnormal semen from couples with otherwise unexplained subfertility (16). Although treatment of varicocele in infertile men may be effective, in adolescents there is a significant risk of overtreatment: most adolescents with a varicocele will have no problem achieving pregnancy later in life (17).

### 6.5 Treatment

Several treatments are available for varicocele (Table 9). The type of intervention chosen depends mainly on the experience of the therapist. Although laparoscopic varicocelectomy is feasible, it must be justified in terms of cost-effectiveness.

**Table 9: Recurrence and complication rates associated with treatments for varicocele**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Ref.</th>
<th>Recurrence/persistence</th>
<th>Complication rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antegrade sclerotherapy</td>
<td>18</td>
<td>9</td>
<td>Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema</td>
</tr>
<tr>
<td>Retrograde sclerotherapy</td>
<td>19</td>
<td>9.8</td>
<td>Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation</td>
</tr>
<tr>
<td>Retrograde embolisation</td>
<td>20,21</td>
<td>3.8-10</td>
<td>Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g., reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction</td>
</tr>
<tr>
<td>Open operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrotal operation</td>
<td></td>
<td>-</td>
<td>Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, postoperative hydrocele</td>
</tr>
<tr>
<td>Inguinal approach</td>
<td>22</td>
<td>13.3</td>
<td>Possibility of missing out a branch of testicular vein</td>
</tr>
<tr>
<td>High ligation</td>
<td>23</td>
<td>29</td>
<td>5-10% incidence of hydrocele (&lt; 1%)</td>
</tr>
<tr>
<td>Microsurgical inguinal or subinguinal</td>
<td>24,25</td>
<td>0.8-4</td>
<td>Postoperative hydrocele arterial injury, scrotal haematoma</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>26,27</td>
<td>3-7</td>
<td>Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis; bleeding; postoperative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum); pneumoscrotum: wound infection</td>
</tr>
</tbody>
</table>

### 6.6 Conclusions and recommendations for varicocele

**Conclusions**

Current information supports the hypothesis that the presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.

Although the treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment.

Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination.</td>
<td>B</td>
</tr>
<tr>
<td>No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended (15-17).</td>
<td>A</td>
</tr>
<tr>
<td>Varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of ≥ 2 years and otherwise unexplained infertility in the couple.</td>
<td>A</td>
</tr>
</tbody>
</table>

**Recommendations**

Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination.

No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended (15-17).

Varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of ≥ 2 years and otherwise unexplained infertility in the couple.
References


7. HYPOGONADISM

7.1 Introduction

Hypogonadism is characterised by impaired testicular function, which may affect spermatogenesis and/or testosterone synthesis. The symptoms of hypogonadism depend on the degree of androgen deficiency and if the condition develops before or after pubertal development of the secondary sex characteristics. The symptoms and signs of hypoandrogenism presenting before and after completion of puberty are provided in Table 10.

Table 10: Symptoms and signs of hypogonadism appearing before and after completion of puberty*

<table>
<thead>
<tr>
<th>Affected organ/function</th>
<th>Before completed puberty</th>
<th>After completed puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>No voice mutation</td>
<td>No voice mutation</td>
</tr>
<tr>
<td>Hair</td>
<td>Horizontal pubic hairline</td>
<td>Diminished secondary body hair</td>
</tr>
<tr>
<td></td>
<td>Straight frontal hairline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diminished beard growth</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Absent sebum production</td>
<td>Decreased sebum production</td>
</tr>
<tr>
<td></td>
<td>Lack of acne</td>
<td>Lack of acne</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td>Pallor</td>
</tr>
<tr>
<td></td>
<td>Skin wrinkling</td>
<td>Skin wrinkling</td>
</tr>
<tr>
<td>Bones</td>
<td>Eunuchoid tall stature</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Mild anaemia</td>
<td>Mild anaemia</td>
</tr>
<tr>
<td>Muscles</td>
<td>Underdeveloped</td>
<td>Hypotrophy</td>
</tr>
<tr>
<td>Prostate</td>
<td>Underdeveloped</td>
<td>Hypotrophy</td>
</tr>
<tr>
<td>Penis</td>
<td>Infantile</td>
<td>No change of size</td>
</tr>
<tr>
<td>Testes</td>
<td>Possibly maldescended testes</td>
<td>Decrease of testicular volume</td>
</tr>
<tr>
<td></td>
<td>Small volume</td>
<td></td>
</tr>
<tr>
<td>Spermatogenesis</td>
<td>Not initiated</td>
<td>Involuted</td>
</tr>
<tr>
<td>Libido and potency</td>
<td>Not developed</td>
<td>Loss</td>
</tr>
</tbody>
</table>

*Modified from Nieschlag et al. (1).
The aetiological and pathogenetic mechanisms of male hypogonadism can be divided into three main
categories:
1. Primary (hypergonadotrophic) hypogonadism due to testicular failure.
2. Secondary (hypogonadotrophic) hypogonadism caused by insufficient gonadotropin-releasing
   hormone (GnRH) and/or gonadotropin (FSH, LH) secretion.
3. Androgen insensitivity (end-organ resistance).
The most common conditions within these three categories are given in Table 11 (see also Chapter 4).

Table 11: Disorders associated with male hypogonadism*

<table>
<thead>
<tr>
<th>Primary (hypergonadotrophic) hypogonadism (testicular failure)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorchia</td>
</tr>
<tr>
<td>Maldeveloped testes</td>
</tr>
<tr>
<td>Klinefelter's syndrome</td>
</tr>
<tr>
<td>Y-chromosome microdeletions</td>
</tr>
<tr>
<td>Numerical and structural chromosomal anomalies</td>
</tr>
<tr>
<td>Trauma, testicular torsion, orchitis</td>
</tr>
<tr>
<td>Iatrogenic (surgery, medications, irradiation, or cytostatic drugs)</td>
</tr>
<tr>
<td>Exogenous factors (toxins, heat, or occupational hazards)</td>
</tr>
<tr>
<td>Systemic diseases (liver cirrhosis, or renal failure)</td>
</tr>
<tr>
<td>Testicular tumour</td>
</tr>
<tr>
<td>Varicocele</td>
</tr>
<tr>
<td>Idiopathic (e.g., late-onset hypogonadism)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary (hypogonadotrophic) hypogonadism (secondary testicular failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>• Idiopathic hypogonadotrophic hypogonadism</td>
</tr>
<tr>
<td>• Normosmic</td>
</tr>
<tr>
<td>• Hiposmic/anosmic (Kallmann syndrome)</td>
</tr>
<tr>
<td>Acquired (tumours in the following regions)</td>
</tr>
<tr>
<td>• Diencephalon (cortiopharyngioma or meningoia)</td>
</tr>
<tr>
<td>• Hypothalamus or pituitary</td>
</tr>
<tr>
<td>Empty sella</td>
</tr>
<tr>
<td>Granulomatous illnesses</td>
</tr>
<tr>
<td>Fractures of the skull base</td>
</tr>
<tr>
<td>Ischaemic or haemorrhagic lesions in hypothalamic area</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
</tr>
<tr>
<td>Drugs/anabolic steroids, radiotherapy</td>
</tr>
<tr>
<td>Target organ resistance to androgens</td>
</tr>
<tr>
<td>Testicular feminisation</td>
</tr>
<tr>
<td>Reifenstein syndrome</td>
</tr>
</tbody>
</table>

*Modified from Nieschlag et al. (1).

7.2 Hypogonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Idiopathic hypogonadotrophic hypogonadism (IHH) is characterised by low levels of gonadotropins and sex
steroid in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis (2).
IHH may be an isolated condition or may be associated with anosmia/hyposmia (Kallmann syndrome). Genetic
factors causing a deficit of gonadotropins may act at the hypothalamic or pituitary level.
Mutations in candidate genes (X-linked or autosomal) can be found in ~30% of congenital cases (2) and
should be screened prior to assisted reproduction (3).
Acquired hypogonadotrophic hypogonadism can be caused by some drugs, hormones, anabolic
steroids, or tumours. A suspected tumour requires imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] of the sella region and a complete endocrine work-up.
Failure of hormonal regulation can easily be determined (4). Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion as a result of decreased secretion of FSH and LH. After having excluded secondary forms (drugs, hormones, or tumours), the therapy of choice depends on whether the goal is to achieve normal androgen levels or fertility.
Normal androgen levels and subsequent development of secondary sex characteristics (in cases of
onset of hypogonadism before puberty) and a eugonadal state can be achieved by androgen replacement
alone. However, stimulation of sperm production requires treatment with human chorionic gonadotropin (hCG) combined with recombinant FSH or urinary FSH or human menopausal gonadotropins (HMGs). In the rare case of “fertile eunuchs”, who have sufficient production of FSH but not LH, treatment with hCG alone may be sufficient to stimulate sperm production and achieve normal testosterone levels (5).

If hypogonadotrophic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is pulsatile GnRH (6). In patients who have developed hypogonadism before puberty and have not been treated with gonadotropins or GnRH, 1-2 years of therapy may be needed to achieve sperm production. Once pregnancy has been established, patients can return to testosterone substitution.

### 7.3 Hypergonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Many conditions in men are associated with hypergonadotrophic hypogonadism (Table 11, see also Chapter 4). Most conditions listed in Table 11 only affect the reproductive function of the testes so that only FSH level is elevated. However, it has been reported that men with infertility are at higher risk for developing impaired Leydig cell function (7), while men with Klinefelter’s syndrome often show high LH values and develop hypoandrogenism with ageing (8). A decrease in testosterone blood concentrations after extensive testicular biopsy in the context of TESE/ICSI has been observed, raising questions about the need for long-term endocrine follow-up of these patients (9).

Hypogonadism affecting both reproductive and endocrine functions of the testes occurs after treatment with GnRH analogues or surgical castration for prostatic cancer (10).

Laboratory diagnosis of hypergonadotrophic hypogonadism is based on a high level of FSH, decreased serum testosterone, and increased LH levels (3). Testosterone levels should be evaluated in view of the serum concentration of sex hormone binding globulin (SHBG). Based on levels of total testosterone, albumin and SHBG, free and bioavailable testosterone can be calculated (http://www.issam.ch/freetesto.htm).

Due to diurnal variation, blood samples for testosterone assessment should be taken before 10.00 h. The existing guidelines for androgen replacement are based on presence of symptoms of hypogonadism and total testosterone levels. There is general agreement that a total testosterone level > 12 nmol/L (350 ng/dL) does not require substitution. Similarly, based on the data of younger men, there is consensus that patients with serum total testosterone levels < 8 nmol/L (230 ng/dL) will usually benefit from testosterone treatment. For the group with serum total testosterone level between 8 and 12 nmol/L (in repeated samples), a 3-6-month trial period with testosterone supplementation can be considered. Generally, androgen replacement should not be given to men not presenting with symptoms of hypogonadism.

Testosterone suppresses pituitary production of LH and FSH, therefore, replacement therapy should not be given for infertility.

In obese men, decision-making may be helped by measuring total testosterone with SHBG to calculate free testosterone or measurement of free testosterone by equilibrium dialysis (11). Injectable, oral and transdermal testosterone preparations are available for clinical use (3). The best preparation to use is one that maintains serum testosterone levels within the physiological concentration (11-13). See also EAU Guidelines on Hypogonadism (14).

### 7.4 Conclusion and recommendation for hypogonadism

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is generally agreed that patients with primary or secondary hypogonadism associated with hypoandrogenism should receive testosterone substitution therapy.</td>
<td>1b</td>
</tr>
</tbody>
</table>

**Recommendation**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism (4).</td>
<td>A*</td>
</tr>
<tr>
<td>Testosterone replacement is strictly contraindicated for the treatment of male infertility (13).</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus

### 7.5 References

8. CRYPTORCHIDISM

8.1 Introduction
Cryptorchidism is the most common congenital abnormality of the male genitalia and is found in 2-5% of newborn boys, depending on gestational age (cryptorchidism occurs more often in premature boys) and age after birth. At the age of 3 months, the incidence of cryptorchidism falls spontaneously to 1-2%. Approximately 20% of undescended testes are non-palpable and may be located within the abdominal cavity.

The aetiology of cryptorchidism is multifactorial, involving disrupted endocrine regulation and several gene defects. The normal descent of the testes requires a normal hypothalamic-pituitary-gonadal axis. Endocrine disruption in early pregnancy can potentially affect gonadal development and normal descent of the testes; however, most boys with maldescended testes show no endocrine abnormalities after birth. It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig cell dysfunction (1).

8.2 Incidence of cryptorchidism
The Caucasian population has a threefold higher incidence of cryptorchidism compared to African-Americans. Even between Caucasians, there are significant differences in the risk of cryptorchidism, for example, it is significantly more common among Danish than Finnish newborns (2). Premature babies have a much higher
incidence of cryptorchidism than full-term babies. In a British study, the incidence of cryptorchidism was 2.7% in > 3,000 boys weighing > 2.5 kg and 21% in premature boys weighing < 2.5 kg. At the age of 3 months, spontaneous descent occurred in most boys, and the incidence of cryptorchidism fell to 0.9% and 1.7%, in the > 2.5 kg and < 2.5 kg group, respectively (3).

8.3  Testicular descent and maldescent
The process of testicular descent has two distinct phases: transabdominal and inguinal. During transabdominal descent, development of the gubernaculum and genitoinguinal ligament plays an important role. The anti-Mullerian hormone regulates transabdominal descent of the testes. Induction of the gubernaculum depends on a functional Insl3 gene in mice (4). This gene is expressed in Leydig cells and its targeted deletion causes bilateral cryptorchidism with free-moving testes and genital ducts (5). Androgens play an important role in both phases of testicular descent, whereas other gene families, for example, the homeobox (HOX) and GREAT/RXFP2 genes (G-protein-coupled receptor affecting testis descent), are important in the development of genital organs and may be associated with testicular maldescent (6,7).

8.4  Hormonal control of testicular descent
Maldescent can be caused by two hormonal factors: hypogonadism and androgen insensitivity. The increasing incidence of reproductive abnormalities in male humans can be explained by increased oestrogen exposure during gestation (8). Some pesticides and synthetic chemicals act as hormonal modulators, often possessing oestrogenic activity (xeno-oestrogens) (9). The oestrogenic and antiandrogenic properties of these chemicals may cause hypospadias, cryptorchidism, reduced sperm density, and an increased incidence of testicular tumours in animal models, via receptor-mediated mechanisms or direct toxic effects associated with Leydig cell dysfunction (10).

8.5  Pathophysiological effects in maldescended testes

8.5.1  Degeneration of germ cells
The degeneration of germ cells in maldescended testes is apparent after the first year of life. Degenerative changes vary, depending on the position of the testis (11). During the second year, the number of germ cells declines. In 10-45% of affected patients, the complete loss of germ cells can be detected. Early treatment is therefore recommended to conserve spermatogenesis; especially in bilateral cases. Surgical treatment is the most effective and reliable method of bringing testes into the scrotum. Hormone treatment with hCG has been used widely in the past, but it has now been abolished because of increased germ cell apoptosis after treatment (12).

8.5.2  Relationship with fertility
Semen parameters are often impaired in men with a history of cryptorchidism (13). Surgical treatment during the first or second year of life may have a positive effect on subsequent fertility (14). However, there is no definitive proof of the protective effect of early orchidopexy. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%).

In men with unilateral cryptorchidism, paternity is independent of age at orchidopexy and preoperative testicular location and size (15). However, a history of unilateral cryptorchidism may result in reduced fertility potential and therefore a longer time to achieve pregnancy.

In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity is only 35-53%. In cases of bilateral cryptorchidism and azoospermia, orchidopexy performed even in adult life might lead to the appearance of spermatozoa in the ejaculate (16).

8.5.3  Germ cell tumours
Cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcification and intratubular germ cell neoplasia of unclassified type (ITGCNU); formerly CIS of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism (17). The risk of a germ cell tumour (GCT) is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour (17). Orchidopexy performed before the age of puberty has been reported to decrease the risk of testicular cancer (18). However, this and other similar reports are based on retrospective data and do not exclude the possibility that boys undergoing early and late orchidopexy represent different pathogenetic groups of testicular maldescent.

8.6  Treatment of undescended testes

8.6.1  Hormonal treatment
Human chorionic gonadotropin or GnRH has been used widely in the past to treat cryptorchidism. Although
15-20% of retained testes descend during hormonal treatment, one-fifth of these reascend later. Also, treatment with hCG may be harmful to future spermatogenesis by increasing the apoptosis of germ cells (12), which is why hormonal treatment is no longer recommended.

8.6.2 Surgical treatment

The success rate of surgical treatment for undescended testes is 70-90% (19). If the spermatic cords or the spermatic vessels are too short to allow proper mobilisation of the testis into the scrotum, a staged orchidopexy (Fowler-Stephenson procedure) can be performed, using open surgery, laparoscopy, or microsurgery.

The optimal age for performing orchidopexy is still debated. Some retrospective studies have indicated that early treatment (during the first 2 years of life) has a beneficial effect on preserving future fertility (20), whereas a recent randomised study showed that surgery at 9 months resulted in a partial catch-up of testicular growth until at least age 4 years versus surgery at 3 years (21). The results clearly indicate that early surgery has a beneficial effect on testicular growth. Testicular volume is an approximate indirect measure of spermatogenic activity, therefore, it is possible that orchidopexy at an early age might improve future spermatogenesis.

A biopsy at the time of orchidopexy (see Section 8.5.3) can reveal (ITGCNU), which can be removed, thereby preventing development of a malignant tumour. If not corrected by adulthood, an undescended testis should not be removed because it still produces testosterone. Furthermore, as indicated above, correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men (16).

Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the postoperative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Postoperative atrophy in staged orchidopexy has been reported in up to 40% of patients (19).

8.7 Conclusions and recommendations for cryptorchidism

Conclusions

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Cryptorchidism is multifactorial in origin and can be caused by genetic</td>
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<tr>
<td>factors and endocrine disruption early in pregnancy.</td>
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<td>Cryptorchidism is often associated with testicular dysgenesis and is a</td>
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<tr>
<td>risk factor for infertility and GCT.</td>
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<tr>
<td>Whether early surgical intervention can prevent germ cell loss is still</td>
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<tr>
<td>debatable, but in a randomised study it improved testicular growth in</td>
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<tr>
<td>boys treated at the age of 9 months compared to those aged 3 years at</td>
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<td>the time of orchidopexy.</td>
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<tr>
<td>Paternity in men with unilateral cryptorchidism is almost equal to that</td>
<td>3</td>
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<tr>
<td>in men without cryptorchidism.</td>
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<tr>
<td>Bilateral cryptorchidism significantly reduces the likelihood of</td>
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<tr>
<td>paternity.</td>
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</table>

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Hormonal treatment of cryptorchidism in adults is not recommended.</td>
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</tr>
<tr>
<td>Early orchidopexy (6-12 months of age) might be beneficial for testicular</td>
<td></td>
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<tr>
<td>development in adulthood.</td>
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<tr>
<td>If undescended testes are corrected in adulthood, testicular biopsy for</td>
<td>B</td>
</tr>
<tr>
<td>detection of ITGCNU (formerly CIS) is recommended at the time of orchidopexy.</td>
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</table>

8.8 References


9. IDIOPATHIC MALE INFERTILITY

9.1 Introduction
No demonstrable cause of infertility is found in at least 44% of infertile men (1).

9.2 Empirical treatments
A wide variety of empirical drug treatments of idiopathic male infertility have been used; however, there is little scientific evidence for an empirical approach (2). Androgens, hCG/HMG, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Follicle-stimulating hormone (3) might be beneficial in a selection of patients (3). A Cochrane analysis showed that men taking oral antioxidants had an associated significant increase in live birth rate (pooled OR = 4.85; 95% CI: 1.92-12.24; P = 0.0008; I(2) = 0%) when compared with men taking the control treatment. No studies have reported harmful side effects from antioxidant therapy. The evidence suggests that antioxidant supplementation in subfertile men may improve the outcomes of live birth and pregnancy rate for subfertile couples undergoing assisted reproduction technique (ART) cycles. Further head-to-head comparisons are necessary to identify the superiority of one antioxidant over another (4).

Recommendation GR
Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism.

9.3 References

10. MALE CONTRACEPTION

10.1 Introduction
“Male contribution to contraception” is a more accurate phrase than “male contraception”, because men do not conceive. Development of male contraceptive methods is important because up to 40% of women have an unmet need for family planning, with approximately 80 million women every year having unintended or unwanted pregnancies (1).

Three of the four methods of male contraception have been in use for hundreds of years (i.e., condoms, periodic abstinence, and withdrawal). The typical first-year failure rates of traditional male methods are high (withdrawal 19%, periodic abstinence 20%, and condoms 3-14%) compared to the failure rates of 0.1-3% for modern reversible female methods (2). For men to take more responsibility for family planning, male contraceptive methods must be acceptable, cheap, reversible, and effective.

Research is attempting to (3):
• Prevent sperm production by using exogenic androgens, progestogen, and GnRH formulations in various combinations.
• Interfere with the ability of sperm to mature and fertilise, by using an epididymal approach to create a hostile environment for sperm.
• Produce better barrier methods (e.g., polyurethane condoms can be used by those with latex allergy, although they have higher breakage rates) (4).
• Produce an antisperm contraceptive vaccine (5).
• Inhibit sperm-egg interactions.

These approaches remain experimental. The method nearest to being generally available clinically is hormonal male contraception, which is based on the suppression of gonadotropins and testosterone substitution to maintain male sexual function and bone mineralization, and to prevent muscle wasting (6). Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/ progestin combinations, testosterone with GnRH analogues, and selective androgen- and progestin-receptor modulators. There are racial differences in the response to androgens alone. However, a combination of testosterone with progesterin results in complete suppression of spermatogenesis in all races, and provides contraceptive efficacy equivalent to female hormonal methods (7). Phase III clinical trials of depot preparations of androgen/progestin combinations are in progress.

10.2 Vasectomy
Vasectomy is an effective method of permanent male surgical sterilisation (8). Extensive guidelines on vasectomy were published by the EAU in 2012 (9). Before vasectomy, the couple should be fully informed about the benefits and risks, especially as an Australian telephone survey found that 9.2% of respondents regretted having a vasectomy (10).

10.2.1 Surgical techniques
Various techniques are available for vasectomy. The least invasive approach is no-scalpel vasectomy (11), which is also associated with a low rate of complications (12). The most effective occlusion technique is cauterisation of the lumen of the vas deferens and fascial interposition (13-15). Most techniques can be carried out safely under local anaesthesia in an outpatient clinic.

10.2.2 Complications
Vasectomy does not significantly alter spermatogenesis and Leydig cell function. The volume of ejaculate remains unchanged. Potential systemic effects of vasectomy, including atherosclerosis, have not been proven, and there is no evidence of a significant increase in any systemic disease after vasectomy. An increased rate of prostate cancer in men who underwent vasectomy has not been detected (16,17). Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases (17). The potential long-term complications (e.g., chronic testicular pain) (18) must be discussed with the patient before the procedure. Epididymal tubal damage is common, and is associated with consequent development of sperm granuloma and time-dependent secondary epididymal obstruction, which limits vasectomy reversal.

10.2.3 Vasectomy failure
If an effective occlusion technique is used, the risk of recanalisation after vasectomy should be < 1% (12). However, patients should be informed preoperatively that, although rare, long-term recanalisation might occur (19). No motile spermatozoa should be detected 3 months after vasectomy. Persistent motility is a sign of vasectomy failure, and the procedure will need to be repeated. A “special clearance” with non-motile spermatozoa < 10,000/mL is still under discussion (20).


10.2.4 Counselling
Counselling with regard to vasectomy must address the following aspects:
• Vasectomy should be considered irreversible.
• Vasectomy is associated with a low complication rate; however, because it is an elective operation, even small risks must be explained, because men (and their partners) might wish to consider these before giving consent.
• Vasectomy can fail, although the failure rate is low.
• Couples should be advised to continue with other effective contraception until clearance is confirmed.
• All available data indicate that vasectomy is not associated with any serious, long-term, side effects (15).
• Vasectomy involving cauterisation and fascial interposition appears to be the most effective technique (12-14).
10.3 Vasectomy reversal
A wide range of surgical success rates has been published for vasectomy reversal (up to 90%), depending on the time between vasectomy and re-fertilisation, type of vasectomy (e.g., open-ended or sealed), type of reversal (vasovasostomy or vasoepididymostomy), and whether reversal was unilateral or bilateral. However, there have been no RCTs comparing macrosurgery (loops) and microsurgery. Microsurgical techniques with the help of magnification and smaller suture materials should be used (21).

10.3.1 Length of time since vasectomy
Vasovasostomy results have shown patency rates up to 90%. The longer the interval is from vasectomy to reversal, the lower is the pregnancy rate. In a study of 1,469 men who had undergone microsurgical vasectomy reversal, patency and pregnancy rates were 97% and 76%, respectively, for an interval up to 3 years after vasectomy; 88% and 53% for 3-8 years, 79% and 44% for 9-14 years, and 71% and 30% for > 15 years (22).

10.3.2 Tubulovasostomy
The chance of secondary epididymal obstruction after vasectomy increases with time. After an interval of 10 years, 25% of men appear to have epididymal blockage. If secondary epididymal obstruction occurs, tubulovasostomy is needed to reverse the vasectomy (see Chapter 5) (23).

10.3.3 Microsurgical vasectomy reversal versus epididymal or testicular sperm retrieval and ICSI
According to the calculations of cost per delivery for vasectomy reversal versus sperm retrieval/ICSI, under a wide variety of initial assumptions, it is clear that vasectomy reversal is associated with a considerably lower cost per delivery and higher delivery rates (24,-27). Sperm retrieval and ICSI must yield an 81% pregnancy rate per cycle to achieve equal costs to vasectomy reversal.

10.4 Conclusions and recommendations for male contraception

**Conclusions**

<table>
<thead>
<tr>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Vasectomy is considered the gold standard for the male contribution to contraception.</td>
<td>1</td>
</tr>
<tr>
<td>All available data indicate that vasectomy is not associated with any serious, long term side effects.</td>
<td>1b</td>
</tr>
<tr>
<td>Pregnancy is still achievable after successful vasectomy reversal.</td>
<td>2a</td>
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<tr>
<td>Methods of male contraception other than vasectomy are associated with high failure rates or are still experimental (e.g., hormonal approach).</td>
<td>3</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
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<tbody>
<tr>
<td>Vasectomy meets best the criteria for the male contribution to contraception, with regard to efficacy, safety and side effects. Cauterisation and fascial interposition are the most effective techniques.</td>
<td>A</td>
</tr>
<tr>
<td>Patients seeking consultation about vasectomy must be informed about the surgical method, risk of failure, irreversibility, the need for post-procedure contraception until clearance, and the risk of complications.</td>
<td>A*</td>
</tr>
<tr>
<td>Microsurgical vasectomy reversal is a low-risk and (cost-) effective method of restoring fertility.</td>
<td>B</td>
</tr>
<tr>
<td>MESA/TESE/PESA and ICSI should be reserved for failed vasectomy reversal surgery.</td>
<td>A</td>
</tr>
<tr>
<td>For couples wanting to achieve pregnancy, sperm aspiration together with ICSI is a second-line option for selected cases and in those with failed vasovasostomy.</td>
<td>B</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus

10.5 References


11. MALE ACCESSORY GLAND INFECTIONS AND INFERTILITY

11.1 Introduction
Infections of the male urogenital tract are potentially curable causes of male infertility (1-3). The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) (2). However, specific data are not available to confirm that these diseases have a negative influence on sperm quality and male fertility in general.

In order to keep the guidelines as short as possible, the MAGI section is discussed in detail in the Guidelines for Urological Infections and Chronic Pelvic Pain (4,5).

11.2. Ejaculate analysis
11.2.1 Introduction
Ejaculate analysis (see Chapter 2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information about sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CPPS) (NIH IIa vs NIH IIIb).

11.2.2 Microbiological findings
After exclusion of urethritis and bladder infection, > 10⁶ peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be performed for common urinary tract pathogens, particularly Gram-negative bacteria.

A concentration of > 10³ cfu/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia. Various microorganisms are found in the genital tract of men seen in infertility clinics; usually with more than one strain of bacteria present (1). The sampling time can influence the positive rate of microorganisms in semen and the frequency of isolation of different strains (6). The ideal diagnostic test for Chlamydia trachomatis in semen has not yet been established (7). In contrast to serological findings in women, antibody tests for C. trachomatis in seminal plasma are not indicative if no type-specific methods are used (7).

Ureaplasma urealyticum is pathogenic only in high concentrations (> 10³ cfu/mL ejaculate). No more than about 10% of samples analysed for ureaplasma exceed this concentration (8). Normal colonisation of the urethra hampers the clarification of mycoplasma-associated urogenital infections, using samples such as the ejaculate (9).

11.2.3 White blood cells
The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial (10). Infection is indicated only by an increased level of leukocytes (particularly polymorphonuclear leukocytes) and their products (e.g., leukocyte elastase) secreted into the seminal fluid. Most leukocytes are neutrophilic granulocytes, as suggested by the specific staining of the peroxidase reaction (2). Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections (11). Earlier findings have shown that elevated leukocyte numbers are not a natural cause of male infertility (12). According to WHO classification, leukocytospermia is defined as > 10⁶ WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis (13,14). Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH IIIb).

11.2.4 Sperm quality
The deleterious effects of chronic prostatitis on sperm density, motility and morphology are under debate (1). All investigations have given contradictory results, and have not confirmed that chronic prostatitis has a decisive role in altering conventional semen parameters (15-17).

11.2.5 Seminal plasma alterations
Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate (1,18,19), with a suggested cut-off level of approximately 600 ng/mL (1). Various cytokines are involved in
inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function (20-22), but no correlations have been found. The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process (23). However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion (EPS) (24).

11.2.6 **Glandular secretory dysfunction**
Infections of the sex glands can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc, and α-glutamyl-transferase activity are indicators of disturbed prostatic secretory parameters (1). Reduced fructose concentration indicates impaired vesicular function (8,25).

11.2.7 **Sperm antibodies**
Serum antibodies to sperm antigens are not useful in the diagnosis of immune infertility. Early studies found an association between increased levels of sperm antibodies in serum and non- or abacterial prostatitis (26,27). However, except for suspected chlamydial infections (28), only a history of vasectomy is predictive of sperm antibody formation (29).

11.2.8 **Reactive oxygen species**
Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers (30). However, their biological significance in prostatitis remains unclear (1).

11.2.9 **Therapy**
Treatment of chronic prostatitis is usually targeted at relieving symptoms (31,32). Andrologically, the aims of therapy for altered semen composition in male adnexitis (acute and chronic infections of the male urogenital tract) are:

- reduction or eradication of microorganisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters to counteract fertility impairment (33).

Treatment includes antibiotics, anti-inflammatory drugs, surgical procedures, normalisation of urine flow, physical therapy, and alterations in general and sexual behaviour.

Only antibiotic therapy of chronic bacterial prostatitis (NIH II) has provided symptomatic relief, eradication of microorganisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. The use of α-blockers for symptom relief is controversial. Although antibiotics might improve sperm quality (33), there is no evidence that treatment of chronic prostatitis increases the probability of conception (1,34).

**11.3 Epididymitis**

11.3.1 **Introduction**
Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men < 35 years of age, epididymitis is most often caused by *C. trachomatis* or *Neisseria gonorrhoea* (35,36). Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with urinary tract infection and occurs more often in men aged > 35 years, those who have recently undergone urinary tract instrumentation or surgery, and those who have anatomical abnormalities (37).

11.3.2 **Ejaculate analysis**
Ejaculate analysis according to WHO criteria, including leukocyte analysis, might indicate persistent inflammatory activity. In many cases, transiently decreased sperm counts and forward motility are observed (36,38,39). Ipsilateral low-grade orchitis (40,41) might be the cause of this slight impairment in sperm quality (Table 14) (42).

Development of stenosis in the epididymal duct, reduction of sperm count, and azoospermia are more important in the follow-up of bilateral epididymitis (see Chapter 5). The extent of azoospermia after epididymitis is unclear.
Table 14: Acute epididymitis and impact on sperm parameters.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Negative influence</th>
<th>Density</th>
<th>Motility</th>
<th>Morphology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludwig &amp; Haselberger (43)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Pyospermia in 19 of 22 cases</td>
</tr>
<tr>
<td>Berger et al. (36)</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weidner et al. (44)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Azoospermia in 3 of 70 men</td>
</tr>
<tr>
<td>Haidl (45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chronic infections; macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elevated</td>
</tr>
<tr>
<td>Cooper et al. (46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decrease in epididymal markers:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>α-glucosidase, L-carnitine</td>
</tr>
</tbody>
</table>

11.3.3 Treatment

Antibiotic therapy is indicated before culture results are available (Table 13). Treatment of epididymitis results in:
- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to refer their sexual partners for evaluation and treatment (47).

11.4 Conclusions and recommendations for male accessory gland infections

**Conclusions**

- Urethritis and prostatitis are not associated clearly with male infertility. 3
- Antibiotic treatment often only eradicates microorganisms; it has no positive effect on inflammatory alterations, and cannot reverse functional deficits and anatomical dysfunction. 2a
- Although antibiotic treatment for MAGI might provide improvement in sperm quality, it does not necessarily enhance the probability of conception. 2a

**Recommendations**

- Patients with epididymitis that is known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be instructed to refer their sexual partners for evaluation and treatment. B

11.5 References


12. GERM CELL MALIGNANCY AND TESTICULAR MICROCALCIFICATION

12.1 Germ cell malignancy and male infertility
Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years and affects approximately 1% of subfertile men. The lifetime risk of TGCT varies between ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and non-seminomas are preceded by CIS, and untreated ITGCNU will eventually progress to invasive cancer (1,2).

The most convincing evidence for a general decline in male reproductive health is the increase in testicular cancer seen in western countries (3). In almost all countries with reliable cancer registers, the incidence of testicular cancer has increased (4). Cryptorchidism and hypospadias are associated with an increased risk of testicular cancer; men with cryptorchidism and/or hypospadias are over-represented among patients with testicular cancer.

Men with dysgenic testes have an increased risk of developing testicular cancer in adulthood. These cancers arise from premalignant gonocytes or CIS cells (5). Testicular microlithiasis (TM), seen on ultrasound, can be associated with GCT and CIS of the testes.

12.2 Testicular germ cell cancer and reproductive function
Men with TGCT have decreased semen quality, even before cancer is diagnosed (6). Orchidectomy implies a risk of azoospermia in these men, with sperm found in the ejaculate before the tumour-bearing testis has been removed. Semen cryopreservation before orchidectomy should therefore be considered (see Chapter 14). Treatment of TGCT can result in additional impairment of semen quality (7).

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis (8). The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pretreatment levels of testosterone, SHBG, LH and oestradiol might help to anticipate post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should receive long-term follow-up because they are at risk of developing hypogonadism as a result of an age-related decrease in testosterone production (9).

The risk of hypogonadism is most pronounced in TGCT patients treated with > 3 cycles of chemotherapy or irradiation of retroperitoneal lymph nodes. However, this risk is greatest at 6-12 months post-treatment. This suggests there may be some improvement in Leydig cell function, and why it is reasonable to expect initiation of androgen replacement, until the patient shows continuous signs of testosterone deficiency, even at 2 years follow-up (10). The risk of low libido and erectile dysfunction is also increased in TGCT patients (11).

12.3 Testicular microlithiasis
Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular ultrasound (12-14). Although the true incidence of microcalcification in the general population is unknown, it is probably rare. However, ultrasound findings of TM are common in men with TGCT, cryptorchidism, testicular dysgenesis, infertility, testicular torsion and atrophy, Klinefelter’s syndrome, hypogonadism, male pseudohermaphroditism, varicocele, epididymal cysts, pulmonary microlithiasis, and non-Hodgkin’s lymphoma. The incidence reported seems to be higher with high-frequency ultrasound machines (16).

The relationship between TM and infertility is unclear, but probably relates to dysgenesis of the testes, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification occurs.

Testicular microlithiasis is found in testes at risk of malignant development. The reported incidence of TM in men with TGCT is 6-46% (17-19), and TM should therefore be considered premalignant. Testicular
biopsies from men with TM have found a higher prevalence of CIS, especially in those with bilateral microlithiasis (20). However, TM is found most often in men with a benign testicular condition and the microcalcification itself is not malignant.

Further investigation of the association between TM and CIS will require testicular biopsies in large series of men without signs of TGCT. However, available data indicate that men in whom TM is found by ultrasound, and who have an increased risk of TGCT, should be offered testicular biopsy for detection of CIS. The list of high-risk patients includes men with infertility and bilateral TM, atrophic testes, undescended testes, a history of TGCT, and contralateral TM (21).

### 12.4 Recommendations for germ cell malignancy and testicular microcalcification

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>As for all men, patients with TM and without special risk factors (see below) should be encouraged to perform self-examination because this might result in early detection of TGCT.</td>
<td>B</td>
</tr>
<tr>
<td>Testicular biopsy should be offered to men with TM, who belong to one of the following high-risk groups: infertility and bilateral TM, atrophic testes, undescended testes, a history of TGCT, or contralateral TM.</td>
<td>B</td>
</tr>
<tr>
<td>If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, surgical exploration with testicular biopsy or orchidectomy should be considered.</td>
<td>B</td>
</tr>
<tr>
<td>Testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic CT is not justified in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).</td>
<td>B</td>
</tr>
<tr>
<td>Men with TGCT are at increased risk of developing hypogonadism and sexual dysfunction and should therefore be followed up.</td>
<td>B</td>
</tr>
</tbody>
</table>

### 12.5 References


13. DISORDERS OF EJACULATION

13.1 Definition
Disorders of ejaculation are uncommon, but important, causes of male infertility. This group includes several heterogeneous dysfunctions, which can be either organic or functional.

13.2 Classification and aetiology
13.2.1 Anejaculation
Anejaculation involves complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate and ejaculatory ducts into the urethra (1). True anejaculation is usually associated with a normal orgasmic sensation. Occasionally (e.g., in incomplete spinal cord injuries), this sensation is altered or decreased. True anejaculation is always associated with central or peripheral nervous system dysfunction or with drugs (2) (Table 15).

13.2.2 Anorgasemia
Anorgasemia is the inability to reach orgasm and can give rise to anejaculation. Anorgasemia is often a primary condition and its cause is usually psychological. Some patients report sporadic events of nocturnal emission or of ejaculation during great emotional excitement unrelated to sexual activity (3).

13.2.3 Delayed ejaculation
In delayed ejaculation, abnormal stimulation of the erect penis is needed to achieve orgasm with ejaculation.
Delayed ejaculation can be considered a mild form of anorgasmia, and both conditions can be found alternately in the same patient. The causes of delayed ejaculation can be psychological, organic (e.g., incomplete spinal cord lesion (3) or iatrogenic penile nerve damage (4), or pharmacological [e.g., selective serotonin re-uptake inhibitors (SSRIs), antihypertensives, or antipsychotics] (5).

### Retrograde ejaculation

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation as a result of semen passing backwards through the bladder neck into the bladder. Patients experience a normal or decreased orgasmic sensation, except in paraplegia. Partial antegrade ejaculation must not be confused with the secretion of bulbourethral glands. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, or urethral, or bladder neck incompetence (Table 15).

<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Cauda equina lesions</td>
<td>α1-adrenoceptor antagonists</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Antipsychotics and antidepressants</td>
</tr>
<tr>
<td>Autonomic neuropathy (diabetes mellitus)</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Retroperitoneal lymphadenectomy</td>
<td>Bladder neck incompetence</td>
</tr>
<tr>
<td>Sympathectomy or aortoiliac surgery</td>
<td>Congenital defects/dysfunction of hemitrigone</td>
</tr>
<tr>
<td>Colorectal and anal surgery</td>
<td>Bladder extrophy</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Bladder neck resection (transurethral resection of the prostate)</td>
</tr>
<tr>
<td>Urethral</td>
<td>Prostatectomy</td>
</tr>
<tr>
<td>Ectopic ureterocele</td>
<td></td>
</tr>
<tr>
<td>Urethral stricture</td>
<td></td>
</tr>
<tr>
<td>Urethral valves or verumontaneum hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Congenital dopamine β-hydroxylase deficiency</td>
<td></td>
</tr>
</tbody>
</table>

### Asthenic ejaculation

Asthenic ejaculation, also defined as partial ejaculatory incompetence or “ejaculation baveuse” (5), is characterised by an altered propulsive phase, with a normal emission phase. The orgasmic sensation is reduced and the typically rhythmical contractions associated with ejaculation are missing, whereas in asthenic ejaculation caused by urethral obstruction, these contractions are present. Asthenic ejaculation generally is caused by the neurogenic or urethral pathologies already listed in Table 16. Asthenic ejaculation does not usually affect semen quality.

### Premature ejaculation

The International Society for Sexual Medicine (ISSM) has adopted the first evidence-based definition of lifelong premature ejaculation (PE): “Premature ejaculation is a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy”.

Premature ejaculation may be strictly organic (e.g., prostatitis-related) or psychogenic, partner-related or non-selective, and can be associated with erectile dysfunction. It does not impair fertility, provided intravaginal ejaculation occurs.

### Painful ejaculation

Painful ejaculation is usually an acquired condition that is often related to lower urinary tract symptoms (6). It sometimes causes moderate sexual dysfunction. The painful sensation might be felt in the perineum, or urethra and urethral meatus (7). It can be caused by ejaculatory duct obstruction, all types of chronic prostatitis/CPPS, urethritis, urethrocele, antidepressant drugs, and psychological problems.

### Diagnosis

Diagnostic management includes the following recommended procedures.

#### Clinical history

The patient must be carefully checked for diabetes, neuropathy, trauma, urogenital infection, previous surgery,
and medication. Particular attention must be paid to the characteristics of micturition and ejaculation (presence of nocturnal emission, ejaculatory ability in given circumstances, and primary or acquired disorder), as well as to psychosexual aspects (education, features of affective relationship, pre-existent psychological trauma, and previous psychological therapy).

13.3.2 Physical examination
Genital and rectal examinations are conducted, including evaluation of the prostate, bulbocavernosus reflex, and anal sphincter tone. Minimal neurological tests include:
- sensitivity of scrotum, testes, and perineum;
- cremasteric and abdominal cutaneous reflex;
- leg osteotendinous and plantar reflexes.

13.3.3 Post-ejaculatory urinalysis
Post-ejaculatory urinalysis of centrifuged urine can be used to determine if there is total or partial retrograde ejaculation.

13.3.4 Microbiological examination
Initial, mid-stream urine, EPS, and/or urine after prostatic massage are cultured for evidence of prostatic infection. In cases of increased leukocytes in semen, semen culture or biochemical infection marker tests are also suggested (8).

13.3.5 Optional diagnostic work-up
This diagnostic work-up can include:
- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;
- videocystometry;
- cystoscopy;
- transrectal ultrasonography;
- uroflowmetry;
- vibratory stimulation of the penis.

13.4 Treatment
Infertility caused by disorders of ejaculation is seldom treated on the basis of aetiology. Treatment usually involves retrieval of spermatozoa for use in ARTs. The following aspects must be considered when selecting treatment:
- age of patient and his partner;
- psychological problems of the patient and his partner;
- couple’s willingness and acceptance of different fertility procedures;
- associated pathology;
- psychosexual counselling.

13.5 Aetiological treatment
If possible, any pharmacological treatment that is interfering with ejaculation should be stopped. In painful ejaculation, tamsulosin can be administered during antidepressant treatment (9). Treatment should be given for urogenital infections (i.e., in cases of painful ejaculation) (8). Dapoxetine is an SSRI that has been introduced for the therapy of PE (10), because it appears that PE is related to serotonin levels. If possible, any underlying urethral pathology or metabolic disorder (e.g., diabetes) should be corrected. Psychotherapy is usually not very effective.

13.6 Symptomatic treatment
13.6.1 Premature ejaculation
Premature ejaculation can be treated with the SSRI dapoxetine, topical anaesthetic agents to increase intravaginal ejaculation latency time, behavioural therapy, and/or psychotherapy. Off-label use of SSRIs (e.g., paroxetine and fluoxetine) should be applied with caution.

13.6.2 Retrograde ejaculation
In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, drug treatment must be used to induce antegrade ejaculation (Table 16). Alternatively, the patient can be
encouraged to ejaculate when his bladder is full to increase bladder neck closure (11).

### Table 16: Drug therapy for retrograde ejaculation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage regimen</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine sulphate</td>
<td>10-15 mg four times daily</td>
<td>12</td>
</tr>
<tr>
<td>Midodrine</td>
<td>5 mg three times daily</td>
<td>13</td>
</tr>
<tr>
<td>Brompheniramine maleate</td>
<td>8 mg twice daily</td>
<td>14</td>
</tr>
<tr>
<td>Imipramine</td>
<td>25-75 mg three times daily</td>
<td>15</td>
</tr>
<tr>
<td>Desipramine</td>
<td>50 mg every second day</td>
<td>16</td>
</tr>
</tbody>
</table>

Sperm collection from post-orgasmic urine for use in ART is recommended if:
- drug treatment is ineffective or intolerable as a result of side effects;
- the patient has a spinal cord injury;
- drug therapy inducing retrograde ejaculation cannot be interrupted.

Sperm retrieval is timed to coincide with the partner’s ovulation. Urine must be alkalised (pH 7.2-7.8) and osmolality must be 200-300 mOsmol/kg. Alternatively, a catheter can be inserted into the bladder to allow instillation of 10-50 mL Tyrode’s or Ham’s F-10 medium. The patient must ejaculate, and a second catheterisation is carried out immediately to retrieve spermatozoa. The latter treatment minimises contact between spermatozoa and urine (17,18).

If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo in vitro reproductive procedures (e.g., ICSI) with fresh or cryopreserved spermatozoa. In the case of insufficient drug therapy, testicular (TESE or PESA) or epididymal (MESA) sperm retrieval techniques can be used for assisted reproduction.

**13.6.3 Anejaculation**

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia is not very effective. In all these cases, and in men who have a spinal cord injury, vibrostimulation (i.e., application of a vibrator to the penis) is first-line therapy.

In anejaculation, vibrostimulation evokes the ejaculation reflex (19), which requires an intact lumbosacral spinal cord segment. Complete spinal injuries and injuries above T10 show a better response to vibrostimulation. Once the safety and efficacy of this procedure has been assessed, patients can manage the process in their own home. Intravaginal insemination using a 10-mL syringe during ovulation can be carried out. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme.

If vibrostimulation has failed, electroejaculation is the therapy of choice (20). Electroejaculation involves electrical stimulation of the periprostatic nerves via a probe inserted into the rectum, which seems unaffected by reflex arc integrity. Anaesthesia is required except in cases of complete spinal cord injury. In 90% of patients, electrostimulation induces ejaculation, which is retrograde in one-third of cases. Semen quality is often poor and most couples will need to enter an IVF programme (21).

When electroejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens (22) (see Chapter 5) or seminal tract washout (23).

When sperm cannot be retrieved, epididymal obstruction or testicular failure must be suspected. If only immotile sperm can be retrieved, DNA damage is very likely and will yield poor IVF results. TESE can then be used (8,24). Anejaculation following either surgery for testicular cancer or total mesorectal excision can be prevented using monolateral lymphadenectomy or autonomic nerve preservation (24), respectively.

**13.7 Conclusion and recommendations for disorders of ejaculation**

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculation disorders can be treated using a wide range of drugs and physical stimulation, with a high level of efficacy.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetiological treatments for ejaculatory disorders should be offered before sperm collection and ART is performed.</td>
<td>B</td>
</tr>
<tr>
<td>Premature ejaculation can be treated successfully with either topical anaesthetic creams or SSRIs.</td>
<td>A</td>
</tr>
<tr>
<td>In men with spinal cord injury, vibrostimulation and electroejaculation are effective methods of sperm retrieval.</td>
<td>B</td>
</tr>
</tbody>
</table>
13.8 References


14. SEMEN CRYOPRESERVATION

14.1 Definition
Cryopreservation is the storage of biological material at subzero temperatures [e.g., -80 or -196°C (the boiling point of liquid nitrogen)], at which biochemical processes of cell metabolism are slowed or interrupted. At -196°C, the biochemical reactions that lead to cell death are stopped.

14.2 Introduction
Cryopreservation was first developed in the 1940s by veterinarians and adapted for human sperm in the 1950s. The first pregnancy that used cryopreservation took place in 1954 (1). In fertility practice, clinical indications for cryopreservation include storage of sperm and testicular tissue.

14.3 Indications for storage
Storage of sperm is available in many clinics for the following indications:
- Before potentially sterilising chemotherapy or radiotherapy for cancer (2) or for non-malignant diseases.
- Before surgery that might interfere with fertility (e.g., bladder neck surgery in a younger man or removal of a testicle in a man with testicular malignancy, or before vasectomy or transgender surgery).
- For men with progressive decrease in semen quality as a result of diseases that have an associated risk of subsequent azoospermia (i.e., pituitary macroadenoma, craniopharyngioma, empty sella syndrome, chronic nephropathy, uncontrolled diabetes mellitus, and multiple sclerosis).
- For men with paraplegia when sperm have been obtained by electroejaculation or obtained by penile vibratory stimulation.
- For men with psychogenic anejaculation, after sperm have been obtained either by electroejaculation or a sperm retrieval procedure.
- After gonadotropin treatment has induced spermatogenesis in men with hypogonadotrophic hypogonadism.
- For men with NOA, the chance of finding sperm using micro-TESE is ~50%.

Cryopreservation can be used for sperm collected through TESE, avoiding repeated sperm retrieval procedures and unnecessary hyperstimulation of the female partner.
- In any situation in which sperm have been obtained by a sperm retrieval procedure (e.g., after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery).
- For storage of donor sperm, because cryopreservation reduces the risk of transmission of infection from sperm donors. According to the European directives 2004/23 EC and 2006/17 EC fresh sperm are no longer to be used for non-partner donations.

14.4 Precautions and techniques

14.4.1 Freezing and thawing process
The cryopreservation techniques currently used are not yet optimal because damage occurs to cells during cryopreservation and prolonged storage. Most damage occurs during freezing and thawing. Major causes of damage during freezing are ice crystal formation and cell dehydration, which disrupt the cell wall and intracellular organelles. Sperm morphology, motility and vitality decrease significantly after thawing, and cryopreservation increases the damage done to sperm DNA (3-6). Further damage can be caused by contamination of samples with microorganisms and high levels of superoxide radicals (7,8). To reduce ice crystal formation, a cryopreservation solution is added before freezing. Various cryopreservation solutions are available commercially, most of which contain varying proportions of glycerol and albumin. After freezing, the
samples are immersed in liquid nitrogen. Several techniques have been developed to try to reduce damage caused by freezing and thawing, including:

- One-step freezing method (9,10): sample is held in the vapour phase for 10 min before being plunged into liquid nitrogen.
- Slow or multi-step method (11): sample is gradually cooled in the vapour phase for approximately 40 min. A programmable automatic freezing machine, which is preset to cool at a rate of 1-10°C/min is used.

The method available depends on the resources of the laboratory. Whichever freezing technique is used, it should be tested using donor sperm and post-thaw examination, and should regularly undergo a quality-control programme.

The likelihood of sperm survival decreases with repeated freezing and thawing. The maximum viable storage time for human sperm is not known. Many laboratory or regulatory authorities apply a storage limit of up to 10 years (12). However, longer storage is sometimes needed (e.g., for a 17-year-old man who has had sperm stored before undergoing chemotherapy for testicular cancer).

14.4.2 Cryopreservation of small numbers of sperm

Standard cryopreservation in straws is an efficient way of storing large numbers of sperm (e.g., for a donor insemination programme). However, in micro-TESE, few sperm might be obtained, and the choice is either to freeze testicular tissue and find sperm after thawing the tissue, or to freeze small numbers of sperm. If sperm are frozen in straws, it can be difficult to find any sperm after thawing. Instead, the sperm should be frozen in a pellet (13) or in a container (14).

14.4.3 Testing for infections and preventing cross-contamination

Sperm storage in straws is used extensively. Large numbers of straws are stored in canisters, with the straws being bathed in a pool of liquid nitrogen. Microbial contamination of the pool of liquid nitrogen results in contamination of the outside of all the straws. The most widely used safeguard is to use so-called high security closed straws. According to the European directives 2004/23 and 2006/17, samples should be tested for hepatitis B and C and human immunodeficiency virus (HIV). In case of non-partner donation, samples are also tested for C. Trachomatis (by NAT) and syphilis, as well as genetics, that is, karyotype and most prevalent genetic disorders in the population to which the non-partner donor belongs.

Until the test results are known, samples must be stored in an individual quarantine vessel (separate storage). If open straws are used (e.g., for vitrification purposes) some laboratories use the additional safeguard of double-wrapping the straws before freezing, although this is more costly. Some centres carry out cytomegalovirus testing and store negative and positive samples separately.

Considerable ethical issues surround the storage of samples before cancer chemotherapy in men who are hepatitis-virus- or HIV-positive. Few clinics have separate storage facilities for HIV-positive samples. However, the success of antiretroviral treatment is increasing the number of HIV-positive men who may wish to store sperm. There is also concern about HIV transmission to children conceived using HIV-positive sperm, because sperm-washing techniques fail in ~5% of cases.

14.4.4 Fail-safe precautions to prevent loss of stored materials

Any laboratory that undertakes long-term storage of human biological materials should have procedures that guard against accidental loss of material caused by storage vessel failure. This is particularly important for sperm stored before potentially sterilising cancer chemotherapy because these patients may not be able to obtain further sperm.

14.4.5 Orphan samples

In malignancy and some other situations, several years might pass before stored samples are required. Inevitably, during this time, the owners of some samples might disappear or die, leaving behind orphan samples for which the owner is no longer contactable. The duty of the laboratory and the legal ownership of these samples can create considerable problems.

14.5 Biological aspects

Cryopreservation induces deterioration of semen quality. After the sample has been thawed, motility (16) and morphology (17,18) are worsened, including mitochondrial acrosomal and sperm tail damage (19). Sperm freezing decreases motility by 31% and mitochondrial activity by 36%, and causes morphological disruption in 37% of sperm (9). Motility is correlated best with IVF capacity of the thawed sample. Further improvement can be achieved by selecting the subpopulation of sperm with the best motility and DNA integrity and freezing these sperm in seminal plasma (13).
14.6 Cryopreservation of testicular stem cells
Spermatogonial stem cell (SSC) preservation and transplantation have been proposed as a promising strategy for fertility preservation in young boys facing SSC loss (20). Since the first publication of SSC transplantation in mice in 1994, remarkable progress has been made towards a clinical application. Cryopreservation protocols for testicular tissue have been developed in animal models, translated to humans, and are already used clinically. Transplantation methods are being used in human testes, and the efficiency and safety of the technique has been evaluated in a mouse model. The application of this technique in humans looks possible, therefore, banking testicular biopsies from prepubertal boys for future stem cell transplantation is being introduced in many centres.

14.7 Conclusions and recommendations for semen cryopreservation

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The purpose of sperm cryopreservation is to enable future assisted reproduction techniques</td>
<td>1b</td>
</tr>
<tr>
<td>Cryopreservation techniques are not optimal, and future efforts are needed to improve the outcome of sperm banking.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryopreservation of semen should be offered to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.</td>
<td>A</td>
</tr>
<tr>
<td>If testicular biopsies are indicated, sperm cryopreservation is strongly advised.</td>
<td>A</td>
</tr>
<tr>
<td>If cryopreservation is not available locally, patients should be advised about the possibility of visiting, or transferring to, the nearest cryopreservation unit before therapy starts.</td>
<td>C</td>
</tr>
<tr>
<td>Consent for cryopreservation should include a record of the man’s wishes for his samples if he dies or is otherwise untraceable.</td>
<td>C</td>
</tr>
<tr>
<td>Precautions should be taken to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient, and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Samples from men who are positive for hepatitis virus or HIV should not be stored in the same container as samples from men who have been tested and are free from infection.</td>
<td>C</td>
</tr>
</tbody>
</table>

14.8 References
15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

<table>
<thead>
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<th>Description</th>
</tr>
</thead>
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<tr>
<td>ABP</td>
<td>acute bacterial prostatitis</td>
</tr>
<tr>
<td>ART</td>
<td>assisted reproduction technique</td>
</tr>
<tr>
<td>CBAVD</td>
<td>congenital bilateral absence of the vas deferens</td>
</tr>
<tr>
<td>CF</td>
<td>cystic fibrosis</td>
</tr>
<tr>
<td>CFTR</td>
<td>cystic fibrosis transmembrane conductance regulator</td>
</tr>
<tr>
<td>CIS</td>
<td>carcinoma in situ</td>
</tr>
<tr>
<td>CPPS</td>
<td>chronic pelvic pain syndrome</td>
</tr>
<tr>
<td>EAA</td>
<td>European Academy of Andrology</td>
</tr>
<tr>
<td>EPS</td>
<td>expressed prostatic excretion</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescent in situ hybridisation</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
</tr>
<tr>
<td>GCT</td>
<td>germ cell tumour</td>
</tr>
<tr>
<td>GnRH</td>
<td>gonadotrophin-releasing hormone</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
</tr>
<tr>
<td>GREAT</td>
<td>G-protein-coupled receptor affecting testis descent</td>
</tr>
<tr>
<td>hCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HMG</td>
<td>human menopausal gonadotropin</td>
</tr>
<tr>
<td>ICSI</td>
<td>intracytoplasmic sperm injection</td>
</tr>
<tr>
<td>IHH</td>
<td>idiopathic hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>IL-6</td>
<td>interleukin-6</td>
</tr>
<tr>
<td>ITGCU</td>
<td>intratubular germ cell neoplasia of unclassified type</td>
</tr>
<tr>
<td>IVF</td>
<td>in vitro fertilisation</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>LH</td>
<td>luteinising hormone</td>
</tr>
<tr>
<td>MAGI</td>
<td>male accessory gland infection</td>
</tr>
<tr>
<td>MAR</td>
<td>mixed antiglobulin reaction</td>
</tr>
<tr>
<td>MESA</td>
<td>microsurgical epididymal sperm aspiration</td>
</tr>
<tr>
<td>NIDDK</td>
<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NOA</td>
<td>non-obstructive azoospermia</td>
</tr>
<tr>
<td>OA</td>
<td>obstructive azoospermia</td>
</tr>
<tr>
<td>OAT</td>
<td>oligo-astheno-teratozoospermia [syndrome]</td>
</tr>
<tr>
<td>PE</td>
<td>premature ejaculation</td>
</tr>
<tr>
<td>PGD</td>
<td>preimplantation genetic diagnosis</td>
</tr>
<tr>
<td>SHBG</td>
<td>sex hormone binding globulin</td>
</tr>
<tr>
<td>SSRIs</td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>TDS</td>
<td>testicular dysgenesis syndrome</td>
</tr>
<tr>
<td>TEFNA</td>
<td>testicular fine-needle aspiration</td>
</tr>
<tr>
<td>TESE</td>
<td>testicular sperm extraction</td>
</tr>
<tr>
<td>TGCT</td>
<td>testicular germ cell tumour</td>
</tr>
<tr>
<td>TM</td>
<td>testicular microlithiasis</td>
</tr>
<tr>
<td>TRUS</td>
<td>transurethral ultrasound</td>
</tr>
<tr>
<td>TURED</td>
<td>transurethral resection of the ejaculatory ducts</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>VB1</td>
<td>first-voided urine</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

Conflict of interest

All members of the Male Infertility Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. INTRODUCTION AND DEFINITION

Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (1).

Androgens play a crucial role in the development and maintenance of male reproductive and sexual functions. Low levels of circulating androgens can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract. Later in life, this may cause reduced fertility, sexual dysfunction, decreased muscle formation and bone mineralisation, disturbances of fat metabolism, and cognitive dysfunction. Testosterone levels decrease as a process of ageing: signs and symptoms caused by this decline can be considered a normal part of ageing. However, low testosterone levels are also associated with several chronic diseases, and symptomatic patients may benefit from testosterone treatment.

This document presents the European Association of Urology (EAU) guidelines on the diagnosis and treatment of male hypogonadism. These guidelines aim to provide practical recommendations on how to deal with primary low testosterone and ageing-related decline in testosterone in male patients, as well as the treatment of testosterone disruption and deficiencies caused by other illnesses.

1.1 Reference


2. METHODOLOGY

The EAU Male Hypogonadism panel consists of a multidisciplinary group of experts, including urologists specialising in the treatment of infertility, endocrinologists and andrologists. There is a need for ongoing re-evaluation of the information presented in the current guidelines by an expert EAU panel. It must be emphasised that clinical guidelines present the best evidence available to the experts at the time of writing. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when treatment decisions for individual patients are being taken. Guidelines help to focus decisions. Clinical decisions must also take into account patients’ personal values and preferences and their individual circumstances.

2.1 Data identification

The recommendations provided in the current guidelines are based on a systematic literature search performed by the panel members. MedLine, Embase and Cochrane databases were searched to identify original articles and review articles. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a ‘free-text’ protocol, combining ‘male hypogonadism’ with the terms ‘diagnosis’, ‘epidemiology’, ‘investigations’, ‘treatment’, ‘testosterone’, ‘androgens’ and ‘hypogonadism’.

All articles published before January 2012 were considered for review. The expert panel reviewed these records and selected articles with the highest level of evidence in accordance with a rating schedule adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence.

2.2 Levels of evidence and grades of recommendation

References used in the text have been assessed according to their level of scientific evidence (Table 1). Guideline recommendations have been graded (Table 2) in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence (LE) (1). The aim of grading recommendations (GR) is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Levels of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
</tbody>
</table>
Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.

Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

* Modified from Sackett et al. (1).

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as ‘upgraded based on panel consensus’. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.

**Table 2: Grades of recommendation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

* Modified from Sackett et al. (1).

### 2.3 Publication history
The present male hypogonadism guidelines are a new publication that underwent a blinded peer-review process before publication. The standard procedure will be an annual assessment of newly published literature in this field, guiding future updates. An ultra-short reference document is published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

### 2.4 References
3. EPIDEMIOLOGY

3.1 Introduction
Androgen deficiency increases with age; an annual decline in circulating testosterone of 0.4-2.0% has been reported (1,2). In middle-aged men, the incidence was found to be 6% (3). It is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a poor health status.

3.2 Role of testosterone for male reproductive health
Androgens, which are produced by the testis and the adrenal glands, play a pivotal role in male reproductive and sexual function. Androgens are also crucial for the development of male reproductive organs, such as the epididymis, vas deferens, seminal vesicle, prostate and penis. In addition, androgens are needed for puberty, male fertility, male sexual function, muscle formation, body composition, bone mineralisation, fat metabolism, and cognitive functions (4).

3.3 Physiology
Male sexual development starts between the 7th and 12th week of gestation. The undifferentiated gonads develop into a foetal testis through expression of the sex-determining region Y gene (SRY), a gene complex located on the short arm of the Y chromosome (5). The foetal testis produces two hormones: testosterone and anti-Müllerian hormone (AMH).

Testosterone is needed for the development of the Wolffian ducts, resulting in formation of the epididymis, vas deferens and seminal vesicle. AMH activity results in regression of the Müllerian ducts (Figure 1). Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period (6).

In addition, testosterone is needed for development of the prostate, penis and scrotum. However, in these organs testosterone is converted into the more potent metabolite dihydrotestosterone (DHT) by the enzyme 5α-reductase (7). The enzyme is absent in the testes, which explains why 5α-reductase inhibitors do not have a marked effect on spermatogenesis. Testosterone and DHT are required for penile growth, both activating the androgen receptor. The androgen receptor (AR) in the penis disappears after puberty, thus preventing further growth of the penis (8).

Intratesticular testosterone is needed to maintain the spermatogenic process and to inhibit germ cell apoptosis (9). The seminiferous tubules of the testes are exposed to concentrations of testosterone 25-100 times greater than circulating levels. Suppression of gonadotrophins (e.g. through excessive testosterone abuse) results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis (10). Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of spermatids (11,12). Testosterone does not appear to act directly on the germ cells, but functions through the Sertoli cells by expression of the AR and influencing the seminiferous tubular microenvironment (12).

Testosterone can also be metabolised into oestradiol by aromatase, present in fatty tissue, the prostate and bone. Oestradiol is essential for bone mineralisation, also in men (13).

The production of testosterone is controlled by luteinizing hormone (LH) from the pituitary gland. Immediately after birth, serum testosterone levels reach adult concentrations over several months. Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotrophins, initiated by GnRH secretion from the hypothalamus and resulting in testosterone production, male sexual characteristics and spermatogenesis (14). Figure 1 shows the development of the male reproductive system.

3.4 The androgen receptor
Testosterone exerts its action through the androgen receptor (AR), located in the cytoplasm and nucleus of target cells. During the foetal period, testosterone increases the number of androgen receptors by increasing the number of cells with the AR, but also by increasing the number of ARs in each individual cell (8,13).

The AR gene is located on the X chromosome (Xq 11-12): defects and mutations in the AR gene can result in male sexual maldevelopment, which may cause testicular feminisation or low virilisation. Less severe mutations in the AR gene may cause mild forms of androgen resistance and male infertility (15). In exon 1 of the gene, the transactivation domain consists of a trinucleotide tract (cytosine–adenine–guanine [CAG-repeats]) of variable length. Androgen sensitivity may be influenced by the length of the CAG repeats in exon 1 of the AR gene (15). The AR CAG repeat length is inversely correlated with serum total and bioavailable testosterone in ageing men. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues (16). CAG repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels (17).
Conclusion
Testosterone is essential for normal male development.

Figure 1: Development of the male reproductive system

FSH = follicle-stimulating hormone; LH = luteinizing hormone; SRY = sex region of the Y chromosome.

3.5 References
4. AETIOLOGY (PRIMARY AND SECONDARY FORMS AND LATE-ONSET HYPOGONADISM)

4.1 Introduction
Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis (Table 3).

Male hypogonadism can be classified in accordance with disturbances at the level of:
- the hypothalamus and pituitary (secondary hypogonadism);
- the testes (primary hypogonadism);
- the hypothalamus/pituitary and gonads (late-onset hypogonadism);
- androgen target organs (androgen insensitivity/resistance).

4.2 Male hypogonadism of hypothalamic-hypopituitary origin (secondary hypogonadism)
Central defects of the hypothalamus or pituitary cause secondary testicular failure. Identifying secondary hypogonadism is of clinical importance, as it can be a consequence of pituitary pathology (including prolactinomas) and can cause infertility, which can be restored by hormonal stimulation in most patients with secondary hypogonadism.
The most relevant forms of secondary hypogonadism are:

- **Hyperprolactinemia (HP)**, caused by prolactin-secreting pituitary adenomas (prolactinomas) (microprolactinomas < 10 mm in diameter vs. macroprolactinomas) or drug-induced (by dopamine-antagonistic effects of substances such as phenothiazine, imipramine and metoclopramide); additional causes may be chronic renal failure or hypothyroidism.
- **Isolated hypogonadotrophic hypogonadism (IHH)** (formerly termed idiopathic hypogonadotrophic hypogonadism, IHH).
- **Kallmann syndrome** (hypogonadotrophic hypogonadism with anosmia, genetically determined, prevalence one in 10,000 males).

These disorders are characterised by disturbed hypothalamic secretion or action of GnRH, as a pathophysiology common to the diseases, resulting in impairment of pituitary LH and FSH secretion. An additional inborn error of migration and homing of GnRH-secreting neurons results in Kallmann syndrome (1,2).

The most important differential diagnosis is the constitutional delay of puberty, as it is the most common cause of delayed puberty (pubertas tarda) with a prevalence of one in 40 in males, caused by a delayed increase in pulsatile GnRH secretion with an autosomal-dominant pattern of inheritance (3). Other rare forms of secondary hypogonadism are listed in Table 3.

### 4.3 Male hypogonadism of gonadal origin (primary hypogonadism)

Primary testicular failure results in low testosterone levels, impairment of spermatogenesis and elevated gonadotrophins. The most important clinical forms of primary hypogonadism are Klinefelter syndrome (one in 500 males) and testicular tumours (12 in 100,000 males).

- **Klinefelter syndrome** affects 0.2% of the male population. It is the most frequent form of male hypogonadism and the most common numerical chromosomal aberration, with 47,XXY in 90% of cases (4). It arises due to non-disjunction during paternal or maternal meiotic division of germ cells (5).
- **Testicular tumours** are the most frequent type of cancer in young males during reproductive age. Risk factors are contralateral germ cell cancer, maldescended testes, gonadal dysgenesis, infertility and familial germ cell cancer. Twenty-five per cent of patients suffer from testosterone deficiency after treatment (6-8).

Other reasons for primary testicular failure are summarised in Table 4.

### 4.4 Male hypogonadism due to mixed dysfunction of hypothalamus/pituitary and gonads

Combined primary and secondary testicular failure results in low testosterone levels, impairment of spermatogenesis and variable gonadotrophin levels. Gonadotrophin levels depend on the predominant primary or secondary failure. This form was named late-onset hypogonadism some years ago (9,10).

### 4.5 Male hypogonadism due to defects of androgen target organs

These forms are primarily rare defects and will not be further discussed in detail in these guidelines. There are androgen receptor defects with complete, partial and minimal androgen insensitivity syndrome; Reifenstein syndrome; bulbospinal muscular atrophy (Kennedy disease); as well as 5α-reductase deficiency (for a review, see Nieschlag et al. 2010) (11).

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with hCG and FSH or alternatively GnRH can restore fertility in most cases (12,13). However, fertility options for males with primary hypogonadism are limited. Detailed evaluation may for example detect pituitary tumours, systemic disease, or testicular tumours.

Combined forms of primary and secondary hypogonadism can be observed in older men, with a concomitant age-related decline in testosterone levels resulting from defects in testicular as well as hypothalamic-pituitary function. A significant percentage of men over the age of 60 years have serum testosterone levels below the lower reference limits in young adults (14-18).
### Table 3: Forms of secondary hypogonadism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causes for deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperprolactinemia</td>
<td>Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced.</td>
</tr>
<tr>
<td>Isolated hypogonadotrophic hypogonadism (IHH) (formerly termed idiopathic hypogonadotrophic hypogonadism, IHH)</td>
<td>GnRH deficiency.</td>
</tr>
<tr>
<td>Kallmann syndrome (hypogonadotrophic hypogonadism with anosmia (prevalence 1 in 10,000))</td>
<td>GnRH deficiency and anosmia, genetically determined.</td>
</tr>
<tr>
<td>Secondary GnRH deficiency</td>
<td>Medication, drugs, toxins, systemic diseases.</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Radiotherapy, trauma, infections, haemochromatosis and vascular insufficiency or congenital.</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases from the pituitary or pituitary stalk.</td>
</tr>
<tr>
<td>Prader-Willi syndrome (PWS) (formerly Prader-Labhart-Willi syndrome) (prevalence 1 in 10,000 individuals)</td>
<td>Congenital disturbance of GnRH secretion.</td>
</tr>
<tr>
<td>Congenital adrenal hypoplasia with hypogonadotrophic hypogonadism (prevalence 1 in 12,500 individuals)</td>
<td>X-chromosomal recessive disease, in the majority of patients caused by mutations in the DAX1 gene.</td>
</tr>
<tr>
<td>Pasqualini syndrome</td>
<td>Isolated LH deficiency.</td>
</tr>
</tbody>
</table>

### Table 4: Forms of primary hypogonadism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causes of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maldescended or ectopic testes</td>
<td>Failure of testicular descent, 85% idiopathic.</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Viral or unspecific orchitis.</td>
</tr>
<tr>
<td>Acquired anorchia</td>
<td>Traumatic, tumour, torsion, inflammation, iatrogenic, surgical removal.</td>
</tr>
<tr>
<td>Secondary testicular dysfunction</td>
<td>Medication, drugs, toxins, systemic diseases.</td>
</tr>
<tr>
<td>(Idiopathic) testicular atrophy</td>
<td>Male infertility (idiopathic or specific causes).</td>
</tr>
<tr>
<td>Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)</td>
<td>Intrauterine torsion is the most probable cause.</td>
</tr>
<tr>
<td>46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)</td>
<td>Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20-desmolase defect, 17β-hydroxysteroid dehydrogenase defect).</td>
</tr>
<tr>
<td>Gonadal dysgenesis (synonym ‘streak gonads’)</td>
<td>XY gonadal dysgenesis can be caused by mutations in different genes.</td>
</tr>
<tr>
<td>46,XX male syndrome (prevalence of 1 in 10,000-20,000)</td>
<td>Males with presence of genetic information from the Y chromosome after translocation of a DNA segment of the Y to the X chromosome during paternal meiosis.</td>
</tr>
<tr>
<td>47,XYY syndrome (prevalence of 1 in 2,000)</td>
<td>Caused by non-disjunction in paternal meiosis.</td>
</tr>
<tr>
<td>Noonan syndrome (prevalence of 1 in 1,000 to 1 in 5,000)</td>
<td>Genetic origin.</td>
</tr>
<tr>
<td>Inactivating LH receptor mutations, Leydig cell hypoplasia (prevalence of 1 in 1,000,000 to 1 in 20,000)</td>
<td>Leydig cells are unable to develop due to the mutation (19).</td>
</tr>
</tbody>
</table>
The two forms of hypogonadism have to be differentiated, as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.

### References


5. **DIAGNOSIS**

5.1 **Introduction**

Hypogonadism is diagnosed on the basis of persistent symptoms and signs related to androgen deficiency and assessment of consistently low testosterone levels (at least on two occasions) with a reliable method (1-5).

5.2 **Clinical symptoms**

Low levels of circulating androgens may be associated with signs and symptoms (Table 5).

---

FSH = follicle-stimulating hormone; GnRH = Gonadotrophin-releasing hormone; LH = luteinizing hormone.
Table 5: Clinical symptoms and signs suggestive for androgen deficiency

<table>
<thead>
<tr>
<th>Delayed puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small testes</td>
</tr>
<tr>
<td>Male-factor infertility</td>
</tr>
<tr>
<td>Decreased body hair</td>
</tr>
<tr>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>Decrease in lean body mass and muscle strength</td>
</tr>
<tr>
<td>Visceral obesity</td>
</tr>
<tr>
<td>Decrease in bone mineral density (osteoporosis) with low trauma fractures</td>
</tr>
<tr>
<td>Reduced sexual desire and sexual activity</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Diminished nocturnal erections</td>
</tr>
<tr>
<td>Hot flushes</td>
</tr>
<tr>
<td>Changes in mood, fatigue and anger</td>
</tr>
<tr>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Insulin resistance and type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Diminished cognitive function</td>
</tr>
</tbody>
</table>

The most prevalent symptoms of male hypogonadism in ageing men are reduced sexual desire and sexual activity, erectile dysfunction, and hot flushes (1).

Symptoms and signs of androgen deficiency vary depending on age of onset, duration and the severity of the deficiency. Reference ranges for the lower normal level of testosterone (percentile 2.5) have recently been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and for calculated free testosterone 243 pmol/L, to distinguish between normal levels and levels possibly associated with deficiency (6). Symptoms suggesting the presence of hypogonadism (1,7) are summarised in Table 5.

In men aged 40-79 years, the threshold for total testosterone was 8 nmol/L for decreased frequency of sexual thoughts, 8.5 nmol/L for erectile dysfunction, 11 nmol/L for decreased frequency of morning erections and 13 nmol/L for diminished vigour (8). The strongest predictor for hypogonadism in this age group was three sexual symptoms (decreased sexual thoughts, weakened morning erections, erectile dysfunction) and either a total testosterone level of < 8 nmol/L or serum testosterone in the range of 8-11 nmol/L and free testosterone < 220 pmol/L. These data are based on serum samples taken in the morning, when levels are highest and best reproducible (9).

Hypogonadism may be more subtle and not always evident by low testosterone levels. For example, men with primary testicular damage often have normal testosterone levels but high LH: this could be considered a subclinical or compensated form of hypogonadism. The clinical consequences of an isolated elevation of LH is not clear yet, but potentially these men may already have signs or symptoms of hypogonadism or will become hypogonadal in the future.

To differentiate between primary and secondary forms of hypogonadism and to clarify late-onset hypogonadism determination of LH serum levels is required. Both LH and testosterone serum levels should be analysed twice.

5.3 History-taking and questionnaires

Symptoms of hypogonadism are listed in Table 5 and should be addressed during history-taking. Early onset of hypogonadism causes a lack of or minimal pubertal development, lack of development of secondary sex characteristics, possibly eunuchoid body proportions and a high-pitched voice. These signs and symptoms strongly suggest hypogonadism. Postpubertal development of hypogonadism causes a loss of androgen-dependent functions and symptoms that may have other etiological backgrounds than low testosterone levels. Published questionnaires are unreliable and have low specificity, while their sensitivity is high, and are not effective for case-finding (10-13). It is important to assess and exclude systemic illnesses, signs of malnutrition and malabsorption, as well as ongoing acute disease. Pharmacological treatments with corticosteroids, abuse of drugs such as marijuana, opiates and alcohol and previous treatment or use of testosterone or abuse of anabolic steroids should also be included in history-taking.
5.4 Physical examination
Assessment of body mass index (BMI), the waist-hip ratio (or sagittal abdominal diameter), body hair, male-pattern hair loss, presence of gynaecomastia and testicular size (measured with an orchidometer or ultrasound [US]) and a structural examination of the penis as well as a digital rectal examination (DRE) of the prostate should be included.

Conclusion

The diagnosis of male hypogonadism is based on symptoms and signs of androgen deficiency, together with consistently low serum testosterone levels.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism (Table 5) (1-7).</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Total testosterone assessment should be repeated at least on two occasions with a reliable method in men with: - Total testosterone levels close to the lower normal range (8-12 nmol/L), the free testosterone level should be measured to strengthen the laboratory assessment. - Suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should also be included (6,8).</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Currently available diagnostic instruments (questionnaires) are not reliable as case-finding tools (10), as they have not been validated.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Testosterone assessment is recommended in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - End-stage renal disease receiving haemodialysis. - Treatment with medications that cause suppression of testosterone levels - e.g. corticosteroids and opiates. - Moderate to severe chronic obstructive lung disease. - Infertility. - Osteoporosis or low-trauma fractures. - HIV infection with sarcopenia. - Type 2 diabetes (14-18).</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>LH serum levels should be analysed to differentiate between primary, secondary, and late-onset hypogonadism.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.5 References


6. **CLINICAL CONSEQUENCES OF HYPOGONADISM**

6.1 **Introduction**
The clinical consequences of hypogonadism are determined by the age of onset and the severity of hypogonadism.

6.2 **Foetal androgen deficiency**
During the first 14 weeks of gestation, the presence of testosterone is crucial for normal virilisation of the external male genitalia. Androgen deficiency or androgen resistance due to deficient androgen receptor
function during this stage of life may result in abnormal genital development, ranging from hypospadias to female external genitalia with intra-abdominal testis. Frequently, patients with disorders of sexual development are diagnosed at an early age because of clearly abnormal external genitalia. However, patients at both ends of the phenotypic spectrum may go unnoticed in childhood and are diagnosed during puberty because of delayed pubertal development in phenotypic men or primary amenorrhea in XY women.

6.3 Prepubertal onset of androgen deficiency
At the start of puberty, rising gonadotrophin levels result in increasing testicular volume and the activation of spermatogenesis and testosterone secretion. During puberty, rising testosterone levels result in the development of male secondary sex characteristics, comprising deepening of the voice, development of terminal body hair, stimulation of hair growth in sex-specific regions, facial hair, increasing penile size, increase in muscle mass and bone size and mass, growth spurt induction and eventually closing of the epiphyses. In addition, testosterone has explicit psychosexual effects, including increased libido.

Delayed puberty is defined as an absence of testicular enlargement at the age of 14. As this is a ‘statistical’ definition, based on reference ranges for the onset of puberty in the normal population, delayed puberty does not necessarily indicate the presence of a disease. In cases of severe androgen deficiency, the clinical picture of prepubertal-onset hypogonadism is evident (Table 6) and diagnosis and treatment are fairly straightforward. The major challenge in younger individuals with presumed idiopathic hypogonadotropic hypogonadism is to differentiate the condition from a constitutional delay in puberty and to determine when to start androgen treatment. In milder cases of androgen deficiency, such as are seen in patients with Klinefelter syndrome, pubertal development can be incomplete or delayed, resulting in a more subtle phenotypic picture. In these patients, several clues may lead to a diagnosis of hypogonadism. These include: small testes, (a history of) cryptorchidism, gynaecomastia, sparse body hair, eunuchoid habitus, low bone mass and subfertility (1).

Table 6: Signs and symptoms suggesting prepubertal-onset hypogonadism

<table>
<thead>
<tr>
<th>Small testes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptorchidism</td>
</tr>
<tr>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>High voice</td>
</tr>
<tr>
<td>Unclosed epiphyses</td>
</tr>
<tr>
<td>Linear growth into adulthood</td>
</tr>
<tr>
<td>Eunuchoid habitus</td>
</tr>
<tr>
<td>Sparse body hair/facial hair</td>
</tr>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Low bone mass</td>
</tr>
<tr>
<td>Sarcopenia</td>
</tr>
<tr>
<td>Reduced sexual desire/activity</td>
</tr>
</tbody>
</table>

6.4 Late-onset hypogonadism
Definition: Late-onset hypogonadism is defined as hypogonadism in a person who has had normal pubertal development and as a result developed normal male secondary sex characteristics.

Depending on the underlying cause of hypogonadism, the decline in gonadal function may be gradual and partial. The resulting clinical picture may be variable, and the signs and symptoms may be obscured by the physiological phenotypic variation. Symptoms that have been associated with late-onset androgen deficiency include: loss of libido, erectile dysfunction, sarcopenia, low bone mass, depressive thoughts, fatigue, loss of vigour, erectile dysfunction, loss of body hair, hot flushes and reduced fertility (Table 7). Most of these symptoms have a multifactorial aetiology, are reminiscent of normal aging and can also be found in men with completely normal testosterone levels (2). As a result, signs and symptoms of adult-onset hypogonadism may be non-specific, and confirmation of a clinical suspicion by hormonal testing is mandatory. For most of the symptoms mentioned above, the probability of their presence increases with lower plasma testosterone levels. Most studies indicate a threshold level below which the prevalence of symptoms starts to increase (3,4). This threshold level is near the lower level of the normal range for plasma testosterone levels in young men, but there appears to be a wide variation between individuals, and even within one individual the threshold level...
may be different for different target organs.

**Table 7: Signs and symptoms associated with late-onset hypogonadism**

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of libido</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Sarcopenia</td>
</tr>
<tr>
<td>Low bone mass</td>
</tr>
<tr>
<td>Depressive thoughts</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Loss of body hair</td>
</tr>
<tr>
<td>Hot flushes</td>
</tr>
<tr>
<td>Loss of vigour</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening of testosterone deficiency is only recommended in adult men with consistent and preferably multiple signs and symptoms listed in Table 7.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Adult men with established severe hypogonadism should be screened for concomitant osteoporosis.</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

6.5 References


7. **INDICATIONS AND CONTRAINDICATIONS FOR TREATMENT**

Testosterone treatment aims to restore testosterone levels to the physiological range in men with consistently low levels of serum testosterone and associated symptoms of androgen deficiency. The aim is to improve quality of life, sense of well-being, sexual function, muscle strength and bone mineral density. Table 8 highlights the main indications for testosterone treatment. Table 9 lists the main contraindications against testosterone therapy.
Table 8: Indications for testosterone treatment

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed puberty (idiopathic, Kallmann syndrome)</td>
</tr>
<tr>
<td>Klinefelter syndrome with hypogonadism</td>
</tr>
<tr>
<td>Sexual dysfunction and low testosterone</td>
</tr>
<tr>
<td>Low bone mass in hypogonadism</td>
</tr>
<tr>
<td>Adult men with consistent and preferably multiple signs and symptoms of hypogonadism (listed in Table 7)</td>
</tr>
<tr>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Testicular dysgenesis and hypogonadism</td>
</tr>
</tbody>
</table>

Table 9: Contraindications against testosterone treatment

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
</tr>
<tr>
<td>PSA &gt; 4 ng/mL</td>
</tr>
<tr>
<td>Male breast cancer</td>
</tr>
<tr>
<td>Severe sleep apnoea</td>
</tr>
<tr>
<td>Male infertility</td>
</tr>
<tr>
<td>Haematocrit &gt; 50%</td>
</tr>
<tr>
<td>Severe lower urinary tract symptoms due to benign prostatic hyperplasia</td>
</tr>
</tbody>
</table>

8. **BENEFITS OF TREATMENT**

Testosterone replacement therapy (TRT) provides several benefits in relation to body composition, metabolic control and psychological and sexual parameters. Randomised trials have shown a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume (1-4). Similar positive results have been reported in meta-analyses evaluating the role of exogenous testosterone in relation to bone mineral density: it is evident that testosterone therapy improves mineral density at the lumbar spine, producing a reduction in bone resorption markers. The available trials failed to demonstrate a similar effect at the femoral neck (4-6). Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease in fat mass and an increase in lean body mass (4). Several studies based on experience with testosterone undecanoate have demonstrated a significant reduction in trunk and waist fat, with a clear decrease in waist size (7,8). In the same trials, testosterone undecanoate administration was associated with an improvement in body weight, body mass index and lipid profile after 3 months of therapy. Testosterone replacement therapy has positive effects on glycaemic and lipid control, insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profiles, with a consequent decrease in the cardiovascular risk (9). Benefits on libido, erection and ejaculation have been reported in several retrospective studies and case reports. In a multicentre prospective study, Moon et al. (10) reported a significant increase in the International Index of Erectile Function (IIEF) score for sexual desire, intercourse satisfaction and overall satisfaction starting 6 weeks after the beginning of treatment. Testosterone replacement therapy has also shown encouraging results in several case reports in which satisfactory sexual intercourse was reported after at least 3 months from therapy induction in hypogonadal men suffering from veno-occlusive erectile dysfunction (4,11). Significant improvement in depressive symptoms in men treated with testosterone undecanoate is reported in a randomised trial, while benefits in relation to the cognitive spectrum have been reported in studies with a lower impact (12,13).

**Conclusion**

Benefits including a reduction in BMI and waist size and improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT.
Testosterone replacement therapy is recommended in patients with:

- A decline in muscle mass and strength
- Reduced bone mineral density at the lumbar spine
- Decreased libido and erection

8.1 References

9. CHOICE OF TREATMENT

9.1 Introduction
The aim of TRT is to restore physiological testosterone levels in hypogonadal men (1). During TRT, periodic observation of the serum concentration of the hormone and its metabolites is recommended in order to alleviate treatment-related side effects (1). Several preparations are available, which differ in the route of administration and pharmacokinetics, and the selection should be a joint decision by both the patient and the physician (2). Short-acting preparations may be preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed and treatment can be discontinued if needed (3).

Testosterone replacement therapy is safe and effective and the agents are available as oral preparations, intramuscular injections and transdermal gel or patches (4).

9.2 Preparations

9.2.1 Testosterone undecanoate
Testosterone undecanoate is the most widely used and safest oral delivery system. It rarely causes a rise in testosterone levels above the mid-range and it is therefore infrequently associated with side effects (1). In oral administration, resorption depends on simultaneous intake of fatty food.

Testosterone undecanoate is also available as a long-acting intramuscular injection (with intervals of up to 3 months). This long period of action ensures a normal testosterone serum concentration for the entire period, but the relatively long wash-out period may cause problems if complications appear (5).

9.2.2 Testosterone cypionate and enanthate
Testosterone cypionate and enanthate are available as short-acting intramuscular delivery systems (with intervals of 2-3 weeks) and represent safe and valid preparations. However, these preparations may cause fluctuations in serum testosterone from high levels to subnormal levels, and they are consequently associated with periods of well-being alternating with periods of unsatisfactory clinical response (6,7).

9.2.3 Transdermal testosterone
Transdermal testosterone preparations are available as skin patches or gel. They provide a uniform and normal serum testosterone level for 24 hours (daily interval). Common side effects consist of skin irritation at the site of application (patches) and risk of interpersonal transfer if appropriate precautions are not taken (gel) (8,9).

9.2.4 Sublingual and buccal testosterone
Sublingual and buccal testosterone tablets are effective and well-tolerated delivery systems that can provide a rapid and uniform achievement of a physiological testosterone level with daily administration (10,11).

9.2.5 Subdermal depots
Subdermal depots need to be implanted every 5-7 months and offer a long period of action without significant serum fluctuation of the testosterone level. The risk with this kind of delivery system lies in infections and extrusions, which may occur in up to 10% of cases (1,12,13).

9.3 Hypogonadism and fertility issues
Exogenous testosterone reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis. If hypogonadism coincides with fertility issues, hCG treatment should be considered.

Human chorionic gonadotrophin (hCG) stimulates testosterone production of Leydig cells. Its administration should be restricted to patients with secondary hypogonadism, if fertility issues are important. Normal physiological serum levels can be achieved with a standard dosage of 1500-5000 IU administered intramuscularly or subcutaneously twice weekly. In patients with secondary hypogonadism, hCG treatment is combined with FSH treatment (usually 150 IU three times weekly i.m. or s.c.) to induce spermatogenesis.

In patients with secondary hypogonadism and fertility issues, and in selected cases of primary hypogonadism, hCG treatment can be chosen to support endogenous testosterone production for the period of infertility treatment. The dosage has to be adjusted individually to prevent suppression of FSH serum levels. hCG treatment has higher costs than testosterone treatment. There is insufficient information about the therapeutic and adverse effects of long-term hCG treatment. This type of treatment can therefore not be recommended for male hypogonadism, except in patients in whom fertility treatment is an issue.
Table 10: Testosterone preparations for replacement therapy

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Administration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone undecanoate</td>
<td>Oral; 2-6 cps every 6 h</td>
<td>Absorbed through the lymphatic system, with consequent reduction of liver involvement.</td>
<td>Variable levels of testosterone above and below the mid-range (1) Need for several doses per day with intake of fatty food.</td>
</tr>
<tr>
<td>Testosterone cypionate</td>
<td>Intramuscular; one injection every 2-3 weeks</td>
<td>Short-acting preparation that allows drug withdrawal in case of onset of side effects.</td>
<td>Possible fluctuation of testosterone levels (5,6).</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Intramuscular; one injection every 2-3 weeks</td>
<td>Short-acting preparation that allows drug withdrawal in case of onset of side effects.</td>
<td>Possible fluctuation of testosterone levels (5,6).</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Intramuscular; one injection every 10-14 weeks</td>
<td>Steady-state testosterone levels without fluctuation.</td>
<td>Long-acting preparation that cannot allow drug withdrawal in case of onset of side effects (7).</td>
</tr>
<tr>
<td>Transdermal testosterone</td>
<td>Gel or skin patches; daily application</td>
<td>Steady-state testosterone level without fluctuation.</td>
<td>Skin irritation at the site of application and risk of interpersonal transfer (8,9).</td>
</tr>
<tr>
<td>Sublingual testosterone</td>
<td>Sublingual; daily doses</td>
<td>Rapid absorption and achievement of physiological serum level of testosterone.</td>
<td>Local irritation (10,11).</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>Buccal tablet; two doses per day</td>
<td>Rapid absorption and achievement of physiological serum level of testosterone.</td>
<td>Irritation and pain at the site of application (10,11).</td>
</tr>
<tr>
<td>Subdermal depots</td>
<td>Subdermal implant every 5-7 months</td>
<td>Long duration and constant serum testosterone level.</td>
<td>Risk of infection and extrusion of the implants (1,12,13).</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient should be fully informed about expected benefits and side effects of each treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Short-acting preparations may be preferred to long-acting depot administration when starting the initial treatment.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>hCG treatment can only be recommended for hypogonadal patients with simultaneous fertility treatment.</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

**9.4 References**


10. RISK FACTORS IN TESTOSTERONE TREATMENT

10.1 Introduction
Physicians are often reluctant to offer TRT, especially in elderly men, due to the potential risk of this form of treatment (1). The most common doubts are associated with the possible consequences for prostatic and breast tissues, the cardiovascular system and sleep apnoea.

10.2 Male breast cancer
Male breast cancer is a rare disease, with an incidence of less than 1% of all male cancers (2). The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer (3). An association between TRT and the development of breast cancer is not supported by strong evidence, although there have been some reports based on small numbers of patients (4).

10.3 Prostate cancer
Prostate cancer growth may be influenced by testosterone. Studies have reported that hypogonadism is associated with a lower incidence of prostate cancer, but if prostate cancer occurs in hypogonadal men, it is usually at an advanced stage and with a higher Gleason score (5,6). Randomised controlled trials support
the hypothesis that TRT does not result in changes in prostatic histology, nor in a significant increase in intraprostatic testosterone and DHT (7,8). The most recent studies indicate that testosterone therapy does not increase the risk of prostate cancer (7-10), but long-term follow-up data are not yet available. A meta-analysis showed a higher (but not statistically significant) percentage of prostate events in middle-aged and older men receiving TRT (11). In view of these observations, PSA testing and digital examination of the prostate before and during therapy are highly recommended (11).

Testosterone therapy is clearly contraindicated in men with prostate cancer. A topic currently under debate involves the use of TRT in hypogonadal men with a history of prostate cancer and no evidence of active disease. So far, only studies with limited numbers of patients and relatively short follow-up periods are available, and these indicate no increased risk for recurrent prostate cancer. No randomised and placebo-controlled trials are available yet to document the long-term safety of the treatment in these patients (12). Men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) and showing symptoms of testosterone deficiency can be cautiously considered for TRT, although this approach is still an ‘off-label’ treatment (13,14). In these patients, treatment should be restricted to patients with a low risk for recurrent prostate cancer (pre-surgery Gleason < 8; pT1-2; PSA < 10 ng/mL). Therapy should not start before 1 year of follow-up after surgery and there should be no PSA recurrence (13-15). Patients who have undergone brachytherapy or external-beam radiotherapy (EBRT) for low-risk prostate cancer can also be cautiously treated with TRT in case of hypogonadism, with close monitoring for prostate cancer recurrence (14-16).

10.4 Cardiovascular diseases
Testosterone treatment is not related to the development of de novo cardiovascular events (17,18). Caution, however, should be used in men with existing cardiovascular diseases, since an increase in red blood cells is a common side effect of testosterone. Haemoglobin and haematocrit measurements are recommended before treatment and periodically thereafter (9,11,19). Patients with erythrocytosis and serious congestive heart failure (NYHA classes III-IV) are at risk of developing cardiovascular deterioration, and testosterone therapy should be discontinued until the resolution of congestive heart failure (9). Cardiovascular adverse events are more frequent in patients with multiple co-morbidities and with limited physical activity (19).

10.5 Obstructive sleep apnoea
There is no consistent evidence correlating TRT with obstructive sleep apnoea (OSA). There is also no evidence that TRT can result in the onset or worsening of the condition (20).

### Conclusions

| Case reports and small cohort studies point to a possible correlation between TRT and the onset of breast cancer, but there is as yet a lack of strong evidence for this relationship. | 3 |
| Randomised controlled trials support the hypothesis that TRT does not result in changes in prostatic histology. | 1b |
| Testosterone therapy is not related to the development of de novo cardiovascular events. | 1a |
| There is no evidence for a relationship between TRT and OSA. | 3 |

### Recommendations

| Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment. | 1a | A |
| Haematocrit and haemoglobin monitoring, PSA and digital rectal examination of prostate and breast examination are recommended assessments during TRT therapy. | 1a | A |
| In patients operated on for localised prostate cancer, testosterone therapy should not start before 1 year of follow-up without PSA recurrence has been completed. | 4 | B |

*PSA = prostate-specific antigen; TRT = testosterone replacement therapy*

10.6 references


11. MONITORING OF PATIENTS RECEIVING TESTOSTERONE REPLACEMENT THERAPY

11.1 Introduction
Regular follow-up is needed in patients receiving testosterone therapy, as potentially androgen-dependent symptoms and conditions may occur as a result of TRT. The side effects of TRT are limited, but their incidence and clinical relevance is as yet unclear.

The primary aim of TRT is to alleviate the clinical symptoms of testosterone deficiency. Careful monitoring of changes in the clinical manifestations of testosterone deficiency should therefore be an essential part of every follow-up visit. Effects of TRT on sexual interest may already appear after 3 weeks of treatment, and reach a plateau at 6 weeks (1). Changes in erectile function and ejaculation may require up to 6 months (1). Effects on quality of life, and also on depressive mood, may become detectable within 1 month, but the maximum effect may take longer (1).

11.2 Testosterone level
There are as yet insufficient data to define optimal serum levels of testosterone during TRT. Expert opinion suggests that TRT should restore the serum testosterone level to the mid-normal range of specific age groups of men, which is usually sufficient to alleviate various manifestations of hormone deficiency. An optimal monitoring schedule for serum testosterone level is also dependent on the formulation of TRT used (LE: 4; GR: C).

11.3 Bone density
Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of TRT. An increase in lumbar spine BMD may already be detectable after 6 months of TRT and may continue for 3 more years (1).

11.4 Haematocrit
It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements (2). Elevated haematocrit is the most frequent side effect of TRT. The clinical significance of a high haematocrit level is unclear, but it may be associated with hyperviscosity and thrombosis (3). The effect of erythropoiesis may become evident at 3 months and peaks at 12 months (1).

11.5 Prostate safety
Testosterone replacement therapy results in a marginal increase in PSA and prostate volume, plateauing at 12 months (1). Previous fears that TRT might increase the risk of prostate cancer have been contradicted by a number of meta-analyses (4-7). However, there are insufficient long-term data available to conclude that there is safety from prostate cancer with TRT.

11.6 Cardiovascular system
Testosterone replacement therapy is not associated with the development of any unsafe cardiovascular events, and special monitoring in this respect is not needed (7,8). There has been one study (9) indicating that testosterone therapy in older men with a high prevalence of chronic diseases may result in a higher risk of cardiovascular adverse events. These patients may need individualised monitoring schemes.
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<td>In men with an abnormal BMD, BMD measurements should be repeated 6 and 12 months after the start of TRT and thereafter annually.</td>
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<td>Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above normal levels.</td>
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<td>Prostate health should be assessed by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually.</td>
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BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy

11.7 References


12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AMH  Anti-Müllerian hormone
AR   Androgen receptor
BMD  Bone mineral density
BMI  Body mass index
CAG  Cytosine-adenine-guanine
DHT  Dihydrotestosterone
DRE  Digital rectal examination
DSD  Disorders of sexual development
EAU  European Association of Urology
EBRT External-beam radiation therapy
FSH  Follicle-stimulating hormone
GnRH Gonadotrophin-releasing hormone
GR   Grade of recommendation
hCG  Human chorionic gonadotrophin
HIV  Human immunodeficiency virus
HP   Hyperprolactinemia
IHH  Isolated hypogonadotrophic hypogonadism
IIEF International Index of Erectile Function
IU   International unit
LE   Level of evidence
LH   Luteinizing hormone
NYHA New York Heart Association
OSA  Obstructive sleep apnoea
PSA  Prostate-specific antigen
PWS  Prader-Willi syndrome
RCT  Randomised controlled trial
TRT  Testosterone replacement therapy
SHBG Sex hormone-binding globulin
SRY  Sex region of the Y chromosome

Conflict of interest statement
All members of the Male Hypogonadism Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. INTRODUCTION

1.1 Background
Urinary tract infections (UTIs) are among the most prevailing infectious diseases with a substantial financial burden on society. In the USA, UTIs are responsible for over 7 million physician visits annually (1). Approximately 15% of all community-prescribed antibiotics in the USA are dispensed for UTI (2) and data from some European countries suggest a similar rate (3). In the US, UTIs account for more than 100,000 hospital admissions annually, most often for pyelonephritis (1). These data do apparently not account for complicated UTI associated with urological patients, the prevalence of which is not known. UTIs represents at least 40% of all hospital acquired infections and are, in the majority of cases, catheter associated (4). Bacteriuria develops in up to 25% of patients who require a urinary catheter for one week or more with a daily risk of 5-7% (5,6). The recent Global Prevalence Infection in Urology (GPIU) studies have shown that 10-12% of patients hospitalised in urological wards have a healthcare-associated infection (HAI). The strains retrieved from these patients are even more resistant (7).

1.2 Bacterial resistance development
The present state of microbial resistance development is alarming (8). The use of antibiotics in the different countries of Europe mirrors the global increase in resistant strains (8). The presence of extended-spectrum β-lactamase (ESBL) producing bacteria showing resistance to most antibiotics, except for the carbapenem group, is steadily increasing in the population (10). Even more alarming are the recent reports from all continents of faecal bacteria carrying the ESBL-\text{carba} \text{enzyme} (i.e New-Delhi metallo-β-lactamase NDM-1) making them resistant to all available antibiotics including the carbapenem group.

Particularly troublesome is the increasing resistance to broad-spectrum antibiotics such as fluoroquinolones and cephalosporins due to an overconsumption of these two groups and the parallel development of co-resistance to other antibiotics (collateral damage) (11). This development is a threat for patients undergoing urological surgery in general and men subjected to prostate biopsy in particular.

An urgent and strong grip on this threatening development is thus required. With only a few new antibiotics expected in the coming 5 to 10 years, prudent use of available antibiotics is the only option to delay the development of resistance (9) and the urological community has a responsibility to participate in this combat. It is essential to consider the local microbial environment and resistance pattern as well as each individual patient’s risk factors for harbouring resistant microbes.

Bacterial resistance development is a threat
- To treatment of UTI
- Prophylaxis in urological surgery

There is a direct correlation between the use of antibiotics and resistance development

There is an urgent need for combating resistance development by a prudent use of available antibiotics

1.3 The aim of the guidelines
It is the ambition of the present guidelines to provide both urologist and physicians from other medical specialities with evidence-based guidance regarding the treatment and prophylaxis of UTI. These guidelines cover male and female UTIs, male genital infections and special fields such as UTI in paediatric urology, immunosuppression, renal insufficiency and kidney transplant recipients. Much attention is given to antibiotic prophylaxis, aiming to reduce the overuse of peri-operative prophylactic antibiotics. High quality clinical research using strict internationally recognised definitions and classifications as presented in this section are encouraged.

1.4 Pathogenesis of UTIs
Microorganisms can reach the urinary tract by haematogenous or lymphatic spread, but there is abundant clinical and experimental evidence to show that the ascent of microorganisms from the urethra is the most common pathway that leads to a UTI, especially organisms of enteric origin (e.g. E. coli and other Enterobacteriaceae). This provides a logical explanation for the greater frequency of UTIs in women than in men, and for the increased risk of infection following bladder catheterisation or instrumentation. A single insertion of a catheter into the urinary bladder in ambulatory patients results in urinary infection in 1-2% of cases. Indwelling catheters with open-drainage systems result in bacteriuria in almost 100% of cases within 3-4 days. The use of a closed-drainage system, including a valve to prevent retrograde flow, delays the onset of infection, but ultimately does not prevent it. It is thought that bacteria migrate within the mucopurulent space between the urethra and catheter, and that this leads to the development of bacteriuria in almost all patients within about 4 weeks.
Haematogenous infection of the urinary tract is restricted to a few relatively uncommon microbes, such as *Staphylococcus aureus*, *Candida* sp., *Salmonella* sp. and *Mycobacterium tuberculosis*, which cause primary infections elsewhere in the body. *Candida albicans* readily causes a clinical UTI via the haematogenous route, but is also an infrequent cause of an ascending infection if an indwelling catheter is present, or following antibiotic therapy.

The concept of bacterial virulence or pathogenicity in the urinary tract infers that not all bacterial species are equally capable of inducing infection. The more compromised the natural defence mechanisms (e.g. obstruction, or bladder catheterisation), the fewer the virulence requirements of any bacterial strain to induce infection. This is supported by the well-documented *in vitro* observation that bacteria isolated from patients with a complicated UTI frequently fail to express virulence factors. The virulence concept also suggests that certain bacterial strains within a species are uniquely equipped with specialised virulence factors, e.g. different types of pili, which facilitate the ascent of bacteria from the faecal flora, introitus vaginae or periurethral area up the urethra into the bladder, or less frequently, allow the organisms to reach the kidneys to induce systemic inflammation.

1.5 Microbiological and other laboratory findings

The number of bacteria is considered relevant for the diagnosis of a UTI. In 1960, Kass developed the concept of significant bacteriuria (≥ 10⁵ cfu/mL) in the context of pyelonephritis in pregnancy (12). Although this concept introduced quantitative microbiology into the diagnosis of infectious diseases, and is therefore still of general importance, it has recently become clear that there is no fixed bacterial count that is indicative of significant bacteriuria, which can be applied to all kinds of UTIs and in all circumstances. As described in Appendix 16.1, the following bacterial counts are clinically relevant:

- ≥ 10³ cfu/mL of uropathogens in a mid-stream sample of urine (MSU) in acute uncomplicated cystitis in women.
- ≥ 10⁴ cfu/mL of uropathogens in an MSU in acute uncomplicated pyelonephritis in women.
- ≥ 10⁵ cfu/mL of uropathogens in an MSU in women, or ≥ 10⁴ cfu/mL uropathogens in an MSU in men, or in straight catheter urine in women, in a complicated UTI.

In a suprapubic bladder puncture specimen, any count of bacteria is relevant. The problem of counting low numbers, however, has to be considered. If an inoculum of 0.1 mL of urine is used and 10 identical colonies are necessary for statistical reasons of confidence, then in this setting, the lowest number that can be counted is 100 cfu/mL of uropathogens. Asymptomatic bacteriuria is diagnosed if two cultures of the same bacterial strain (in most cases the species only is available), taken ≥ 24 h apart, show bacteriuria of ≥ 10⁵ cfu/mL of uropathogens.

It is obvious that methods of urine collection and culture, as well as the quality of laboratory investigations, may vary. Two levels of standard must therefore be used for the management of patients. A basic standard level is necessary for routine assessment, whereas a higher standard level is required for scientific assessment and in special clinical circumstances, e.g. fever of unknown origin in immunocompromised patients. In research, the need for a precise definition of sampling methods, such as the time that urine is kept in the bladder, must be recognised, and these parameters carefully recorded.

In clinical routine assessment, a number of basic criteria must be looked at before a diagnosis can be established, including:

- clinical symptoms;
- results of selected laboratory tests (blood, urine or expressed prostatic secretion [EPS]);
- evidence of the presence of microorganisms by culturing or other specific tests;
- most of these investigations can today be performed in any laboratory.

It has to be considered, however, that microbiological methods and definitions applied must follow accepted standards with regard to specimen transport, pathogen identification, and antimicrobial susceptibility testing. These methods and microbiological definitions may vary between countries and institutions. One example is the breakpoints for classification of pathogen susceptibility. It is important to report not only the results, but also which methods and standards were applied, such as the European Committee for Antimicrobial Susceptibility Testing (EUCAST) (13,14), or the National Committee for Clinical Laboratory Standards (NCCLS) (15). Mixing results obtained by different methods, e.g. rates of bacterial resistance, can be problematic and requires careful interpretation. Histological investigation sometimes shows the presence of non-specific inflammation. Only in some cases, such findings (e.g. prostatitis in patients who have elevated levels of prostate-specific antigen [PSA]) might help determine the appropriate treatment, whereas in more specific inflammation, such as tuberculosis and actinomycosis, histology can be diagnostic. In general, however, histological findings usually contribute very little to the treatment decisions.
1.6 Methodology

The EAU Urological Infections guidelines panel consists of a group of urologists, specialised in the treatment of UTIs. It must be emphasised that clinical guidelines present the best evidence available to the experts at the time of writing. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when treatment decisions for individual patients are being taken. Guidelines help to focus decisions. Clinical decisions must also take into account patients’ personal values and preferences and their individual circumstances.

1.6.1 Level of evidence and grade of guideline recommendations

References used in the text have been assessed according to their level of scientific evidence (Table 1). Guideline recommendations have been graded (Table 2) in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence (LE) (16). The aim of grading recommendations (GR) is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
<td>1a</td>
</tr>
<tr>
<td>Evidence obtained from at least one randomised trial.</td>
<td>1b</td>
</tr>
<tr>
<td>Evidence obtained from at least one well-designed controlled study without randomisation.</td>
<td>2a</td>
</tr>
<tr>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
<td>2b</td>
</tr>
<tr>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
<td>3</td>
</tr>
<tr>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
<td>4</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (16).

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Conversely, an absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (17-19).

The EAU Guidelines Office, do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Nature of recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
<td>A</td>
</tr>
<tr>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
<td>B</td>
</tr>
<tr>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
<td>C</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (16).

1.6.2 Publication history

A first version of the guidelines on the management of UTI and male genital infections was published in the EAU guidelines 2001 and in European Urology (20). A second updated version was included in the EAU guidelines 2006. The EAU/ICUD textbook on Urogenital Infections (21) has become the book of reference for the Guidelines and the recent update 2011. Guidelines on special conditions of the urogenital tract have also been published elsewhere (22-24).
Standard procedure for EAU publications includes an annual assessment of newly published literature in this field, guiding future updates. An ultra-short reference document is being published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

1.7 References


2. CLASSIFICATION OF UTIs

2.1 Introduction

Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings. Practically, UTIs have been divided in uncomplicated and complicated UTIs, and sepsis. It is important to underline that the following proposed classification is still not validated or recognised. It is a working instrument useful for daily assessment and eventually for clinical research.

A critical review of present classifications was undertaken for the EAU/ICUD Urogenital Infections initiative (1) in Appendix 16.1. The overall aim is to provide the clinician and researcher with a standardised tool and nomenclature for UTI. The present guidelines give a short summary of a tentative improved system of classification of UTI based on:

- anatomical level of infection;
- grade of severity of infection;
- underlying risk factors;
- microbiological findings.

The symptoms, signs and laboratory finding focus on the anatomical level and the degree of severity of the infection. The risk factor analysis contributes to define any additional therapeutic measure required (i.e. drainage).

2.2 Anatomical level of infection

The symptoms, as presented in the Appendix 16.1, focus on the anatomical level of infection, defined as:

- urethra: urethritis (UR);
- urinary bladder: cystitis (CY);
- kidney: pyelonephritis (PN);
- blood stream: sepsis (US).
Figure 2.1 illustrates the basic diagnostic and treatment strategy for UTI. Urethritis, being poorly understood, is for the time being not included. Also the male accessory gland or genital infections (MAGI) orchitis, epididymitis and prostatitis are not included.

Asymptomatic bacteriuria (ABU) needs to be considered a special entity because it can have its source in both the lower and upper urinary tracts, and requires no treatment unless the patient is subjected to urological surgery.

2.3 Grade of severity
The grade of severity is set on a scale of 1-6 that is related to the risk of fatal outcome (Figure 2.1).

**Figure 2.1: Classification of UTI as proposed by the EAU European Section of Infection in Urology (ESIU) (1)**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Gradient of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>Local symptoms</td>
</tr>
<tr>
<td>Dysuria, frequency, urgency, pain or bladder tenderness</td>
<td>Fever, Flank pain</td>
</tr>
<tr>
<td>Investigations</td>
<td>Dipstick (MSU Culture + S as required)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Risk factor assessment according to ORENUC (Table 2.1)</td>
</tr>
<tr>
<td>Medical and surgical treatment</td>
<td>NO*</td>
</tr>
</tbody>
</table>

* Two exceptions: during pregnancy and prior to urological surgery.
Table 2.1: Host risk factors in UTI

<table>
<thead>
<tr>
<th>Type</th>
<th>Category of risk factor</th>
<th>Examples of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>No known/associated RF</td>
<td>- Healthy premenopausal women</td>
</tr>
<tr>
<td>R</td>
<td>RF of recurrent UTI, but no risk of severe outcome</td>
<td>- Sexual behaviour and contraceptive devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hormonal deficiency in post menopause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Secretory type of certain blood groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Controlled diabetes mellitus</td>
</tr>
<tr>
<td>E</td>
<td>Extra-urogenital RF, with risk or more severe outcome</td>
<td>- Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male gender</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Badly controlled diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Relevant immunosuppression*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Connective tissue diseases*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prematurity, new-born</td>
</tr>
<tr>
<td>N</td>
<td>Nephropathic disease, with risk of more severe outcome</td>
<td>- Relevant renal insufficiency*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Polycystic nephropathy</td>
</tr>
<tr>
<td>U</td>
<td>Urological RF, with risk or more severe outcome, which can be resolved during therapy</td>
<td>- Ureteral obstruction (i.e. stone, stricture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Transient short-term urinary tract catheter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Asymptomatic Bacteriuria**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Controlled neurogenic bladder dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Urological surgery</td>
</tr>
<tr>
<td>C</td>
<td>Permanent urinary Catheter and non resolvable urological RF, with risk of more severe outcome</td>
<td>- Long-term urinary tract catheter treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Non-resolvable urinary obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Badly controlled neurogenic bladder</td>
</tr>
</tbody>
</table>

RF = Risk Factor; * = not well defined; ** = usually in combination with other RF (i.e. pregnancy, urological intervention).

2.4 Pathogens
Urine culture will usually identify the causative pathogen (> 10^4 cfu/mL) and its susceptibility pattern. Both characteristics can be introduced in the final classification of the clinical stage of infection. The degree of susceptibility is defined as grade a (susceptible) to c (resistant).

2.5 Classification of UTI
Figure 2.2 shows a summary of the additive parameters that make up an individual class of UTI.
By cumulating the different parameters, a UTI can be classified as follows (1):

- **CY-1R**: *E. coli* (a): simple cystitis but recurrent with susceptibility to standard antibiotics.
- **PN-3U**: *K pneumoniae* (b): severe pyelonephritis (with high fever and vomiting), with underlying urological disease (e.g. stones or obstruction) due to *Klebsiella* sp., with a moderate antibiotic resistance profile.
- **US-5C**: *Enterococcus* sp. (a): severe urosepsis with an antibiotic-sensitive *Enterococcus* sp. in a patient with an indwelling catheter.

### Reference

### 3. UNCOMPLICATED UTIs IN ADULTS

#### 3.1 Summary and recommendations
This chapter is by itself the summary of the EAU/ICUD initiative on urogenital infections, Chapter 3 on uncomplicated UTI (1).

#### 3.2 Definition
Acute, uncomplicated UTIs in adults include episodes of acute cystitis and acute pyelonephritis in otherwise healthy individuals. These UTIs are seen mostly in women without structural and functional abnormalities within the urinary tract, kidney diseases, or comorbidity that could lead to more serious outcomes and therefore require additional attention (2).

##### 3.2.1 Aetiological spectrum
The spectrum of aetiological agents is similar in uncomplicated upper and lower UTIs, with *E. coli* the causative pathogen in 70-95% of cases and *Staphylococcus saprophyticus* in 5-10%. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* sp., are isolated (3) (LE: 2a).

#### 3.3 Acute uncomplicated cystitis in premenopausal, non-pregnant women

##### 3.3.1 Diagnosis

1. **Clinical diagnosis**
   The diagnosis of acute uncomplicated cystitis can be made with a high probability based on a focused history of urinary irritative symptomatology (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation, in those women who have no other risk factors for complicated UTIs (4) (LE: 2a, GR: B).

2. **Laboratory diagnosis**
   Urine dipstick testing, as opposed to urinary microscopy, is a reasonable alternative to urinalysis for diagnosis of acute uncomplicated cystitis (5,6) (LE: 2a, GR: B).

   Urine cultures are recommended for those with: (i) suspected acute pyelonephritis; (ii) symptoms that do not resolve or recur within 2-4 weeks after the completion of treatment; and (iii) those women who present with atypical symptoms (7,8) (LE: 4, GR: B).

   A colony count of $\geq 10^3$ cfu/mL of uropathogens is microbiologically diagnostic in women who present with symptoms of acute uncomplicated cystitis (9) (LE: 3, GR: B).

   Women who present with atypical symptoms of either acute uncomplicated cystitis or acute uncomplicated pyelonephritis, as well as those who fail to respond to appropriate antimicrobial therapy should be considered for additional diagnostic studies (LE: 4, GR: B).

##### 3.3.2 Therapy
Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo (10) (LE: 1a, GR: A).

The choice of an antibiotic for therapy should be guided by:
- spectrum and susceptibility patterns of the aetiologial uropathogens;
- efficacy for the particular indication in clinical studies;
- tolerability;
• adverse effects;
• cost;
• availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available (11-13) (LE: 1a, GR: A).

Cotrimoxazole 160/800 mg bid for 3 days or trimethoprim 200 mg for 5 days should only be considered as drugs of first choice in areas with known resistance rates for \(E. coli\) of < 20% (14,15) (LE: 1b, GR: B).

Alternative antibiotics are ciprofloxacin 250 mg bid, ciprofloxacin extended release 500 mg qd, levofloxacin 250 mg qd, norfloxacin 400 mg bid, and ofloxacin 200 mg bid, each as a 3-day course (16) (LE: 1b, GR: B). However, adverse effects have to be considered (Table 3.1).

Table 3.1: Recommended antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy premenopausal women

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Daily dose</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosfomycin trometamol(^*)</td>
<td>3 g SD</td>
<td>1 day</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50 mg q6h</td>
<td>7 days</td>
</tr>
<tr>
<td>Nitrofurantoin macrocrystal</td>
<td>100 mg bid</td>
<td>5-7 days</td>
</tr>
<tr>
<td>Pivmecillinam(^*)</td>
<td>400 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Pivmecillinam(^*)</td>
<td>200 mg bid</td>
<td>7 days</td>
</tr>
<tr>
<td>Alternatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>250 mg qd</td>
<td>3 days</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>100 mg bid</td>
<td>3 days</td>
</tr>
</tbody>
</table>

If local resistance pattern is known (E. coli resistance < 20%)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Daily dose</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulphamethoxazole</td>
<td>160/800 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>200 mg bid</td>
<td>5 days</td>
</tr>
</tbody>
</table>

\(^*\)not available in all countries.
\(^*\)available only in Scandinavia, the Netherlands, Austria, and Canada.

3.3.3 Follow-up
Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated (17) (LE: 2b, GR: B). In women whose symptoms do not resolve by the end of treatment, and in those whose symptoms resolve but recur within 2 weeks, urine culture and antimicrobial susceptibility tests should be performed (LE: 4, GR: B). For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a 7-day regimen using another agent should be considered (LE: 4, GR: C).

3.4 Acute uncomplicated pyelonephritis in premenopausal, non-pregnant women

3.4.1 Diagnosis
3.4.1.1 Clinical diagnosis
Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness, and it can occur in the absence of symptoms of cystitis (18).

3.4.1.2 Laboratory diagnosis
Urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis (19) (LE: 4, GR: C).

Colony counts \(\geq 10^6\) cfu/mL of uropathogens are considered to be indicative of clinically relevant bacteriuria (20) (LE: 2b, GR: C).
### 3.4.1.3 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound should be performed to rule out urinary obstruction or renal stone disease (LE: 4, GR: C).

Additional investigations, such as an unenhanced helical computed tomography (CT), excretory urography, or dimercaptosuccinic acid (DMSA) scanning, should be considered if the patients remain febrile after 72 h of treatment (LE: 4, GR: C).

### 3.4.2 Therapy

As a result of the lack of suitable surveillance studies, the spectrum and susceptibility patterns of uropathogens that cause uncomplicated cystitis can be used as a guide for empirical therapy (3) (LE: 4, GR: B). However, *S. saprophyticus* is less frequent in acute pyelonephritis as compared to acute cystitis (LE: 4, GR: B).

#### 3.4.2.1 Mild and moderate cases of acute uncomplicated pyelonephritis (Table 3.2)

In mild and moderate cases of acute uncomplicated pyelonephritis, oral therapy of 10-14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still < 10% (21) (LE: 1b, GR: A). If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days (22,23) (LE: 1b, GR: B). However, increasing numbers of fluoroquinolone-resistant *E. coli* in the community have already been found in some parts of the world, thus restricting the empirical use of fluoroquinolones.

A third-generation oral cephalosporin, such as cefpodoxime proxetil or ceftibuten, could be an alternative (24,25) (LE: 1b, GR: B). However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin.

As a result of increasing *E. coli* resistance rates >10%, cotrimoxazole is not suitable for empirical therapy in most areas, but it can be used after sensitivity has been confirmed through susceptibility testing (26) (LE: 1b, GR: B).

Co-amoxiclav is not recommended as a drug of first choice for empirical oral therapy of acute pyelonephritis (LE: 4, GR: B). It is recommended when susceptibility testing shows a susceptible Gram-positive organism (LE: 4, GR: C).

In communities with high rates of fluoroquinolone-resistant and extended-spectrum β-lactamase (ESBL)-producing *E. coli* (> 10%), initial empirical therapy with an aminoglycoside or carbapenem has to be considered until susceptibility testing demonstrates that oral drugs can also be used (LE: 4, GR: B).

#### 3.4.2.2 Severe cases of acute uncomplicated pyelonephritis (Table 3.2)

Patients with severe pyelonephritis who cannot take oral medication because of systemic symptoms such as nausea and vomiting, have to be treated initially with one of the following parenteral antibiotics:

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A parenteral fluoroquinolone, in communities with <em>E. coli</em> fluoroquinolone-resistance rates &lt; 10%.</td>
<td>1b</td>
</tr>
<tr>
<td>A third-generation cephalosporin, in communities with ESBL-producing <em>E. coli</em> resistance rates &lt; 10%.</td>
<td>1b</td>
</tr>
<tr>
<td>An aminopenicillin plus a β-lactamase-inhibitor in cases of known susceptible Gram-positive pathogens.</td>
<td>4</td>
</tr>
<tr>
<td>An aminoglycoside or carbapenem in communities with fluoroquinolone and/or ESBL-producing <em>E. coli</em> resistance rates &gt; 10%.</td>
<td>1b</td>
</tr>
</tbody>
</table>

Hospital admission should be considered if complicating factors cannot be ruled out by available diagnostic procedures and/or the patient has clinical signs and symptoms of sepsis (LE: 4, GR: B).

After improvement, the patient can be switched to an oral regimen using one of the above-mentioned antibacterials, if active against the infecting organism, to complete the 1-2-week course of therapy (LE: 1b, GR: B).
Table 3.2: Recommended initial empirical antimicrobial therapy in acute uncomplicated pyelonephritis in otherwise healthy premenopausal women

I. Oral therapy in mild and moderate cases

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Daily dose</th>
<th>Duration of therapy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin¹</td>
<td>500-750 mg bid</td>
<td>7-10 days</td>
<td>(21)</td>
</tr>
<tr>
<td>Levofloxacin¹</td>
<td>250-500 mg qd</td>
<td>7-10 days</td>
<td>(27)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg qd</td>
<td>5 days</td>
<td>(22,23)</td>
</tr>
</tbody>
</table>

Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones):

- Cefpodoxime proxetil 200 mg bid 10 days (25)
- Cefditoren 400 mg qd 10 days (24)

Only if the pathogen is known to be susceptible (not for initial empirical therapy):

- Trimethoprim-sulphamethoxazole 160/800 mg bid 14 days (21)
- Co-amoxiclav²,³ 0.5/0.125 g tid 14 days

¹lower dose studied, but higher dose recommended by experts.
²not studied as monotherapy for acute uncomplicated pyelonephritis.
³mainly for Gram-positive pathogens.

II. Initial parenteral therapy in severe cases

After improvement, the patient can be switched to an oral regimen using one of the above-mentioned antibacterials (if active against the infecting organism) to complete the 1-2-week course of therapy. Therefore, only daily dose and no duration of therapy are indicated.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Daily dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg bid</td>
<td>(21)</td>
</tr>
<tr>
<td>Levofloxacin¹</td>
<td>250-500 mg qd</td>
<td>(27)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg qd</td>
<td>(22)</td>
</tr>
</tbody>
</table>

Alternatives:

- Cefotaxime² 2 g tid
- Ceftriaxone¹,⁴ 1-2 g qd (28)
- Ceftazidime² 1-2 g tid (29)
- Cefepime¹,⁴ 1-2 g bid (30)
- Co-amoxiclav²,³ 1.5 g tid
- Piperacillin/tazobactam¹,⁴ 2.5-4.5 g tid (31)
- Gentamicin² 5 mg/kg qd
- Amikacin² 15 mg/kg qd
- Ertapenem⁴ 1 g qd (28)
- Imipenem/cilastatin⁴ 0.5/0.5 g tid (31)
- Meropenem⁴ 1 g tid (29)
- Doripenem⁴ 0.5 g tid (32)

¹lower dose studied, but higher dose recommended by experts.
²not studied as monotherapy in acute uncomplicated pyelonephritis.
³mainly for Gram-positive pathogens.
⁴same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Figure 3.1: Clinical management of acute pyelonephritis

**symptoms/signs of pyelonephritis**
- fever, flank pain
  - nausea, vomiting

**NO**
- urinalysis und urine culture
- sonography (if anomaly suspected)
- outpatient therapy
- initial oral therapy
  - ➢ ciprofloxacin or levofloxacin
  - ➢ aminopenicillin plus BLI
  - ➢ group 3 cephalosporin (e.g. cefpodoxime proxetil)
  - ➢ TMP-SMX, only if susceptibility of pathogen is known (not for empirical therapy)

**clinical improvement within 72 h**
- oral therapy continued (test confirm)
- total duration of therapy 1-2 Weeks

**additional urine and blood cultures**
  - urological investigation for complicating factors drainage, in case of obstruction or abscess
  - total duration of therapy 2-3 Weeks

**no clinical improvement or even deterioration**
- switch to parenteral therapy (test confirm)
- Outpatient therapy
- hospitalisation
- total duration of therapy 1-2 Weeks

**YES**
- urinalysis und urine culture
- sonography (in all patients)
- hospitalisation
- initial parenteral therapy for 1-3 days
  - ➢ ciprofloxacin or levofloxacin
  - ➢ aminopenicillin- or piperacillin plus BLI
  - ➢ group 3 cephalosporin
  - ➢ aminoglycosid

**clinical improvement within 72 h**
- switch to oral therapy (test confirm)
- Outpatient therapy
- hospitalisation
- total duration of therapy 1-2 Weeks

**no clinical improvement or even deterioration**
- parenteral therapy continued (test confirm)
- hospitalisation continued

**additional urine and blood cultures**
  - urological investigation for complicating factors drainage, in case of obstruction or abscess
  - total duration of therapy 2-3 Weeks

*BLI = β-lactamase inhibitor; TMP = trimethoprim; SMX = sulphamethoxazole.*
3.4.3 **Follow-up**

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C).

In women whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal ultrasound, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

In patients with no urological abnormality, it should be assumed that the infecting organism is not susceptible to the agent originally used, and an alternative tailored treatment should be considered based on culture results (LE: 4, GR: B).

For patients who relapse with the same pathogen, the diagnosis of uncomplicated pyelonephritis should be reconsidered. Appropriate diagnostic steps are necessary to rule out any complicating factors (LE: 4, GR: C).

An algorithm of the clinical management of acute pyelonephritis is shown in Figure 3.1.

3.5 **Recurrent (uncomplicated) UTIs in women**

3.5.1 **Diagnosis**

Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts (33) (LE: 2a).

Recurrent UTIs need to be diagnosed by urine culture (LE: 4, GR: A). Excretory urography, cystography and cystoscopy are not routinely recommended for evaluation of women with recurrent UTIs (34) (LE: 1b, GR: B).

3.5.2 **Prevention**

Different therapeutic options can be recommended to the patient.

3.5.2.1 **Antimicrobial prophylaxis**

Antimicrobial prophylaxis for prevention of recurrent UTI should be considered only after counselling and behavioural modification has been attempted (LE: 4, GR: A).

Before any prophylaxis regimen is initiated, eradication of a previous UTI should be confirmed by a negative urine culture 1-2 weeks after treatment (LE: 4, GR: A).

Continuous or postcoital antimicrobial prophylaxis should be considered to prevent recurrent uncomplicated cystitis in women in whom non-antimicrobial measures have been unsuccessful (35) (LE: 1a, GR: A). The choice of antibiotics should be based upon the identification and susceptibility pattern of the organism that causes the UTI and the patient's history of drug allergies. Drug regimens are shown in Tables 3.3 and 3.4.

**Table 3.3: Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs (33)**

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Expected UTIs per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX* 40/200 mg once daily</td>
<td>0-0.2</td>
</tr>
<tr>
<td>TMP-SMX 40/200 mg thrice weekly</td>
<td>0.1</td>
</tr>
<tr>
<td>Trimethoprim 100 mg once daily</td>
<td>0-1.5**</td>
</tr>
<tr>
<td>Nitrofurantoin 50 mg once daily</td>
<td>0-0.6</td>
</tr>
<tr>
<td>Nitrofurantoin 100 mg once daily</td>
<td>0-0.7</td>
</tr>
<tr>
<td>Cefaclor 250 mg once daily</td>
<td>0.0</td>
</tr>
<tr>
<td>Cephalexin 125 mg once daily</td>
<td>0.1</td>
</tr>
<tr>
<td>Cephalexin 250 mg once daily</td>
<td>0.2</td>
</tr>
<tr>
<td>Norfloxacin 200 mg once daily</td>
<td>0.0</td>
</tr>
<tr>
<td>Ciprofloxacin 125 mg once daily</td>
<td>0.0</td>
</tr>
<tr>
<td>Fosfomycin 3 g every 10 days</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Trimethoprim-sulfamethoxazole
**high recurrence rates observed with trimethoprim use associated with trimethoprim resistance
Table 3.4: Postcoital antimicrobial prophylaxis regimens for women with recurrent UTIs (33)

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Expected UTIs per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX* 40/200 mg</td>
<td>0.30</td>
</tr>
<tr>
<td>TMP-SMX 80/400 mg</td>
<td>0.00</td>
</tr>
<tr>
<td>Nitrofurantoin 50 or 100 mg</td>
<td>0.10</td>
</tr>
<tr>
<td>Cephalaxin 250 mg</td>
<td>0.03</td>
</tr>
<tr>
<td>Ciprofloxacin 125 mg</td>
<td>0.00</td>
</tr>
<tr>
<td>Norfloxacin 200 mg</td>
<td>0.00</td>
</tr>
<tr>
<td>Ofloxacin 100 mg</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Trimethoprim-sulfamethoxazole

In appropriate women with recurrent uncomplicated cystitis, self-diagnosis and self-treatment with a short-course regimen of an antimicrobial agent should be considered (36) (LE: 2b, GR: A).

3.5.2.2  Immunoactive prophylaxis
OM-89 (Uro-Vaxom®) is sufficiently well-documented and has been shown to be more effective than placebo in several randomised trials. Therefore, it can be recommended for immunoprophylaxis in female patients with recurrent uncomplicated UTI (37,38) (LE: 1a, GR: B). Its efficacy in other groups of patients, and its efficacy relative to antimicrobial prophylaxis remain to be established.

For other immunotherapeutic products on the market, larger phase III studies are still missing. In smaller phase II studies, StroVac® and Solco-Urovac® have been shown to be effective when administered with a booster cycle of the same agents (LE: 1a, GR: C).

For other immunotherapeutic products, such as Urostim® and Urvakol®, no controlled studies are available. Therefore, no recommendations are possible.

3.5.2.3  Prophylaxis with probiotics
Accessibility of clinically proven probiotics for UTI prophylaxis is currently not universal. Only the Lactobacillus strains specifically tested in studies should be used for prophylaxis.

When commercially available, it is reasonable to consider the use of intravaginal probiotics that contain L. rhamnosus GR-1 and L. reuteri RC-14 for the prevention of recurrent UTI (39), and these products can be used once or twice weekly (LE: 4, GR: C).

Daily use of the oral product with strains GR-1 and RC-14 is worth testing given that it can restore the vaginal lactobacilli, compete with urogenital pathogens, and prevent bacterial vaginosis, a condition that increases the risk of UTI (39) (LE: 1b, GR: C).

3.5.2.4  Prophylaxis with cranberry
Despite the lack of pharmacological data and the small number of weak clinical studies, there is evidence to suggest that cranberry (Vaccinium macrocarpon) is useful in reducing the rate of lower UTIs in women (40,41) (LE: 1b, GR: C).

For everyday practice, the daily consumption of cranberry products, giving a minimum of 36 mg/day proanthocyanidin A (the active compound), is recommended (LE: 1b, GR: C). The best approach is to use those compounds that have demonstrated clear bioactivity in urine.

3.6  UTIs in pregnancy
Urinary tract infections and asymptomatic bacteriuria are common during pregnancy. Most women are prone to or acquire asymptomatic bacteriuria before pregnancy, and 20-40% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy.

3.6.1  Diagnosis of UTI in pregnant women
Diagnostic criteria of acute cystitis and pyelonephritis in otherwise healthy pregnant women are similar to that of non-pregnant women (3.3.1 and 3.4.1). However, physical examination and urinalysis including urine culture are highly recommended in cystitis. In addition, in case of suspicion of pyelonephritis, ultrasound of the kidneys and urinary tract is necessary.

3.6.2  Definition of bacteriuria
- In a pregnant woman, asymptomatic bacteriuria is diagnosed in case of two consecutive voided urine
specimens with growth of $\geq 10^5$ cfu/mL of the same bacterial species; or a single catheterised specimen with growth of $\geq 10^5$ cfu/mL of a uropathogen (LE: 2a, GR: A).

- In a pregnant woman with symptoms compatible with UTI, bacteriuria is considered relevant if a voided or catheterised urine specimen grows $\geq 10^3$ cfu/mL of a uropathogen (LE: 4, GR: B).

3.6.3 Screening
Pregnant women should be screened for bacteriuria during the first trimester (LE: 1a, GR: A).

3.6.4 Treatment of asymptomatic bacteriuria and acute cystitis
Asymptomatic bacteriuria detected during pregnancy should be eradicated with antimicrobial therapy (LE: 1a, GR: A). Acute cystitis should be adequately treated. Recommended antibiotic regimens are listed in Table 3.5.

Table 3.5: Treatment regimens for asymptomatic bacteriuria and cystitis in pregnancy (44)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Duration of therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin (Macrobid®) 100 mg</td>
<td>q12 h, 3-5 days</td>
<td>Avoid in G6PD deficiency</td>
</tr>
<tr>
<td>Amoxicillin 500 mg</td>
<td>q8 h, 3-5 days</td>
<td>Increasing resistance</td>
</tr>
<tr>
<td>Co-amoxicillin/clavulanate</td>
<td>500 mg q12 h, 3-5 days</td>
<td></td>
</tr>
<tr>
<td>Cephalexin (Keflex®) 500 mg</td>
<td>q8 h, 3-5 days</td>
<td>Increasing resistance</td>
</tr>
<tr>
<td>Fosfomycin 3 g</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>q12 h, 3-5 days</td>
<td>Avoid trimethoprim in first trimester/term</td>
</tr>
</tbody>
</table>

G6PD = glucose-6-phosphate dehydrogenase

3.6.5 Duration of therapy
Short courses of antimicrobial therapy (3 days) should be considered for the treatment of asymptomatic bacteriuria and cystitis in pregnancy (LE: 1a, GR: A).

3.6.6 Follow-up
Urine cultures should be obtained 1-2 weeks after completion of therapy for asymptomatic bacteriuria and symptomatic UTI in pregnancy (LE: 4, GR: A).

3.6.7 Prophylaxis
Postcoital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI (LE: 2b, GR: B).

3.6.8 Treatment of pyelonephritis
Outpatient management with appropriate antibiotics should be considered in women with pyelonephritis in pregnancy, provided symptoms are mild and close follow-up is feasible (LE: 1b, GR: A). Recommended parenteral antibiotic regimens are shown in Table 3.6 (45,46). After clinical improvement parenteral therapy can be switched to oral therapy for a total treatment duration of 7-10 days (LE: 4; GR:B).

Table 3.6: Treatment regimens for pyelonephritis in pregnancy

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>1-2 g IV or IM q24 h</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1 g IV q8-12 h</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>3.375-4.5 g IV q6 h</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1 g IV q12 h</td>
</tr>
<tr>
<td>Imipenem-claistatin</td>
<td>500 mg IV q6 h</td>
</tr>
<tr>
<td>Ampicillin +</td>
<td>2 g IV q6 h</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3-5 mg/kg/day IV in 3 divided doses</td>
</tr>
</tbody>
</table>

3.6.9 Complicated UTI
For diagnostics of complicating factors within the urinary tract, ultrasonography or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus (LE: 4; GR: B). Treatment
follows the same general principles as outlines in 4.4. Appropriate antimicrobial therapy for 7-10 days and the management of any urological abnormality are mandatory. Hospitalisation is usually required and supportive care as required.

### 3.7 UTIs in postmenopausal women

#### 3.7.1 Risk factors

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>2a</td>
</tr>
</tbody>
</table>

In older institutionalised women, urine catheterisation and functional status deterioration appear to be the most important risk factors associated with UTI.

Atrophic vaginitis.

Incontinence, cystocele and post-voiding residual urine.

UTI before menopause.

Non-secretor status of blood group antigens.

#### 3.7.2 Diagnosis

Diagnosis of UTI in postmenopausal women should always consider the following:

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

#### 3.7.3 Treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>1b</td>
<td>C</td>
</tr>
</tbody>
</table>

Treatment of acute cystitis in postmenopausal women is similar to that in premenopausal women, however, short-term therapy is not so well-established as in premenopausal women.

Treatment of pyelonephritis in postmenopausal women is similar to that in premenopausal women.

Asymptomatic bacteriuria in elderly women should not be treated with antibiotics.

Optimal antimicrobials, doses and duration of treatment in elderly women appear to be similar to those recommended for younger postmenopausal women.

Oestrogen (especially vaginal) can be administered for prevention of UTI, but results are contradictory.

Alternative methods, such as cranberry and probiotic lactobacilli, can contribute but they are not sufficient to prevent recurrent UTI.

If complicating factors, such as urinary obstruction and neurogenic bladder, are ruled out, antimicrobial prophylaxis should be carried out as recommended for premenopausal women.

### 3.8 Acute uncomplicated UTIs in young men

#### 3.8.1 Men with acute uncomplicated UTI

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only a small number of 15-50-year-old men suffer from acute uncomplicated UTI. Such men should receive, as minimum therapy, a 7-day antibiotic regimen.
### 3.8.2  
**Men with UTI and concomitant prostate infection**

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most men with febrile UTI have a concomitant infection of the prostate, as measured by transient increases in serum PSA and prostate volume.</td>
<td>53</td>
<td>2a</td>
</tr>
<tr>
<td>Urological evaluation should be carried out routinely in adolescents and men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected.</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>A minimum treatment duration of 2 weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent.</td>
<td>54</td>
<td>2a B</td>
</tr>
</tbody>
</table>

### 3.9  
**Asymptomatic bacteriuria**

#### 3.9.1  
**Diagnosis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For women, a count of ≥ 10^5 cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.</td>
<td>17</td>
<td>2b B</td>
</tr>
<tr>
<td>For men, a count of ≥ 10^3 cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.</td>
<td>55</td>
<td>2a B</td>
</tr>
<tr>
<td>For men with specimens collected using an external condom catheter, ≥ 10^5 cfu/mL is an appropriate quantitative diagnostic criterion.</td>
<td>56</td>
<td>2a B</td>
</tr>
<tr>
<td>For patients with indwelling urethral catheters, a count of ≥ 10^5 cfu/mL is diagnostic of bacteriuria.</td>
<td>17</td>
<td>2b B</td>
</tr>
<tr>
<td>For a urine specimen collected by in and out catheter, a count of ≥ 100 cfu/mL is consistent with bacteriuria.</td>
<td>17</td>
<td>2a B</td>
</tr>
<tr>
<td>Pyuria in the absence of signs or symptoms in a person with bacteriuria should not be interpreted as symptomatic infection or as an indication for antimicrobial therapy.</td>
<td>17</td>
<td>2b B</td>
</tr>
</tbody>
</table>

#### 3.9.2  
**Screening**

Screening for and treatment of asymptomatic bacteriuria is recommended:

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For pregnant women.</td>
<td>42</td>
<td>1a A</td>
</tr>
<tr>
<td>Before an invasive genitourinary procedure for which there is a risk of mucosal bleeding.</td>
<td>17</td>
<td>1b A</td>
</tr>
</tbody>
</table>

Screening for or treatment of asymptomatic bacteriuria is not recommended for:

<table>
<thead>
<tr>
<th>Reference</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal, non-pregnant women</td>
<td>17</td>
<td>1a A</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>17</td>
<td>1b A</td>
</tr>
<tr>
<td>Women with diabetes</td>
<td>57</td>
<td>1b A</td>
</tr>
<tr>
<td>Healthy men</td>
<td>58</td>
<td>2b B</td>
</tr>
<tr>
<td>Residents of long-term care facilities</td>
<td>17</td>
<td>1a A</td>
</tr>
<tr>
<td>Patients with an indwelling urethral catheter</td>
<td>17</td>
<td>1b</td>
</tr>
<tr>
<td>Patients with nephrostomy tubes or ureteric stents</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Patients with spinal cord injury</td>
<td>59</td>
<td>2a B</td>
</tr>
<tr>
<td>Patients with candiduria</td>
<td>60</td>
<td>1b A</td>
</tr>
</tbody>
</table>

Screening for or treatment of asymptomatic bacteriuria in renal transplant patients beyond the first 6 months is not recommended (LE: 2b, GR: B).
No recommendation can be made with respect to screening for or treatment of bacteriuria in patients with neutropenia (LE: 4).

### 3.10 References


   http://emedicine.medscape.com/article/245559-workup#aw2aab6b5b3
31. Naber KG, Salmen HC. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/ cilastatin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents 2002 Feb;19(2):95-103.


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC332712/


http://content.karger.com/ProdukteDB/produkte.asp?Doi=61396


4. COMPLICATED UTIs DUE TO UROLOGICAL DISORDERS

4.1 Summary and recommendations
A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defence mechanisms, which increase the risks of acquiring infection or of failing therapy. Examples of risk factors are listed in Table 2.1.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than in uncomplicated UTIs, and bacteria are more likely to be resistant to antimicrobials, especially in a treatment-related complicated UTI.

Enterobacteriaceae are the predominant pathogens, with *E. coli* being the most common pathogen. However, non-fermenters (e.g. *Pseudomonas aeruginosa*) and Gram-positive cocci (e.g. staphylococci and enterococci) may also play an important role, depending on the underlying conditions.

Treatment strategy depends on the severity of the illness. Treatment encompasses three goals: management of the urological abnormality, antimicrobial therapy, and supportive care when needed. Hospitalisation is often required. To avoid the emergence of resistant strains, therapy should be guided by urine culture whenever possible.

If empirical therapy is necessary, the antibacterial spectrum of the antibiotic agent should include the most relevant pathogens (GR: A). A fluoroquinolone with mainly renal excretion, an aminopenicillin plus a β-lactamase inhibitor (BLI), a Group 2 or 3a cephalosporin or, in the case of parenteral therapy, an aminoglycoside, are recommended alternatives (LE: 1b, GR: B).

In case of failure of initial therapy, or in case of clinically severe infection, a broader-spectrum antibiotic should be chosen that is also active against *Pseudomonas* (LE: 1b, GR: B), e.g. a fluoroquinolone (if not used for initial therapy), an acylaminopenicillin (piperacillin) plus a BLI, a Group 3b cephalosporin, or a carbapenem, with or without combination with an aminoglycoside (LE: 1b, GR: B).

The duration of therapy is usually 7-14 days (LE: 1b, GR: A), but sometimes has to be prolonged for up to 21 days (LE: 1b, GR: A).

Until predisposing factors are completely removed, true cure without recurrent infection is usually not possible. Therefore, a urine culture should be carried out 5-9 days after completion of therapy and also 4-6 weeks later (GR: B).

4.2 Definitions and classification
A complicated UTI is an infection associated with a condition, such as structural or functional abnormalities
of the genitourinary tract or the presence of an underlying disease, which increases the risks of acquiring an infection or of failing therapy (1-3). Two criteria are mandatory to define a complicated UTI: a positive urine culture and one or more of the factors listed in Table 4.1.

Table 4.1: Factors that suggest a potential complicated UTI

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>The presence of an indwelling catheter, stent or splint (urethral, ureteral, renal) or the use of intermittent bladder catheterisation</td>
</tr>
<tr>
<td>Post-void residual urine of &gt; 100 mL</td>
</tr>
<tr>
<td>An obstructive uropathy of any aetiology, e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumour</td>
</tr>
<tr>
<td>Vesicoureteric reflux or other functional abnormalities</td>
</tr>
<tr>
<td>Urinary tract modifications, such as an ileal loop or pouch</td>
</tr>
<tr>
<td>Chemical or radiation injuries of the uroepithelium</td>
</tr>
<tr>
<td>Peri- and postoperative UTI</td>
</tr>
<tr>
<td>Renal insufficiency and transplantation, diabetes mellitus and immunodeficiency</td>
</tr>
</tbody>
</table>

Complicated UTI can arise in a heterogeneous group of patients. However, neither patient age nor sex per se are part of the definition of a complicated UTI. With regard to prognosis and clinical studies, it is advisable to stratify complicated UTIs due to urological disorders into at least two groups (4):

1. Patients in whom the complicating factors could be eliminated by therapy, e.g. stone extraction, removal of an indwelling catheter.
2. Patients in whom the complicating factor could not be or is not removed satisfactorily during therapy, e.g. permanent indwelling catheter, stone residues after treatment or neurogenic bladder.

4.2.1 **Clinical presentation**

A complicated UTI may or may not be associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever). Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a catheter-associated postoperative UTI, which might disappear spontaneously as soon as the catheter is removed. It also has to be recognised that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as benign prostatic hyperplasia (BPH) or transurethral resection of the prostate (TURP).

Apart from urological abnormalities, concomitant medical conditions, such as diabetes mellitus (10%) and renal failure, which can be related to urological abnormalities (5), are often present in a complicated UTI. These are discussed in more details in Sections 8.1.3 and 8.1.4 on UTIs in renal insufficiency, transplant recipients, diabetes mellitus and immunosuppression.

4.2.2 **Urine cultures**

Significant bacteriuria in a complicated UTI is defined by counts of \( \geq 10^5 \) cfu/mL and \( \geq 10^4 \) cfu/mL, in the midstream urine (MSU) of women and men, respectively (1,2). If a straight catheter urine sample is taken, \( \geq 10^4 \) cfu/mL can be considered relevant. For an asymptomatic patient, two consecutive urine cultures (at least 24 h apart) yielding \( \geq 10^6 \) cfu/mL of the same microorganism are required. The requirement for pyuria is \( \geq 10 \) white blood cells (WBC) per high-power field (x400) in the resuspended sediment of a centrifuged aliquot of urine or per mm\(^3\) in unspun urine. A dipstick method can also be used for routine assessment, including a leukocyte esterase test, haemoglobin and probably a nitrite reaction.

4.3 **Microbiology**

4.3.1 **Spectrum and antibiotic resistance**

Patients with a complicated UTI, both community and hospital-acquired, tend to show a diversity of microorganisms with a higher prevalence of resistance against antimicrobials, and higher rates of treatment failure if the underlying abnormality cannot be corrected.

However, the presence of a resistant strain on its own is not enough to define a complicated UTI. Urinary abnormality (anatomical or functional) or the presence of an underlying disease predisposing to a UTI is also necessary.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than with an uncomplicated UTI and the bacteria are more likely to be antibiotic-resistant (especially in a treatment-related complicated UTI) than those isolated in an uncomplicated UTI. *E. coli, Proteus, Klebsiella, Pseudomonas and*
4.3.2 Complicated UTIs associated with urinary stones
In the subset of complicated UTIs related to urinary stones, the frequency of *E. coli* and enterococci infection seems less important pathogens. In contrast, a greater portion of *Proteus* and *Pseudomonas* sp. (9) is found. Of the urease-producing organisms, *Proteus, Providencia* and *Morganella* sp., and *Corynebacterium urealyticum* are predominant, but *Klebsiella, Pseudomonas* and *Serratia* sp. and staphylococci are also urease producers to a certain extent.

Among patients with staghorn calculus disease, 88% were found to have a UTI at the time of diagnosis, with 82% of patients infected with urease-producing organisms (10). The enzyme, urease, splits urea into carbon dioxide and ammonia. The resultant increase in ammonia in the urine injures the glycosaminoglycan layer, which in turn increases bacterial adherence (11) and enhances the formation of struvite crystals. These aggregate to form renal stones and incrustations on urinary catheters (12).

The pathogenic potential of coagulase-negative staphylococci and non-group D streptococci is controversial (13,14). Under certain circumstances, such as the presence of a stone or foreign bodies, staphylococci can be relevant pathogens. Otherwise, staphylococci are not so common in complicated UTIs (0-11%), according to published reports (6,15).

4.3.3 Complicated UTIs associated with urinary catheters
In catheter-associated UTIs, the distribution of microorganisms is similar (16), and biofilm has to be considered. Antimicrobial therapy may only be effective in the early stages of the infection (15). For more details see Chapter 6 on catheter-associated UTIs.

4.4 Treatment

4.4.1 General principles
Treatment strategy depends on the severity of the illness. Appropriate antimicrobial therapy and the management of the urological abnormality are mandatory. If needed, supportive care is given. Hospitalisation is often necessary depending on the severity of the illness.

4.4.2 Choice of antibiotics
Empirical treatment of a symptomatic complicated UTI requires a knowledge of the spectrum of possible pathogens and local antibiotic resistance patterns, as well as assessment of the severity of the underlying urological abnormality (including the evaluation of renal function).

Bacteraemia is usually reported too late to influence the choice of antibiotics. However, suspicion of bacteraemia must influence the empirical treatment. The severity of the associated illness and the underlying urological condition are still of the utmost importance for prognosis.

Many therapeutic trials have been published on the use of specific antimicrobial therapies in complicated UTIs. Unfortunately, most reports are of limited use for the practical management of the patient in a day-to-day situation because of limitations such as:

- poor characterisation of the patient populations;
- unclear evaluation of the severity of the illness;
- nosocomial and community-acquired infections are not accurately distinguished;
- urological outcome is seldom taken into consideration.

Intense use of any antimicrobial, especially when used on an empirical basis in this group of patients with a high likelihood of recurrent infection, will lead to the emergence of resistant microorganisms in subsequent infections. Whenever possible, empirical therapy should be replaced by a therapy adjusted for the specific infective organisms identified in the urine culture. Therefore, a urine specimen for culture must be obtained before initiation of therapy, and the selection of an antimicrobial agent should be re-evaluated once culture results are available (7). To date, it has not been shown that any agent or class of agents is superior in cases in which the infective organism is susceptible to the drug administered.

In patients with renal failure, whether related to a urological abnormality or not, appropriate dose adjustments have to be made.

If empirical treatment is necessary, fluoroquinolones with mainly renal excretion are recommended because they have a large spectrum of antimicrobial activity that covers most of the expected pathogens, and they reach high concentration levels both in the urine and the urogenital tissues. Fluoroquinolones can be used orally as well as parenterally. An aminopenicillin plus a BLI, a Group 2 or 3a cephalosporin, or, in the case of parenteral therapy, an aminoglycoside, are alternatives. A new Group 1 oral carbapenem, ertapenem, in a
prospective randomised trial, has been shown to be as effective as ceftriaxone (16).

In most countries, \textit{E. coli} shows a high rate of resistance against TMP-SMX (18-25% in the latest evaluation in the USA) (17) and should therefore be avoided as a first-line treatment. Fosfomycin trometamol is licensed only for a single-dose therapy of uncomplicated cystitis (18). The aminopenicillins, ampicillin or amoxicillin, are no longer sufficiently active against \textit{E. coli}.

In the case of failure of initial therapy, or if microbiological results are not yet available, or as initial therapy in the case of clinically severe infection, treatment should be switched to an antibiotic with a broader spectrum that is also active against \textit{Pseudomonas}, such as a fluoroquinolone (if not used for initial therapy), an acylaminopenicillin (piperacillin) plus a BLI, a Group 3b cephalosporin, or a carbapenem, eventually in combination with an aminoglycoside. Similarly, many experts concur that empirical therapy for the institutionalised or hospitalised patients with a serious UTI should include an intravenous antipseudomonal agent because of an increased risk of urosepsis (19).

Patients can generally be treated as outpatients. In more severe cases (e.g. hospitalised patients), antibiotics have to be given parenterally. A combination of an aminoglycoside with a BLI or a fluoroquinolone is widely used for empirical therapy. After a few days of parenteral therapy and clinical improvement, patients can be switched to oral treatment. Therapy has to be reconsidered when the infective strains have been identified and their susceptibilities are known.

The successful treatment of a complicated UTI always combines effective antimicrobial therapy, optimal management of the underlying urological abnormalities or other diseases, and sufficient life-supporting measures. The antibacterial treatment options are summarised in Table 4.2 and Appendix 16.2 (Recommendations for antimicrobial therapy in urology).

4.4.3 \textbf{Duration of antibiotic therapy}

Treatment for 7-14 days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality (1). Sometimes, a prolongation for up to 21 days, according to the clinical situation, is necessary (2).

4.4.4 \textbf{Complicated UTIs associated with urinary stones}

If a nidus of a stone or an infection remains, stone growth will occur. Complete removal of the stones and adequate antimicrobial therapy are both needed. Eradication of the infection will probably eliminate the growth of struvite calculi (20). Long-term antimicrobial therapy should be considered if complete removal of the stone cannot be achieved (21).

4.4.5 \textbf{Complicated UTIs associated with indwelling catheters}

Current data do not support the treatment of asymptomatic bacteriuria, either during short-term catheterisation (< 30 days) or during long-term catheterisation, because it will promote the emergence of resistant strains (22,23). In short-term catheterisation, antibiotics may delay the onset of bacteriuria, but do not reduce complications (24).

A symptomatic complicated UTI associated with an indwelling catheter is treated with an agent with as narrow a spectrum as possible, based on culture and sensitivity results. The optimal duration is not well established. Treatment durations that are too short as well as too long may cause the emergence of resistant strains. A 7-day course could be a reasonable compromise.

4.4.6 \textbf{Complicated UTIs in patients with spinal cord injury}

In case of persistent UTIs and suspicion of urinary retention, a full urodynamic assessment to appraise bladder function is to be carried out. Priority is to ensure proper drainage of the bladder to protect the urinary tract. For further details, see the EAU guidelines on Neurogenic Lower Urinary Tract Dysfunction (25).

It is generally accepted that asymptomatic bacteriuria in patients with spinal cord injury should not be treated (26), even in cases of intermittent catheterisation. For symptomatic episodes of infection in patients with spinal cord injury, only a few studies have investigated the most appropriate agent and duration of therapy. Currently, 7-10 days of therapy is most commonly used. There is no superiority of one agent or class of antimicrobials in this group of patients.

Antimicrobial treatment options are summarised in Table 4.2.
Table 4.2: Antimicrobial treatment options for empirical therapy

<table>
<thead>
<tr>
<th>Antibiotics recommended for initial empirical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Aminopenicillin plus a BLI</td>
</tr>
<tr>
<td>Cephalosporin (Groups 2 or 3a)</td>
</tr>
<tr>
<td>Aminoglycoside</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone (if not used for initial therapy)</td>
</tr>
<tr>
<td>Ureidopenicillin (piperacillin) plus BLI</td>
</tr>
<tr>
<td>Cephalosporin (Group 3b)</td>
</tr>
<tr>
<td>Carbapenem</td>
</tr>
<tr>
<td>Combination therapy:</td>
</tr>
<tr>
<td>- Aminoglycoside + BLI</td>
</tr>
<tr>
<td>- Aminoglycoside + fluoroquinolone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics not recommended for empirical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminopenicillins, e.g. amoxicillin, ampicillin</td>
</tr>
<tr>
<td>Trimethoprim-sulphamethoxazole (only if susceptibility of pathogen is known)</td>
</tr>
<tr>
<td>Fosfomycin trometamol</td>
</tr>
</tbody>
</table>

BLI = β-lactam inhibitor

4.4.7 Follow-up after treatment
The greater likelihood of the involvement of resistant microorganisms in complicated UTIs is another feature of these infectious diseases. This is not a priori related to the urinary abnormality, but is related more to the fact that patients with a complicated UTI tend to have recurrent infection. For these reasons, before and after the completion of the antimicrobial treatment, urine cultures must be obtained for the identification of the microorganisms and the evaluation of susceptibility testing.

4.5 References


5. SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

5.1 Summary and recommendations
Patients with urosepsis should be diagnosed at an early stage, especially in the case of a complicated UTI. The systemic inflammatory response syndrome, known as SIRS (fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia, tachypnoea), is recognised as the first event in a cascade to multi-organ failure. Mortality is considerably increased when severe sepsis or septic shock are present, although the prognosis of urosepsis is globally better than that of sepsis from other infectious sites.

The treatment of urosepsis calls for the combination of adequate life-supporting care, appropriate and prompt antibiotic therapy, adjunctive measures (e.g. sympathomimetic amines, hydrocortisone, blood glucose control) and the optimal management of urinary tract disorders (LE: 1a, GR: A). The drainage of any obstruction in the urinary tract is essential as first-line treatment (LE: 1b, GR: A). Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists (LE: 2a, GR: B).

Urosepsis is seen in both community-acquired and healthcare associated infections. Most nosocomial urosepsis can be avoided by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urethral catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily asepsis techniques to avoid cross-infection (LE: 2a, GR: B).

5.2 Background
Urinary tract infections can manifest as bacteriuria with limited clinical symptoms, sepsis or severe sepsis, depending on localised or systemic extension. Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia). Severe sepsis is defined by the presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.

Severe sepsis is a severe situation with a reported mortality rate of 20-42% (1). Most severe sepsis reported in the literature is related to pulmonary (50%) or abdominal (24%) infections, with UTIs accounting for only 5% (2). Sepsis is more common in men than in women (3). In recent years, the incidence of sepsis has increased by 8.7% per year (1), but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% during 1995-2000) (4). Globally (this is not true for urosepsis), the rate of sepsis due to fungal organisms has increased while Gram-positive bacteria have become the predominant pathogen in sepsis, even if Gram-negative bacteria remain predominant in urosepsis.

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include: elderly patients; diabetics; immunosuppressed patients, such as transplant recipients; patients receiving cancer chemotherapy or corticosteroids; and patients with AIDS. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract. Moreover, it is now recognised that SIRS may be present without infection (e.g. pancreatitis, burns, or non-septic shock) (5).

For therapeutic purposes, the diagnostic criteria of sepsis should identify patients at an early stage of the syndrome, which should prompt urologists and intensive care specialists to search for and treat infection, apply appropriate therapy, and monitor for organ failure and other complications.

5.3 Definition and clinical manifestation of sepsis in urology
The clinical evidence of UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. The following definitions apply (Table 5.1):
- Sepsis is a systemic response to infection. The symptoms of SIRS which were initially considered to be “mandatory” for the diagnosis of sepsis (5), are now considered to be alerting symptoms (6). Many
other clinical or biological symptoms must be considered.  
- Severe sepsis is sepsis associated with organ dysfunction.  
- Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation.  
- Refractory septic shock is defined by an absence of response to therapy.

Table 5.1: Clinical diagnostic criteria of sepsis and septic shock (5,6)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>Bacteria present in blood as confirmed by culture. May be transient.</td>
</tr>
</tbody>
</table>
| Systemic inflammatory response syndrome (SIRS) | Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following conditions:  
  - Temperature > 38°C or < 36°C  
  - Heart rate > 90 bpm  
  - Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg (< 4.3 kPa)  
  - WBC > 12,000 cells/mm3 or < 4,000 cells/mm3 or > 10% immature (band) forms |
| Sepsis                           | Activation of the inflammatory process due to infection.                   |
| Hypotension                      | Systolic blood pressure < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes of hypotension. |
| Severe sepsis                    | Sepsis associated with organ dysfunction, hypoperfusion or hypotension.    
  Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or acute alteration of mental status. |
| Septic shock                     | Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotrope or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured. |
| Refractory septic shock          | Septic shock that lasts for > 1 h and does not respond to fluid administration or pharmacological intervention. |

5.4 Physiology and biochemical markers
Microorganisms reach the urinary tract by way of the ascending, haematogenous, or lymphatic routes. For urosepsis to be established, the pathogens have to reach the bloodstream. The risk of bacteraemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis, and is facilitated by obstruction of the urinary tract. E. coli remains the most prevalent microorganism. In several countries, some bacterial strains can be resistant to quinolones or third-generation cephalosporins. Some microorganisms are multi-resistant, such as methicillin-resistant Staphylococcus aureus (MRSA), P. aeruginosa and Serratia sp. and therefore difficult to treat. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection. A fatal outcome is described in 20-40% of all patients.

5.4.1 Cytokines as markers of the septic response
Cytokines are involved in the pathogenesis of sepsis syndrome. They are peptides that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. When they become bound to specific receptors on other cells, cytokines change their behaviour in the inflammatory response. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Other cytokines are involved such as interleukins (ILs).
Tumour necrosis factor (TNF)-α, IL-1, IL-6 and IL-8 are cytokines that are associated with sepsis. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood (2).

5.4.2 Procalcitonin is a potential marker of sepsis
Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise to > 100 ng/mL. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. The exact site of procalcitonin production during sepsis is not known. Procalcitonin monitoring may be useful in patients likely to develop a SIRS of infectious origin. High procalcitonin levels, or an abrupt increase in levels in these patients, should prompt a search for the source of infection. Procalcitonin may be useful in differentiating between infectious and non-infectious causes of severe inflammatory status (7,8).

5.5 Prevention
Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for a combination of treatment of the cause (obstruction of the urinary tract), adequate life-supporting care, and appropriate antibiotic therapy (2). In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

5.5.1 Preventive measures of proven or probable efficacy (9,10)
The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections:

• Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
• Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
• Reduction in hospital stay. It is well known that long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
• Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting (11). Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
• Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
• Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
• Attention to simple everyday techniques to assure asepsis, including the routine use of protective, disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

5.5.2 Appropriate perioperative antimicrobial prophylaxis
For appropriate perioperative antimicrobial prophylaxis, see Section 15. The potential side effects of antibiotics must be considered before their administration in a prophylactic regimen.

5.5.3 Preventive measures of debatable efficacy
• Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.
• Use of urinary catheters coated with antibiotics or silver.

5.5.4 Ineffective or counterproductive measures
• Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase the risk of infection with resistant bacteria (9,12).
• Routine administration of antimicrobial drugs to catheterised patients, which reduces the incidence of bacteriuria only for a few days and increases the risk of infection with multi-resistant bacteria (9,12). Its use may be reserved for immunosuppressed patients.
5.6 Algorithm for the management of urosepsis

Figure 5.1: Clinical algorithm for the management of urosepsis

5.7 Treatment

5.7.1 Clinical algorithm for management of urosepsis

Table 5.2: Early goal directed therapy

<table>
<thead>
<tr>
<th>Early goal directed therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous pressure (CVP)</td>
<td>8-12 mmHg</td>
</tr>
<tr>
<td>Mean arterial pressure (MAP)</td>
<td>65-90 mmHg</td>
</tr>
<tr>
<td>Central venous oxygen (CVO2)</td>
<td>≥ 70%</td>
</tr>
<tr>
<td>Haematocrit (HKT)</td>
<td>&gt; 30 %</td>
</tr>
<tr>
<td>Urine output</td>
<td>&gt; 40 mL/h</td>
</tr>
</tbody>
</table>

Table 5.3: Levels of therapy in sepsis

<table>
<thead>
<tr>
<th>Levels of therapy in sepsis</th>
<th></th>
</tr>
</thead>
</table>
| Causal therapy                  | 1. Antimicrobial treatment  
|                                  | 2. Source control |
| Supportive therapy              | 1. Haemodynamic stabilisation  
|                                  | 2. Airways, respiration |
| Adjunctive therapy              | 1. Glucocorticosteroids  
|                                  | 2. Intensified insulin therapy |
5.7.2 **Relief of obstruction**
Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, should lead to resolution of symptoms and recovery. These are key components of the strategy. This condition is an absolute emergency.

5.7.3 **Antimicrobial therapy**
Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the basis of culture results. The dosage of the antibiotic substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure. Antimicrobials must be administered not later than 1 h after clinical assumption of sepsis (see algorithm). The antibacterial treatment options are summarised in Appendix 16.1 and 16.2.

5.7.4 **Adjunctive measures (12,13)**
The management of fluid and electrolyte balance is a crucial aspect of patient care in sepsis syndrome; particularly when the clinical course is complicated by shock. The use of human albumin is debatable. Early goal-directed therapy has been shown to reduce mortality (14). Volaemic expansion and vasopressor therapy have a considerable impact on the outcome. Early intervention with appropriate measures to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilisation of arterial pressure, and providing sufficient oxygen transport capacity are highly effective.

   Hydrocortisone (with a debate on dosage) is useful in patients with relative insufficiency in the pituitary gland-adrenal cortex axis (adrenocorticotropic test) (15).
   
   Tight blood glucose control by administration of insulin doses up to 50 U/h is associated with a reduction in mortality (16).
   
   Current evidence does not support the use of human recombinant activated protein C in adults and children with severe sepsis and septic shock (17).

   The best strategy has been summarised and graded according to a careful evidence-based methodology in the recently published ‘Surviving Sepsis Guidelines’ (18).

5.8 **Conclusion**
Sepsis syndrome in urology remains a severe situation with a mortality rate as high as 20-40%. A recent campaign, ‘Surviving Sepsis Guidelines’, aimed at reducing mortality by 25% in the next few years has been published recently (18). Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patient survival. The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using antibiotic prophylaxis and therapy in a prudent and well-accepted manner.

5.9 **Acknowledgement**
The authors are thankful to Jean M. Carlet, Head of Intensive Care, Hôpital Saint Joseph, Paris, France, for reviewing this manuscript on urosepsis.

5.10 **References**
6. CATHETER-ASSOCIATED UTIs

Based on the EAU guidelines published in 2007 (ISBN-13:978-90-70244-59-0), the following text presents the findings of a comprehensive update produced as a collaborative effort by the ESIU (a full EAU section office), the Urological Association of Asia, the Asian Association of UTI/STD, the Western Pacific Society for Chemotherapy, the Federation of European Societies for Chemotherapy and Infection, and the International Society of Chemotherapy for Infection and Cancer. This text was recently published as “The European and Asian guidelines on management and prevention of catheter-associated urinary tract infections” (1). Since the complete document is available online, only the abstract and a summary of the recommendations are presented here.

6.1 Abstract

We surveyed the extensive literature regarding the development, therapy and prevention of catheter-associated UTIs (CAUTIs). We systematically searched for meta-analyses of randomised controlled trials available in Medline, and gave preference to the Cochrane Central Register of Controlled Trials, and also considered other relevant publications, rating them on the basis of their quality. Studies were identified through a PubMed search. The recommendations of the studies, rated according to a modification of the US Department of Health...
and Human Services (1992), give a close-to-evidence-based guideline for all medical disciplines, with special emphasis on urology, in which catheter care is an important issue.

The survey found that the urinary tract is the commonest source of nosocomial infection, particularly when the bladder is catheterised (LE: 2a). Most CAUTIs are derived from the patient’s own colonic flora (LE: 2b) and the catheter predisposes to UTI in several ways. The most important risk factor for the development of catheter-associated bacteriuria is the duration of catheterisation (LE: 2a). Most episodes of short-term catheter-associated bacteriuria are asymptomatic and are caused by a single organism (LE: 2a). Further organisms tend to be acquired by patients who are catheterised for > 30 days.

The clinician should be aware of two priorities: the catheter system should remain closed and the duration of catheterisation should be minimal (GR: A). The use of nurse-based or electronic reminder systems to remove unnecessary catheters can decrease the duration of catheterisation and the risk of CAUTI (LE: 2a). The drainage bag should be always kept below the level of the bladder and the connecting tube (GR: B). In case of short-term catheterisation, routine prophylaxis with systemic antibiotics is not recommended (GR: B). There are sparse data about antibiotic prophylaxis in patients on long-term catheterisation, therefore, no recommendation can be made (GR: C). For patients using intermittent catheterisation, routine antibiotic prophylaxis is not recommended (GR: B). Antibiotic irrigation of the catheter and bladder is of no advantage (GR: A). Healthcare workers should be constantly aware of the risk of cross-infection between catheterised patients. They should observe protocols on hand washing and the need to use disposable gloves (GR: A).

A minority of patients can be managed with the use of the non-return (flip) valve catheters, thus avoiding the closed drainage bag. Such patients may exchange the convenience of on-demand drainage with an increased risk of infection. Patients with urethral catheters in place for ≥ 10 years should be screened annually for bladder cancer (GR: C). Clinicians should always consider alternatives to indwelling urethral catheters that are less prone to causing symptomatic infection. In appropriate patients, suprapubic catheters, condom drainage systems and intermittent catheterisation are each preferable to indwelling urethral catheterisation (GR: B). While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended (GR: A), except for some special cases. Routine urine culture in an asymptomatic catheterised patient is also not recommended (GR: C) because treatment is in general not necessary. Antibiotic treatment is recommended only for symptomatic infection (GR: B). After initiation of empirical treatment, usually with broad-spectrum antibiotics based on local susceptibility patterns (GR: C), the choice of antibiotics might need to be adjusted according to urine culture results (GR: B). Long-term antibiotic suppressive therapy is not effective (GR: A).
### 6.2 Summary of recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General aspects</strong></td>
<td></td>
</tr>
<tr>
<td>1. Written catheter care protocols are necessary.</td>
<td>B</td>
</tr>
<tr>
<td>2. Health care workers should observe protocols on hand hygiene and the need to use disposable gloves between catheterised patients.</td>
<td>A</td>
</tr>
<tr>
<td><strong>Catheter insertion and choice of catheter</strong></td>
<td></td>
</tr>
<tr>
<td>3. An indwelling catheter should be introduced under antiseptic conditions.</td>
<td>B</td>
</tr>
<tr>
<td>4. Urethral trauma should be minimised by the use of adequate lubricant and the smallest possible catheter calibre.</td>
<td>B</td>
</tr>
<tr>
<td>5. Antibiotic-impregnated catheters may decrease the frequency of asymptomatic bacteriuria within 1 week. There is, however, no evidence that they decrease symptomatic infection. Therefore, they cannot be recommended routinely.</td>
<td>B</td>
</tr>
<tr>
<td>6. Silver alloy catheters significantly reduce the incidence of asymptomatic bacteriuria, but only for &lt; 1 week. There was some evidence of reduced risk for symptomatic UTI. Therefore, they may be useful in some settings.</td>
<td>B</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>7. The catheter system should remain closed.</td>
<td>A</td>
</tr>
<tr>
<td>8. The duration of catheterisation should be minimal.</td>
<td>A</td>
</tr>
<tr>
<td>9. Topical antiseptics or antibiotics applied to the catheter, urethra or meatus are not recommended.</td>
<td>A</td>
</tr>
<tr>
<td>10. Benefits from prophylactic antibiotics and antiseptic substances have never been established, therefore, they are not recommended.</td>
<td>A</td>
</tr>
<tr>
<td>11. Removal of the indwelling catheter after non-urological operation before midnight might be beneficial.</td>
<td>B</td>
</tr>
<tr>
<td>12. Long-term indwelling catheters should be changed at intervals adapted to the individual patient, but must be changed before blockage is likely to occur, however, there is no evidence for the exact intervals of changing catheters.</td>
<td>B</td>
</tr>
<tr>
<td>13. Chronic antibiotic suppressive therapy is generally not recommended.</td>
<td>A</td>
</tr>
<tr>
<td>14. The drainage bag should always be kept below the level of the bladder and the connecting tube.</td>
<td>B</td>
</tr>
<tr>
<td><strong>Diagnostics</strong></td>
<td></td>
</tr>
<tr>
<td>15. Routine urine culture in asymptomatic catheterised patients is not recommended.</td>
<td>B</td>
</tr>
<tr>
<td>16. Urine, and in septic patients, also blood for culture must be taken before any antimicrobial therapy is started.</td>
<td>C</td>
</tr>
<tr>
<td>17. Febrile episodes are only found in &lt; 10% of catheterised patients living in a long-term facility. It is therefore extremely important to rule out other sources of fever.</td>
<td>A</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>18. While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended, except in certain circumstances, especially before traumatic urinary tract interventions.</td>
<td>A</td>
</tr>
<tr>
<td>19. In case of asymptomatic candiduria, neither systemic nor local antifungal therapy is indicated, but removal of the catheter or stent should be considered.</td>
<td>A/C</td>
</tr>
<tr>
<td>20. Antimicrobial treatment is recommended only for symptomatic infection.</td>
<td>B</td>
</tr>
<tr>
<td>21. In case of symptomatic CAUTI, it might be reasonable to replace or remove the catheter before starting antimicrobial therapy if the indwelling catheter has been in place for &gt; 7 days.</td>
<td>B</td>
</tr>
<tr>
<td>22. For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns.</td>
<td>C</td>
</tr>
<tr>
<td>23. After culture results are available, antibiotic therapy should be adjusted according to pathogen sensitivity.</td>
<td>B</td>
</tr>
</tbody>
</table>
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| 24. | In case of candiduria associated with urinary symptoms, or if candiduria is the sign of systemic infection, systemic therapy with antifungals is indicated. | B |
| 25. | Elderly female patients may need treatment if bacteriuria does not resolve spontaneously after catheter removal. | C |

**Alternative drainage systems**

| 26. | There is limited evidence that postoperative intermittent catheterisation reduces the risk of bacteriuria compared with indwelling catheters. No recommendation can be made. | C |
| 27. | In appropriate patients, a suprapubic, condom drainage system or intermittent catheter is preferable to an indwelling urethral catheter. | B |
| 28. | There is little evidence to suggest that antibiotic prophylaxis decreases bacteriuria in patients using intermittent catheterisation, therefore, it is not recommended. | B |

**Long-term follow up**

| 29. | Patients with urethral catheters in place for ≥ 10 years should be screened for bladder cancer. | C |

### 6.3 Reference


### 7. UTIs IN CHILDREN

#### 7.1 Summary and recommendations

Urinary tract infection in children is a frequent health problem, with the incidence only a little lower than that of upper respiratory and digestive infections.

The incidence of UTI varies depending on age and sex. In the first year of life, mostly the first 3 months, UTI is more common in boys (3.7%) than in girls (2%), after which the incidence changes, being 3% in girls and 1.1% in boys. Paediatric UTI is the most common cause of fever of unknown origin in boys aged < 3 years. The clinical presentation of UTI in infants and young children can vary from fever to gastrointestinal and lower or upper urinary tract symptoms.

Investigation should be undertaken after two episodes of UTI in girls and one in boys (GR: B). The objective is to rule out the unusual occurrence of obstruction, vesicoureteric reflux (VUR) and dysfunctional voiding, e.g. as caused by a neuropathic disorder.

Chronic pyelonephritic renal scarring develops very early in life due to the combination of a UTI, intrarenal reflux and VUR. It sometimes arises *in utero* due to dysplasia. Although rare, renal scarring may lead to severe long-term complications such as hypertension and chronic renal failure.

VUR is treated with long-term prophylactic antibiotics (GR: B). Surgical re-implantation or endoscopic treatment is reserved for the small number of children with breakthrough infection (GR: B).

For treatment of UTI in children, short courses are not advised and therefore treatment is continued for 5-7 days and longer (GR: A). If the child is severely ill with vomiting and dehydration, hospital admission is required and parenteral antibiotics are given initially (GR: A).

#### 7.2 Background

The urinary tract is a common source of infection in children and infants. It represents the most common bacterial infection in children < 2 years of age (1) (LE: 2a). The outcome of a UTI is usually benign, but in early infancy, it can progress to renal scarring, especially when associated with congenital anomalies of the urinary tract. Delayed sequelae related to renal scarring include hypertension, proteinuria, renal damage and even chronic renal failure, which requires dialysis treatment in a significant number of adults (2) (LE: 2a).

The risk of UTI during the first decade of life is 1% in males and 3% in females (3). It has been suggested that 5% of schoolgirls and up to 0.5% of schoolboys undergo at least one episode of UTI during their school life. The incidence is different for children < 3 months of age, when it is more common in boys. The incidence of asymptomatic bacteriuria is 0.7-3.4% in neonates, 0.7-1.3% in infants < 3 months of age, and 0.2-0.8% in preschool boys and girls (3). The incidence of symptomatic bacteriuria is 0.14% in neonates, with a further increase to 0.7% in boys and 2.8% in girls aged < 6 months. The overall recurrence rate for the neonatal period has been reported to be 25% (3,4).
7.3 **Aetiology**
The common pathogenic sources are Gram-negative, mainly enteric, bacteria. Of these, *E. coli* is responsible for 90% of UTI episodes (5). Gram-positive bacteria (particularly enterococci and staphylococci) represent 5-7% of cases. Hospital-acquired infections show a wider pattern of aggressive bacteria, such as *Klebsiella, Serratia* and *Pseudomonas* sp. Groups A and B streptococci are relatively common in new-born infants (6). There is an increasing trend towards the isolation of *S. saprophyticus* in UTIs in children, although the role of this bacterium is still debatable (7).

7.4 **Pathogenesis and risk factors**
The urinary tract is a sterile space with an impermeable lining. Retrograde ascent is the most common mechanism of infection. Nosocomial infection and involvement as part of a systemic infection are less common (8).

Obstruction and dysfunction are among the most common causes of urinary infection. Phimosis predisposes to UTI (9,10) (LE: 2a). Enterobacteria derived from intestinal flora colonise the preputial sac, glandular surface and the distal urethra. Among these bacteria are strains of *E. coli* that express P fimbriae, which adhere to the inner layer of the preputial skin and to uroepithelial cells (11).

A wide variety of congenital urinary tract abnormalities can cause UTIs through obstruction, e.g. urethral valves, ureteropelvic junction obstruction or non-obstructive urinary stasis (e.g. prune belly syndrome, or VUR). More mundane but significant causes of UTIs include labial adhesion and chronic constipation (7).

Dysfunctional voiding in an otherwise normal child may result in infrequent bladder emptying aided by delaying manoeuvres, e.g. crossing legs, sitting on heels (12). Neuropathic bladder dysfunction (e.g. spina bifida, or sphincter dyssynergia) may lead to post-void residual urine and secondary VUR (4).

The link between renal damage and UTIs is controversial. The mechanism in obstructive nephropathy is self-evident, but more subtle changes occur when there is VUR. Almost certainly, the necessary components include VUR, intrarenal reflux and UTI. These must all work together in early childhood when the growing kidney is likely to be susceptible to parenchymal infection. Later on in childhood, the presence of bacteriuria seems irrelevant to the progression of existing scars or the very unusual formation of new scars. Another confounding factor is that many so-called scars are dysplastic renal tissue which develop in utero (13).

7.5 **Signs and symptoms**
Symptoms are non-specific, and vary with the age of the child and the severity of the disease. Epididymo-orchitis is extremely unusual. With scrotal pain and inflammation, testicular torsion has to be considered.

A UTI in neonates may be non-specific and with no localisation. In small children, a UTI may present with gastrointestinal signs, such as vomiting and diarrhoea. In the first weeks of life, 13.6% of patients with fever have a UTI (14). Rarely, septic shock is the presentation. Signs of UTI may be vague in small children, but later on, when they are older than 2 years, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain may appear with or without fever.

7.6 **Classification**
UTIs may be classified as a first episode or recurrent, or according to severity (simple or severe). Recurrent UTI may be subclassified into three groups (8):

- **Unresolved infection**: subtherapeutic level of antimicrobial, non-compliance with treatment, malabsorption, resistant pathogens.
- **Bacterial persistence**: may be due to a nidus for persistent infection in the urinary tract. Surgical correction or medical treatment for urinary dysfunction may be needed.
- **Reinfection**: each episode is a new infection acquired from periurethral, perineal or rectal flora. From the clinical point of view, severe and simple forms of UTIs should be differentiated because to some extent the severity of symptoms dictates the degree of urgency with which investigation and treatment are to be undertaken (Table 7.1).

### Table 7.1: Clinical classification of UTIs in children

<table>
<thead>
<tr>
<th>Severe UTI</th>
<th>Simple UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 39°C</td>
<td>Mild pyrexia</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>Good fluid intake</td>
</tr>
<tr>
<td>Serious dehydration</td>
<td>Slight dehydration</td>
</tr>
<tr>
<td>Poor treatment compliance</td>
<td>Good treatment compliance</td>
</tr>
</tbody>
</table>
7.6.1 **Severe UTI**
Severe UTI is related to the presence of fever of \(\geq 39^\circ\text{C}\), the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

7.6.2 **Simple UTI**
A child with a simple UTI may have only mild pyrexia, but is able to take fluids and oral medication. The child is only slightly or not dehydrated and has a good expected level of compliance. When a low level of compliance is expected, such a child should be managed as one with a severe UTI.

7.7 **Diagnosis**

7.7.1 **Physical examination**
It is mandatory to look for phimosis, labial adhesion, signs of pyelonephritis, epididymo-orchitis, and stigmata of spina bifida, e.g. hairy patch on the sacral skin. The absence of fever does not exclude the presence of an infective process.

7.7.2 **Laboratory tests**
The definitive diagnosis of infection in children requires a positive urine culture (8,15). Urine must be obtained under bacteriologically reliable conditions when undertaking a urine specimen culture (16). A positive urine culture is defined as the presence of > 100,000 cfu/mL of one pathogen. The urine specimen may be difficult to obtain in a child < 4 years old, and different methods are advised because there is a high risk of contamination (17,18).

7.7.2.1 **Collection of the urine**

7.7.2.1.1 Suprapubic bladder aspiration
Suprapubic bladder aspiration is the most sensitive method, even though urine may be obtained in 23-99% of cases (8,18).

7.7.2.1.2 Bladder catheterisation
Bladder catheterisation is also a very sensitive method, even though there is the risk of introduction of nosocomial pathogens (8,19).

7.7.2.1.3 Plastic bag attached to the genitalia
Prospective studies have shown a high incidence of false-positive results, ranging from 85 to 99% (8,18). It is helpful when the culture is negative (8,18) and has a positive predictive value of 15% (16). To obtain a urine sample in the best condition in children < 2 years of age (girls and uncircumcised boys without sphincteric control), it is better to use suprapubic bladder aspiration or bladder catheterisation. In older children with sphincteric control, MSU collection is possible and reliable (18).

7.7.2.2 **Quantification of bacteriuria**
The final concentration of bacteria in urine is directly related to the method of collection, diuresis, and method of storage and transport of the specimen (15). The classical definition of significant bacteriuria of > 10^5 cfu/mL is still used and depends on the clinical environment (15,17).

The presence of pyuria (> 5 leukocytes per field) and bacteriuria in a fresh urine sample reinforce the clinical diagnosis of UTI (17).

In boys, when the urine is obtained by bladder catheterisation, the urine culture is considered positive with > 10^6 cfu/mL. Even though Hoberman (20) has identified a microorganism in 65% of cases with colony counts between 10,000 and 50,000 cfu/mL, there was a mixed growth pattern suggesting contamination. In these cases, it is better to repeat the culture or to evaluate the presence of other signs, such as pyuria, nitrites or other biochemical markers (15). The collection of MSU or in a collecting bag of \(\geq 10^6\) cfu/mL is considered positive (16) (Table 7.2).

**Table 7.2: Criteria for UTI in children**

<table>
<thead>
<tr>
<th>Urine specimen from suprapubic bladder puncture</th>
<th>Urine specimen from bladder catheterisation</th>
<th>Urine specimen from midstream void</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any number of cfu/mL (at least 10 identical colonies)</td>
<td>(\geq 1,000-50,000) cfu/mL</td>
<td>(\geq 10^4) cfu/mL with symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\geq 10^6) cfu/mL without symptoms</td>
</tr>
</tbody>
</table>
7.7.2.3 Other biochemical markers

The presence of other biochemical markers in a urine sample are useful to establish the diagnosis of UTI (8). The most frequent markers are nitrite and leukocyte esterase usually combined in a dipstick test.

7.7.2.3.1 Nitrite

Nitrite is the degradation product of nitrate in bacterial metabolism, particularly in Gram-negative bacteria. When an infection is caused by Gram-positive bacteria, the test may be negative (8,16). Limitations of the nitrite test include:

- not all uropathogens reduce nitrate to nitrite, e.g. *P. aeruginosa*, or enterococci;
- even nitrite-producing pathogens may show a negative test result, due to the short transit time in the bladder in cases of high diuresis and urine dilution, e.g. neonates;
- the nitrite test has a sensitivity of only 45-60%, but a very good specificity of 85-98% (8,17,21).

7.7.2.3.2 Leukocyte esterase

Leukocyte esterase is produced by the activity of leukocytes. The test for leukocyte esterase has a sensitivity of 48-86% and a specificity of 17-93% (8,17,20,21).

A combination of nitrite and leukocyte esterase testing improves sensitivity and specificity, but carries the risk of false-positive results (21).

The dipstick test has become useful to exclude rapidly and reliably the presence of a UTI, provided both nitrite and leukocyte esterase tests are negative. If the tests are positive, it is better to confirm the results in combination with the clinical symptoms and other tests (17,21).

Bacteriuria without pyuria may be found:

- in bacterial contamination;
- in colonisation (asymptomatic bacteriuria);
- when collecting a specimen before the onset of an inflammatory reaction.

In such cases, it is advisable to repeat the urinalysis after 24 h to clarify the situation. Even in febrile children with a positive urine culture, the absence of pyuria may cast doubt on the diagnosis of UTI. Instead, asymptomatic bacteriuria with a concomitant septic focus responsible for the febrile syndrome has to be considered.

Bacteriuria without pyuria is found in 0.5% of specimens. This figure corresponds well with the estimated rate of asymptomatic bacteriuria in childhood (20,22) (LE: 2a).

Pyuria without bacteriuria may be due to:

- incomplete antimicrobial treatment of UTI;
- urolithiasis and foreign bodies;
- infections caused by *M. tuberculosis* and other fastidious bacteria, e.g. Chlamydia trachomatis.

Thus, either bacteriuria or pyuria may not be considered reliable parameters to diagnose or exclude UTI. Their assessment can be influenced by other factors, such as the degree of hydration, method of specimen collection, mode of centrifugation, volume in which sediment is resuspended and subjective interpretation of results (23). However, according to Landau et al. (24), pyuria in febrile children is indicative of acute pyelonephritis.

For all of these reasons, in neonates and children < 6 months of age, either pyuria, bacteriuria or the nitrite test, separately, have minimal predictive value for UTI (25,26) (LE: 3). In contrast, the positive predictive value of significant Gram staining with pyuria is 85% (20) (LE: 2b). In older children, pyuria with a positive nitrite test is more reliable for the diagnosis of UTI, with a positive predictive value of 98%.

Combining bacteriuria and pyuria in febrile children, the findings of ≥ 10 WBC/mm³ and ≥ 50,000 cfu/mL in a specimen collected by catheterisation are significant for a UTI, and discriminate between infection and contamination (20,25).

7.7.2.3.3 C-reactive protein

Although non-specific in febrile children with bacteriuria, C-reactive protein seems to be useful in distinguishing between acute pyelonephritis and other causes of bacteriuria. It is considered significant at a concentration > 20 μg/mL.

7.7.2.3.4 Urinary N-acetyl-β-glucosaminidase

Urinary N-acetyl-β-glucosaminidase is a marker of tubular damage. It is increased in febrile UTI and may become a reliable diagnostic marker for UTIs, although it is also elevated in VUR (27).

7.7.2.3.5 IL-6

The clinical use of urinary concentrations of IL-6 in UTIs (28) is still at the research stage.
7.7.3  Imaging of the urinary tract
A gold standard imaging technique has to be cost-effective, painless, safe, and have minimal or no radiation, as well as have the ability to detect any significant structural anomaly. Current techniques do not fulfil all such requirements.

7.7.3.1  Ultrasonography
Ultrasonography (US) has become very useful in children because of its safety, speed and high accuracy in identifying the anatomy and size of the renal parenchyma and collecting system (29). It is subjective and therefore operator-dependent, and gives no information on renal function. However, scars can be identified, although not as well as with Tc-99m DMSA scanning (29,30) (LE: 2a). This technique has been shown to be very sensitive and excretory urography must be reserved only for when images need to be morphologically clarified (31) (LE: 2a).

7.7.3.2  Radionuclide studies
Tc-99m DMSA is a radiopharmaceutical that is bound to the basement membrane of proximal renal tubular cells; half of the dose remains in the renal cortex after 6 h. This technique is helpful in determining functional renal mass and ensures an accurate diagnosis of cortical scarring by showing areas of hypoactivity, which indicates lack of function. A UTI interferes with the uptake of this radiotracer by the proximal renal tubular cells, and may show areas of focal defect in the renal parenchyma. A star-shaped defect in the renal parenchyma may indicate an acute episode of pyelonephritis. A focal defect in the renal cortex usually indicates a chronic lesion or a renal scar (32-34) (LE: 2a).

Focal scarring or a smooth uniform loss of renal substance as demonstrated by Tc-99m DMSA is generally regarded as being associated with VUR (reflux nephropathy) (35,36). However, Rushton et al. (37) have stated that significant renal scarring may develop, regardless of the existence or absence of VUR. Ransley and Risdon (38) have reported that Tc-99m DMSA shows a specificity of 100% and sensitivity of 80% for renal scarring.

The use of Tc-99m DMSA scanning can be helpful in the early diagnosis of acute pyelonephritis. About 50-85% of children show positive findings in the first week. Minimal parenchymal defects, when characterised by a slight area of hypoactivity, can resolve with antimicrobial therapy (39,40). However, defects lasting > 5 months are considered to be renal scarring (41) (LE: 2a).

Tc-99m DMSA scans are considered more sensitive than excretory urography and US in the detection of renal scars (42-45). It remains questionable whether radionuclide scans can substitute for echography as a first-line diagnostic approach in children with a UTI (46,47).

7.7.3.3  Cystourethrography
7.7.3.3.1 Conventional voiding cystourethrography
Voiding cystourethrography (VCU) is the most widely used radiological exploration for the study of the lower urinary tract and especially of VUR. It is considered mandatory in the evaluation of UTIs in children < 1 year of age. Its main drawbacks are the risk of infection, the need for retrogrades filling of the bladder, and the possible deleterious effect of radiation on children (48). In recent years, tailored low-dose fluoroscopic VCU has been used for the evaluation of VUR in girls to minimise radiological exposure (49). VCU is mandatory in the assessment of febrile childhood UTI, even in the presence of normal US. Up to 23% of these patients may reveal VUR (50).

7.7.3.3.2 Radionuclide cystography (indirect)
This investigation is performed by prolonging the period of scanning after the injection of Tc-99m diethylene triamine pentaacetate (DTPA) or mercaptoacetyltriglycine (MAG-3) as part of dynamic renography. It represents an attractive alternative to conventional cystography, especially when following patients with reflux, because of its lower dose of radiation. Disadvantages are poor image resolution and difficulty in detecting lower urinary tract abnormalities (51,52).

7.7.3.3.3 Cystosonography
Contrast-material-enhanced voiding ultrasonography has been introduced for the diagnoses of VUR without irradiation (47,52). Further studies are necessary to determine the role of this new imaging modality in UTI.

7.7.3.4  Additional imaging
Excretory urography remains a valuable tool in the evaluation of the urinary tract in children, but its use in UTIs is debatable unless preliminary imaging has demonstrated abnormalities that require further investigation. The major disadvantages in infants are the risks of side effects from exposure to contrast media and radiation (53). However, the role of excretory urography is declining with the increasing technical superiority of CT (54) and
MRI. However, the indications for their use is still limited in UTI.

7.7.3.5 Urodynamic evaluation
When voiding dysfunction is suspected, e.g. incontinence, residual urine, increased bladder wall thickness, urodynamic evaluation with uroflowmetry, (video) cystometry, including pressure flow studies, and electromyography should be considered.

7.8 Schedule of investigation
Screening of infants for asymptomatic bacteriuria is unlikely to prevent pyelonephritic scar formation, as these usually develop very early in infancy. Only a minority of children with a UTI have an underlying urological disorder, but when present, such a disorder can cause considerable morbidity. Thus, after a maximum of two UTI episodes in a girl and one in a boy, investigations should be undertaken (Figure 7.1), but not in the case of asymptomatic bacteriuria (51-58). The need for DTPA/MAG-3 scanning is determined by the ultrasound findings, particularly if there is suspicion of an obstructive lesion.

Figure 7.1: Schedule of investigation of a UTI in a child

![Diagram showing schedule of investigation]

DMSA = dimercaptosuccinic acid; UTI = urinary tract infection; VCU = voiding cystourethrography.

7.9 Treatment
Treatment has four main goals:
1. elimination of symptoms and eradication of bacteriuria in the acute episode;
2. prevention of renal scarring;
3. prevention of a recurrent UTI;
4. correction of associated urological lesions.

7.9.1 Severe UTIs
A severe UTI requires adequate parenteral fluid replacement and appropriate antimicrobial treatment, preferably with cephalosporins (third generation). If a Gram-positive UTI is suspected by Gram stain, it is useful to administer aminoglycosides in combination with ampicillin or amoxicillin/clavulanate (59) (LE: 2a). Antimicrobial treatment has to be initiated on an empirical basis, but should be adjusted according to culture results as soon as possible. In patients with an allergy to cephalosporins, aztreonam or gentamicin may be used. When aminoglycosides are necessary, serum levels should be monitored for dose adjustment. Chloramphenicol, sulphonamides, tetracyclines, rifampicin, amphotericin B and quinolones should be avoided. The use of ceftriaxone must also be avoided due to its undesired side effect of jaundice.

A wide variety of antimicrobials can be used in older children, with the exception of tetracyclines (because of tooth staining). Fluorinated quinolones may produce cartilage toxicity (58), but if necessary, may be used as second-line therapy in the treatment of serious infections, because musculoskeletal adverse events are of moderate intensity and transient (60,61). For a safety period of 24-36 h, parenteral therapy should be administered. When the child becomes afebrile and is able to take fluids, he/she may be given an oral agent to complete the 10-14 days of treatment, which may be continued on an outpatient basis. This provides some advantages, such as less psychological impact on the child and more comfort for the whole family. It is also less expensive, well tolerated and eventually prevents opportunistic infections (20). The preferred oral antimicrobials are: trimethoprim (TMP), co-trimoxazole (TMP plus sulphamethoxazole), an oral cephalosporin,
or amoxycillin/clavulanate. However, the indications for TMP are declining in areas with increasing resistance.

In children < 3 years of age, who have difficulty taking oral medications, parenteral treatment for 7-10 days seems advisable, with similar results to those with oral treatment (62).

If there are significant abnormalities in the urinary tract (e.g. VUR, or obstruction), appropriate urological intervention should be considered. If renal scarring is detected, the patient will need careful follow-up by a paediatrician in anticipation of sequelae such as hypertension, renal function impairment, and recurrent UTI.

An overview of the treatment of febrile UTIs in children is given in Figure 7.2 and the dosing of antimicrobial agents is outlined in Table 7.3 (63).

**Figure 7.2: Treatment of febrile UTIs in children**

<table>
<thead>
<tr>
<th>Severe UTI</th>
<th>Simple UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral therapy until afebrile</td>
<td></td>
</tr>
<tr>
<td>• Adequate hydration</td>
<td></td>
</tr>
<tr>
<td>• Cephalosporins (third generation)</td>
<td></td>
</tr>
<tr>
<td>• Amoxycillin/clavulanate if cocci are present</td>
<td></td>
</tr>
<tr>
<td>Oral therapy</td>
<td></td>
</tr>
<tr>
<td>• Parenteral single-dose therapy (only in case of doubtful compliance)</td>
<td></td>
</tr>
<tr>
<td>• Cephalosporins (third generation)</td>
<td></td>
</tr>
<tr>
<td>• Gentamicin</td>
<td></td>
</tr>
</tbody>
</table>

**7.9.2 Simple UTIs**
A simple UTI is considered to be a low-risk infection in children. Oral empirical treatment with TMP, an oral cephalosporin or amoxycillin/clavulanate is recommended, according to the local resistance pattern. The duration of treatment in uncomplicated UTIs treated orally should be 5-7 days (64,65) (LE: 1b). A single parenteral dose may be used in cases of doubtful compliance and with a normal urinary tract (66) (LE: 2a). If the response is poor or complications develop, the child must be admitted to hospital for parenteral treatment (67).

**7.9.3 Prophylaxis**
If there is an increased risk of pyelonephritis, e.g. VUR, and recurrent UTI, low-dose antibiotic prophylaxis is recommended (68,69) (LE: 2a). It may also be used after an acute episode of UTI until the diagnostic work-up is completed. The most effective antimicrobial agents are: nitrofurantoin, TMP, cephalexin and cefaclor (68).

**7.10 Acknowledgement**
With our grateful thanks, the chapter on UTIs in children was updated also by Jorge Caffaratti Sfulcini, Paediatric Urology, Fundació Puigvert, Barcelona, Spain, as co-author.
Table 7.3: Dosing of antimicrobial agents in children aged 3 months to 12 years*

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Application</th>
<th>Age</th>
<th>Total dose per day</th>
<th>No. of doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Intravenous</td>
<td>3-12 months</td>
<td>100-300 mg/kg BW</td>
<td>3</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Intravenous</td>
<td>1-12 years</td>
<td>60-150 (-300) mg/kg BW</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Oral</td>
<td>3 months to 12 years</td>
<td>50-100 mg/kg BW</td>
<td>2-3</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>Intravenous</td>
<td>3 months to 12 years</td>
<td>60-100 mg/kg BW</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>Oral</td>
<td>3 months to 12 years</td>
<td>37.5-75 mg/kg BW</td>
<td>2-3</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>Treatment</td>
<td>Oral</td>
<td>3 months to 12 years</td>
<td>50-100 mg/kg BW</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td>Oral</td>
<td>1-12 years</td>
<td>10 mg/kg BW</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Treatment</td>
<td>Oral</td>
<td>3 months to 12 years</td>
<td>50-100 mg/kg BW</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td>Oral</td>
<td>1-12 years</td>
<td>10 mg/kg BW</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Oral</td>
<td>3 months to 12 years</td>
<td>8-12 mg/kg BW</td>
<td>1-2</td>
</tr>
<tr>
<td>Cetriaxone</td>
<td>Intravenous</td>
<td>3 months to 12 years</td>
<td>50-100 mg/kg BW</td>
<td>1</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Intravenous</td>
<td>3 months to 12 years</td>
<td>(50)-100 mg/kg BW</td>
<td>3</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Intravenous</td>
<td>3-12 months</td>
<td>5-7.5 mg/kg BW</td>
<td>1-3</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Intravenous</td>
<td>1-2 years</td>
<td>5 mg/kg BW</td>
<td>1-3</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Treatment</td>
<td>Oral</td>
<td>1-12 years</td>
<td>6 mg/kg BW</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td>Oral</td>
<td>1-12 years</td>
<td>1-2 mg/kg BW</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Treatment</td>
<td>Oral</td>
<td>1-12 years</td>
<td>3-5 mg/kg BW</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td>Oral</td>
<td>1-12 years</td>
<td>1 mg/kg BW</td>
</tr>
</tbody>
</table>

BW = body weight.
* Adapted from ref. 63.

7.11 References


17. Watson AR. Pediatric urinary tract infection. EAU Update Series 2, 2004 Sep, pp. 94-100. 
http://www.journals.elsevierhealth.com/periodicals/euoas/article/PIIS1570912404000406/abstract


http://cat.inist.fr/?aModele=afficheN&cpsidt=14436165


8. **UTIs IN RENAL INSUFFICIENCY, TRANSPLANT RECIPIENTS, DIABETES MELLITUS AND IMMUNOSUPPRESSION**

8.1 **Summary and recommendations**

8.1.1 **Acute effects of UTI on the kidney**

In acute pyelonephritis, very dramatic changes can occur with focal reduction in perfusion on imaging and corresponding renal tubular dysfunction. However, if in the adult the kidney is normal beforehand, chronic renal damage is unlikely. There is no evidence that prolonged or intensive antibiotic treatment of acute pyelonephritis shortens the episode or prevents complications.

In diabetes mellitus, overwhelming infection can predispose to pyogenic infection with intrarenal perinephric abscess formation, emphysematous pyelonephritis, and rarely, a specific form of infective interstitial nephropathy. Papillary necrosis is a common consequence of pyelonephritis in patients with diabetes. Women are more prone to asymptomatic bacteriuria than men with diabetes, but in both sexes, progression to clinical pyelonephritis is more likely than in normal individuals. The risk factors for developing asymptomatic bacteriuria differ between type 1 and type 2 diabetes.

It is arguable that diabetic patients are susceptible to rapid progression of parenchymal infection. However, the clearance of asymptomatic bacteriuria should not be attempted if the intention is to prevent complications, notably acute pyelonephritis (GR: A).

8.1.2 **Chronic renal disease and UTI**

There are several factors of general potential importance that predispose to infection in uraemia, including the loss of several urinary defence mechanisms and a degree of immunosuppression. Typically, adult polycystic kidney disease (APCKD), gross VUR and end-stage obstructive uropathy harbour infective foci or promote ascending infection, but not invariably so. Clearly, severe UTI with accompanying bacteraemia can hasten progression of renal failure, but there is little evidence that vigorous treatment of lesser degrees of infection or prophylaxis will slow renal functional impairment once it is established (GR: C).

In patients with VUR and UTI in end-stage chronic renal failure, bilateral nephroureterectomy should only be undertaken as a last resort (GR: B).

8.1.2.1 **APCKD**

In patients with acute pyelonephritis and infected cysts (presenting as recurrent bacteraemia or local sepsis), treatment requires a long course of high-dose systemic fluoroquinolones, followed by prophylaxis. Bilateral
nephrectomy should be utilised as a last resort (GR: B).

8.1.2.2 **Calculi and UTI**
Management is similar to that for patients without renal impairment, i.e. to clear the stones if possible and to minimise antibiotic treatment if the calculus cannot be removed. Nephrectomy should be performed as a last resort, but even residual renal function may be of vital importance (GR: B).

8.1.2.3 **Obstruction of the urinary tract and UTI**
As in all other situations, the combination of obstruction and infection is dangerous and should be treated vigorously. Obstruction may be covert and require specific diagnostic tests, e.g. video-urodynamics, or upper urinary tract pressure flow studies.

8.1.3 **UTI in renal transplantation and immunosuppression**
The need to correct uropathy or to remove a potential focus of infection in an end-stage disease kidney is more pressing in patients enlisted for renal transplantation. Even so, the results of nephrectomy for a scarred or hydronephrotic kidney may be disappointing.

Immunosuppression is of secondary importance, although if this is extreme, it can promote persistent bacteriuria, which may become symptomatic. In the context of renal transplantation, UTI is very common, but immunosuppression is only one of many factors that are mainly classified as ‘surgical’.

HIV infection is associated with acute and chronic renal disease, possibly through the mechanisms of thrombotic microangiopathy and immune-mediated glomerulonephritis. Steroids, angiotensin-converting enzyme (ACE) inhibitors and highly active retroviral therapy appear to reduce progression to end-stage renal disease.

8.1.4 **Antibiotic treatment for UTI in renal insufficiency and after renal transplantation**
The principles of antibiotic treatment for UTI in the presence of renal impairment, during dialysis treatment and after renal transplantation are discussed in the text and summarised in Tables 8.1-8.4.

8.2 **Background**
Whenever UTI is present in patients with renal insufficiency, problems arise in both the treatment of infection and the management of renal disease. There are also important scientific issues to be considered concerning the cause, special susceptibilities, effects and complications of renal parenchymal infection, particularly in the immunosuppressed patient.

This part of the guidelines can be subdivided into four sections.

1. What are the acute effects of UTI on the kidney and do the lesions become chronic?
2. Does chronic renal disease progress more quickly as a result of infection, and do particular renal diseases predispose to UTI?
3. Are immunosuppressed patients prone to UTI, particularly in the context of renal transplantation? Is UTI a significant cause of graft failure?
4. Which problems arise in antibiotic therapy in patients with renal insufficiency and after renal transplantation?

8.3 **Acute effects of UTI on the kidney**
Some authors regard acute pyelonephritis as complicated because, in their view, it may cause renal scarring in a previously normal kidney (1,2) (LE: 2a). Pathologically, a similar process may occur in such fundamentally different situations as obstructive and reflux nephropathy, although the distribution and extent of the lesions may be different (3-5) (LE: 2a).

8.3.1 **VUR and intrarenal reflux**
The effects of VUR and intrarenal reflux on the renal parenchyma, and the contribution of ascending infection are still unresolved. Renal scarring can certainly be acquired as a result of these three factors, although, in almost all cases, this usually occurs very early in life. In this narrow age range, developmental renal dysplasia must be a major consideration in the pathogenesis of chronic pyelonephritis.

Although acute infection is important in the early stages of this disease, the status of either recurrent acute UTI or asymptomatic bacteriuria specifically in the progression of scar formation is tenuous. Prophylactic antibiotics therefore offer little benefit in preserving renal tissue in reflux nephropathy in older children and adults, even if the reflux has not already been successfully treated (6) (GR: A). However, further discussion of reflux nephropathy is beyond the scope of these guidelines.
8.3.2 **Obstructive neuropathy**

Obstruction occurring through a voiding disorder or supravesically causes renal tubular dysfunction and ultimately renal damage, mainly through the process of apoptosis. Infection enhances the process of parenchymal loss. In extreme cases, pyonephrosis, perinephric abscess and widespread systemic sepsis develop. Obstruction has to be cleared if infection is to be eradicated (7) (GR: A).

A detailed discussion of obstructive nephropathy is not appropriate here, but the kidney that is permanently damaged by any cause has less reserve to withstand the effects of reflux, obstruction and infection. In any circumstances, the combination of obstruction and infection is a surgical emergency and both must be relieved without delay. It is sometimes difficult to exclude an element of obstruction when discussing the pathogenesis of putative infective renal damage in the alleged normal kidney. Urinary calculi and pregnancy can cause urinary stasis and an intermittent increase in pressure in the upper urinary tract, which can cause subtle and persistent damage.

8.3.3 **Renal effects of severe UTI**

Severe infection can lead to renal functional impairment through sepsis, endotoxaemia, hypotension and poor renal perfusion, as a part of the process of multiorgan failure. The presence of renal calculi and diabetes mellitus further reduces host defences (8).

8.3.4 **Acute effects of UTI on the normal kidney**

The acute effects of UTI on the normal kidney are complex. They are worth reviewing because they may provide a lead in deciding how chronic changes can occur and therefore a basis for the development of guidelines on the prevention of renal damage.

*E. coli* is the most common of the Gram-negative bacteria that are isolated in the majority of patients with acute pyelonephritis. The proportion of infections caused by *E. coli* is lower in adults than children (69% vs. 80%) (9) (LE: 2b).

Virulent microorganisms cause direct cellular injury, usually after colonising the renal pelvis. Damage can also occur indirectly from the effects of inflammatory mediators. Metastatic infection rarely causes renal infection, which presents as cortical abscesses, and usually only in susceptible individuals (see the sections below on Diabetes mellitus and Immunosuppression) (10).

Bacterial infection in the urinary tract can induce fever and elevate acute phase reactants, such as C-reactive protein, and erythrocyte sedimentation rate (ESR). Bacterial infection also elicits immunoglobulin A and cytokine responses (11) (LE: 2b). In particular, serum levels of IL-6 and IL-8 are elevated (12,13) (LE: 2b).

Tissue damage is reflected by urinary secretion of tubular proteins and enzymes, such as α2-macroglobulin, β2-microglobulin and N-acetyl-β-D-glucosaminidase. In functional terms, there may be a loss of concentrating power that can persist in the long term (14,15) (LE: 2b). The fact that there is a serological immune response and bacteria become coated with antibodies to various antigenic components of the microorganism is regarded as evidence of an immune response, and therefore, of exposure to microorganisms that are potentially damaging to the renal parenchyma (16) (LE: 2b).

There are many identifiable factors relating to virulence of the bacterial cell and to its ability to adhere to the mucosa as a preliminary to invasion (17). For example, type 1 pili or fimbriae combine with mannose receptors on the uromucoid, which is part of the protective mucopolysaccharide layer found on uroepithelial cells lining the urinary tract. Type 2 or P fimbriae bind to glycolipids of the blood group substances that are secreted by the host urothelium. In practical terms, *E. coli*, which is pathological to the kidney, appears to express P (or pyelonephritis-associated) or type 2 fimbriae, at least in children in whom 90% of individuals with acute pyelonephritis express these bacteria, compared with a much smaller proportion of those who have had cystitis or asymptomatic bacteriuria (18) (LE; 2b).

Bacterial adhesion may be of variable benefit to the bacterium, because its attachment may mean that it is easier for host defence mechanisms to localise and abolish it (19). The cellular and humoral inflammatory host response is also a crucial part of host defences. Various cytokines (e.g., IL-6 and IL-8) are responsible for inducing leukocyte migration, and may be intrinsically deficient in converting asymptomatic bacterial colonisation to clinical infection.

Paradoxically, reduced adhesiveness can facilitate silent penetration into the renal parenchyma. In a Swedish study, a group of 160 patients who had recently suffered acute UTI all developed reduced concentrating power, even though a significant proportion (40%) did not develop a febrile illness. In the majority of these patients, the infiltrating bacteria had reduced adhesive characteristics, perhaps facilitating their penetration into the renal parenchyma and promoting more permanent structural and functional damage (15) (LE: 2b).

8.3.5 **Renal scarring**

The possible development of scarring, as a result of UTI in the absence of reflux, obstruction or calculi, is
controversial (20) (LE: 2a). It is agreed that dramatic reduction in renal perfusion and excretion can occur acutely and so-called ‘lobar nephronia’ has been demonstrated with the newer methods of imaging, such as CT or DMSA scanning, but not with standard intravenous urography (IVU).

A study has shown that 55% of patients with no pre-existing lesions developed acute parenchymal lesions during an episode of acute pyelonephritis (2) (LE: 2a). These lesions were found to have persisted after 3-6 months follow-up in 77% of patients (9) (LE: 3).

An earlier study by Alwall (21) has described 29 women who were followed for 20-30 years, with evidence of increasing renal damage and chronic pyelonephritis upon biopsy (LE: 3). That study would have used cruder diagnostic techniques, which might not have identified pre-existing disease, therefore, patients may have had renal damage initially. Over such a long period, it was impossible to exclude other causes of renal impairment and interstitial nephropathy, e.g. analgesic abuse. This important issue is clarified by a recent more critical study of DMSA scanning during the acute phase of acute pyelonephritis. In the study, 37 of 81 patients had one or more perfusion defects, of which, the majority resolved within 3 months. In lesions that persisted, further imaging invariably showed evidence of reflex or obstructive nephropathy that must have predated the acute infective episode (22) (LE: 2a).

In summary, small parenchymal scars demonstrated by modern imaging may develop as a result of acute non-obstructive pyelonephritis. However, such patients do not develop chronic renal failure and the scar is a very different lesion from the typical scar of reflux nephropathy. This is reflected in clinical experience. Thus, in acute pyelonephritis, IVU or DMSA scanning during an acute urinary infection can have alarming and dramatic results, but in practical terms the observed changes mostly resolve.

The poor correlation between the severity of the symptoms in an episode of acute pyelonephritis and the risk of permanent damage, which is very small, should discourage the clinician from prescribing excessive antibiotic treatment beyond that needed to suppress the acute inflammatory reaction (GR: A).

In future, the rare occurrence of renal damage apparently arising from acute or recurrent uncomplicated UTI may be prevented by targeting long-term treatment at selected patients. These patients will have been identified as having an intrinsic genetic defect in the host response of cytokine release to infection. Such a genetic defect would be even more important if a patient also had structural abnormalities that cause complicated UTI.

8.3.6 Specific conditions in which an acute UTI causes renal damage

There are several specific conditions in which acute UTI can cause renal damage.

8.3.6.1 Diabetes mellitus

Asymptomatic bacteriuria is common in diabetic women. In a prospective study of non-pregnant women with diabetes mellitus, 26% had significant bacteriuria (≥ 10^5 cfu/mL) compared with 6% of controls. Women with type 1 diabetes are particularly at risk if they have had diabetes for a long time or complications have developed, particularly peripheral neuropathy and proteinuria. Risk factors in patients with type 2 diabetes were old age, proteinuria, a low body mass index and a past history of recurrent UTIs (23) (LE: 2a).

Diabetes mellitus increases the risk of acute pyelonephritis from infection by Enterobacteriaceae That originate in the lower urogenital tract. Klebsiella infection is particularly common (25% compared with 12% in non-diabetics).

Asymptomatic bacteriuria is common in women with diabetes (though not in men). If left untreated, it may lead to renal functional impairment (24). The mechanism is ill-understood and, as in uncomplicated acute pyelonephritis, a direct causal link is dubious. Other subtle factors may be present, such as underlying diabetic nephropathy (25) and autonomic neuropathy that causes voiding dysfunction. Impaired host resistance is thought to predispose to persistence of nephropathogenic organisms, but specific evidence is lacking for the development of renal complications. Glycosuria inhibits phagocytosis and perhaps cellular immunity, and encourages bacterial adherence. However, diabetic women with asymptomatic bacteriuria can have good glycaemic control, but still show reduced urinary cytokine and leukocyte concentrations (although polymorph function is normal). Poor glycaemic control has not been shown to increase the risk of bacteriuria (26).

It has always been recognised that diabetic patients are particularly susceptible to rapid progression of renal parenchymal infection and ensuing complications. Until recently, there was no consensus on the questions of pre-emptive screening, treatment and prophylaxis of asymptomatic bacteriuria. However, these issues have been addressed in a placebo-controlled, double-blind randomised trial (27) (LE: 1b), which has concluded that treatment does not reduce complications, and diabetes should not therefore be regarded as an indication for screening or treatment of asymptomatic bacteriuria. The findings from this trial have been subsequently recognised in the guidelines published by the Infectious Diseases Society of America (IDSA) on the diagnosis and treatment of asymptomatic bacteriuria in general (28).

Diabetic patients are also prone to an under-reported and probably unusual form of infective interstitial nephritis, which sometimes includes infection by gas-forming organisms, with a high mortality (emphysematous
pyelonephritis) (29). This is characterised histologically by acute pyogenic infiltration with micro-abscesses and the development of acute renal failure. The origin of the organisms may be haematogenous. Even in the absence of obstruction, acute parenchymal infection may progress insidiously to form an intrarenal abscess that ruptures, which leads to a perinephric collection and a psoas abscess. The presentation can occasionally be indolent.

Papillary necrosis is common in diabetics, particularly in association with acute pyelonephritis. It is certainly associated with permanent renal parenchymal scarring, although it is difficult to exclude obstruction by the sloughed papillae as the cause of the nephropathy. Antibiotic prophylaxis for the treatment of asymptomatic bacteriuria is probably required (GR: C).

8.3.6.2 Tuberculosis
Tuberculosis can cause acute and chronic renal damage through bilateral renal infiltration. Rarely, this can lead to end-stage renal failure. However, a more subtle form of interstitial granulomatous disease can occur, which is sufficient to cause renal failure in the absence of fibrosis, calcification or obstruction (30,31) (LE: 3).

Tuberculosis and leprosy can cause renal damage through the development of amyloid and a form of proliferative glomerulonephritis (32,33) (LE: 2b). For more details see the EAU guidelines on genitourinary tuberculosis (34).

8.4 Chronic renal disease and UTI
There are good reasons why all uraemic patients should be prone to UTI, and why UTI should increase the rate of deterioration of renal function. The antibacterial properties of normal urine, due to urea or low pH and high osmolality, may be lost (35). Uraemic patients are also mildly immunosuppressed and the formation of protective uroepithelial mucus may be inhibited (36-38) (LE: 2b).

However, apart from a few exceptions, there is little evidence for a causal relationship between pre-existing chronic renal disease and persistent UTI (7). The results of removing a scarred or hydronephrotic kidney in the hope of curing infection are often disappointing.

The few exceptions include the following.

8.4.1 Adult dominant polycystic kidney disease (ADPKD)
UTI is a prominent complication of ADPKD, with symptomatic UTI being the presenting feature in 23-42% of patients, who are usually female (39). It may be difficult to obtain a positive culture on standard laboratory media, but pyuria is common, particularly in the later stages of disease progression. Acute pyelonephritis is common and may originate from pyogenic infection in the cysts (40) (LE: 3).

The efficacy of antibiotic treatment may depend on whether cysts are derived from proximal (active secretion) or distal tubules (passive diffusion) and on the lipid solubility of the agent used. Cephalosporins, gentamicin and ampicillin, which are standard treatments of acute pyelonephritis and require active transport, are often ineffective (41) (LE: 2b). Fluoroquinolones are generally the most effective (GR: A).

After transplantation, overall graft and patient survival rates do not differ between ADPKD and control groups (42) (LE: 2a). However, despite close monitoring of patients, UTI and septicaemic episodes are still a significant cause of morbidity, such that bilateral nephrectomy may be the only option.

Polycystic disease is not to be confused with acquired renal cystic disease of the end-stage kidney, which has no predisposition to UTI.

The issue of whether urological complications, including UTI, affect the progression of renal failure in polycystic disease or in any other renal pathology is controversial. Severe symptomatic UTIs may indicate an adverse prognosis, particularly in men with ADPKD.

8.4.2 Renal calculi
Nephrolithiasis, particularly from infective struvite stones, obstructive uropathy and gross reflux, clearly does promote infection, although not always. However, it is doubtful whether vigorous treatment of asymptomatic bacteriuria or even mild clinical UTI makes any difference to the progression of renal disease (43) (LE: 3).

It is disappointing that, as yet, few studies have provided long-term serial data that identify renal damage and its causal relationship with infection. In this respect, it is of some interest that a study of 100 patients who underwent reflux prevention surgery at least 20 years before has recently been published (44). It was concluded that even patients whose reflux prevention surgery had been successful were prone to recurrent UTI, hypertension and complications, which even occasionally included progressive renal scarring. Such consequences should at least inform the patient's decision in deciding between surgical and medical treatment of VUR.
8.5 UTI in renal transplantation

UTI is common after renal transplantation. Bacteriuria is present in 35-80% of patients, although the risk has been reduced by improvements in donation surgery, which have lowered the dose of immunosuppressive therapy and prophylactic antibiotics (45).

8.5.1 Donor organ infection

Early factors predisposing to UTI include infection in the transplanted kidney. Clearly, the organ donor should be screened for a variety of viral and bacterial infections. Detailed discussion of this process is beyond the limits of these guidelines. However, it must be acknowledged that the urinary tract of the cadaver donor is rarely investigated, even if the mid-stream urine (MSU) culture is positive. Antibiotics are given empirically, but usually the first suspicion of occurrence of a renal tract abnormality is raised during the organ donation operation. Under these circumstances, only the most obvious renal or ureteric abnormality will be detected. Very occasionally, organ donation will be abandoned at this late stage.

After the kidney is removed from its storage box, the effluent from the renal vein and surrounding fluid in the sterile plastic bags that contain the excised kidney should ideally be cultured because microorganisms are likely to have been introduced during the donation process. Bladder catheters and ureteric stents promote the loss of the glycosoaminoglycan layer from the uroepithelium, as well as providing a source of microorganisms within the mucous biofilm that covers the foreign body. Infection in the native kidney may worsen considerably as a result of maximum immunosuppression.

In renal transplant recipients, the following problems are most troublesome: papillary necrosis, particularly in diabetes mellitus (46), massive infective VUR, polycystic disease, and infective calculi. There is also concern about the increasing number of children with congenital uropathy, often associated with neuropathic bladder dysfunction and the sinister combination of intravesical obstruction, poor bladder compliance, residual urine, and VUR. A full urodynamic assessment, establishing a routine of intermittent self-catheterisation and any necessary bladder surgery must be completed well in advance of renal transplantation.

Urinary diversions and bladder augmentation and substitution have also been successfully completed in patients on dialysis treatment and after transplantation, although bacteriuria is common and may require antibiotic treatment (47).

In the first 3 months, UTI is more likely to be symptomatic with a high rate of relapse. Later on, there is a lower rate of pyelonephritis and bacteraemia, and a better response to antibiotics unless there are urological complications (e.g. fistula, or obstruction of the urinary tract). Infarction, either of the whole kidney or of a segment due to arterial damage, can promote UTI through bacterial colonisation of dead tissue. This often occurs by commensal or fastidious pathogens. The infection may be impossible to eradicate until the kidney, or at least the dead segment, is removed.

8.5.2 Graft failure

There are several potential mechanisms by which severe UTI can cause graft failure. There was an early suggestion that reflux into the graft could lead to pyelonephritis and parenchymal scarring. However, these findings have not been confirmed and most surgeons do not make a special effort to perform an antireflux anastomosis.

Infection can theoretically induce graft failure by three other mechanisms, such as by the direct effect of cytokines, growth factors (e.g. tumour necrosis factor [TNF]) and free radicals as part of the inflammation cascade (45). UTIs can also reactivate cytomegalovirus infection, which can lead to acute transplant rejection. Sometimes it can be very difficult to distinguish rejection from infection (48) (LE: 2b).

For many years, the polyomavirus type BK has been listed as a possible candidate for causing transplant ureteric stenosis. Improved detection of so-called ‘decoy cells’ in urine and of virus DNA by polymerase chain reaction has confirmed the causal relationship between infection and obstruction, but also with interstitial nephropathy progressing to graft loss in possibly 5% of recipients. The virus is susceptible to treatment with the antiviral agent cidofovir (49) (LE: 2a).

8.5.3 Kidney and whole-organ pancreas transplantation

Simultaneous kidney and whole-organ pancreas transplantation can present specific urological complications when the bladder is chosen for drainage of exocrine secretions. These may include recurrent UTI, chemical urethritis and bladder calculi of sufficient severity to warrant cystoenteric conversion. The risk of such complications is minimised if urodynamic abnormalities, e.g. obstruction, are identified and corrected well in advance of the transplant procedure (50) (LE: 3).

8.6 Antibiotic therapy in renal failure and transplant recipients

Much of the detailed information on antibiotic prescribing in renal failure is summarised in Tables 8.1-8.5 and Appendix 16.3. It is important to note that peritoneal dialysis and haemodialysis clear certain antibiotics, which
should either be avoided or given at much higher doses. Also, there are important interactions to consider between immunosuppressive agents and antibiotics.

**Table 8.1: Use of antibiotics for UTI with renal impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR &lt; 20 mL/min</th>
<th>GFR &lt; 10 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/amoxicillin</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Cephalosporins*</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Aminoglycosides*</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Aztreonam*</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Fluconazole*</td>
<td>Slightly dialysed</td>
<td>Not dialysed</td>
</tr>
</tbody>
</table>

* Drugs cleared by peritoneal dialysis.

**Table 8.2: Clearance of antibiotics at haemodialysis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Slightly dialysed</th>
<th>Not dialysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin/ampicillin</td>
<td>Fluoroquinolones*</td>
<td>Amphotericin</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Co-trimoxazole</td>
<td>Methicillin</td>
</tr>
<tr>
<td>Cephalosporins*</td>
<td>Erythromycin</td>
<td>Teicoplanin</td>
</tr>
<tr>
<td>Aminoglycosides*</td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 8.3: Treatment of tuberculosis in renal failure**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR &lt; 30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin and isoniazid (INH)</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Avoid rifampicin with cyclosporin.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 8.4: Recommendations for prevention and treatment of UTI in renal transplantation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR &lt; 20 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX</td>
<td></td>
</tr>
</tbody>
</table>

**Table 8.5: Drug interactions with cyclosporin and tacrolimus**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR &lt; 10 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>TMP-SMX</td>
<td></td>
</tr>
</tbody>
</table>

**8.6.1 Treatment of UTI in renal transplant recipients**

The treatment of a symptomatic UTI is similar to treatment given to non-transplant patients. However, a short
course of treatment has yet to be established, and in most cases a 10-14-day course of treatment is given.

The choice of antibiotic is dictated by the special need for penetration into the renal parenchyma rather than for merely a ‘mucosal’ antibiotic. Fluoroquinolones seem to be particularly effective.

There is good evidence for the beneficial effects of treating asymptomatic bacteriuria in the first 6 months after renal transplantation (51) (LE: 2a). Patients must be investigated for surgical complications.

In most units, the combination of trimethoprim and sulphamethoxazole (co-trimoxazole) is effective in preventing UTI (52) (LE: 1b). It will also prevent Pneumocystis carinii pneumonia (PCP) and infection with other rare fastidious organisms. Low-dose antibiotic prophylaxis with co-trimoxazole has been recommended for 6 months after transplantation. This will cover the high-risk period when infection is more likely to be symptomatic and associated with acute graft impairment. At a low dose, adverse interactions with cyclosporin do not occur, although the higher dose advocated by some units results in synergistic nephrotoxicity with trimethoprim.

A number of other drug interactions need to be considered, e.g. gentamicin, co-trimoxazole and amphotericin B promote cyclosporin and tacrolimus toxicity. Rifampicin and erythromycin also interact with calcineurin inhibitors by increasing cytochrome p450 synthetase and inhibiting hepatic cyclosporin A metabolism.

In any patients with relapsing or recurrent infection, an anatomical cause, such as a urological complication in the transplant kidney or recipient bladder dysfunction, must be considered and treated vigorously.

8.6.2 Fungal infections
Candidal infections can occur in any immunosuppressed patient, but are more common in diabetic patients and those with chronic residual urine and in whom there is an indwelling catheter or stent. It is wise to treat all patients with antifungal agents (fluconazole, amphotericin B plus flucytosine) even when they are asymptomatic. Removal of the catheter or stents is usually necessary (GR: B).

8.6.3 Schistosomiasis
Schistosomiasis is a familiar problem for patients treated for end-stage renal failure from locations where the disease is endemic. Renal transplantation is possible, even when live donors and recipients have active lesions, provided they are treated. Combined medication (praziquantil and oxaminoquine) is recommended for 1 month. In a trial that compared infected patients with those free of schistosomiasis, there was no difference between the incidence of acute and chronic rejection. However, UTI and urological complications occurred in the infected group and a higher cyclosporin dose was required. Despite this, however, it was concluded that active schistosomiasis did not preclude transplantation (53) (LE: 3). For further details on schistosomiasis in genitourinary tract infections see Bichler et al. (54).

8.7 Immunosuppression
It is well known that viral and fungal infections are common in immunosuppressed patients.

8.7.1 Human immunodeficiency virus (HIV) infection
HIV infection can lead to acute renal failure through non-specific severe systemic illness, and to chronic renal failure through a variety of nephropathies. These include HIV-induced thrombotic microangiopathy, immune-mediated glomerulonephritis and nephropathy due to virus-induced cellular damage, primarily to the glomerular epithelial cell. Combination therapy using corticosteroids, ACE inhibitors and highly active antiretroviral therapy seems to delay and prevent progression of nephropathy, although evidence from randomised trials is not available (55). HIV infection is therefore no longer a contraindication to renal replacement therapy.

The place of immunosuppression per se in the development of UTI remains unresolved (56). Patients with end-stage renal failure are generally not particularly susceptible to the usual Gram-negative urinary pathogens, although they may acquire unusual and granulomatous infections. Patients have evidence of reduced cellular and humoral immunity.

However, the situation is a little clearer in male patients with HIV and AIDS, in whom there is a close relationship between CD4 counts and the risk of bacteriuria, particularly in patients whose counts are < 200 cells/mL (57). About 40% of patients with bacteriuria are asymptomatic. In these patients, PCP prophylaxis of the type used in transplant patients may not reduce the rate of bacteriuria, perhaps due to the previous development of resistant organisms.

8.7.2 Viral and fungal infections
Viral and fungal infections are relatively common in immunosuppressed patients.
References


http://www.ncbi.nlm.nih.gov/pubmed/1996041


8.8.1 Further reading
Antibiotic prescribing in renal failure: evidence base of guidelines. Information has been derived from the following standard reference sources:


9. URETHRITIS

9.1 Epidemiology
From a therapeutic and clinical point of view, gonorrhoeal urethritis has to be differentiated from non-specific urethritis. In Central Europe, non-specific urethritis is much more frequent than gonorrhoeal urethritis. There is a correlation between promiscuity and low socioeconomic status and the frequency of infections due to Neisseria gonorrhoeae and C. trachomatis. Infection is spread by sexual contact.

9.2 Pathogens
Pathogens include N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium and Trichomonas vaginalis. The frequency of the different species varies between patient populations (1-5). Mycoplasma hominis probably does not cause urethritis, and Ureaplasma urealyticum is an infrequent cause. In most cases, clinical evidence of Mycoplasma or Ureaplasma is caused by asymptomatic colonisation of the urogenital tract.

9.3 Route of infection and pathogenesis
Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (N. gonorrhoeae and C. trachomatis) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women. Recent evidence has suggested that Myc. genitalium can also cause cervicitis and pelvic inflammatory disease in women (6) (LE: 3).

9.4 Clinical course
Mucopurulent or purulent discharge, alguria, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

9.5 Diagnosis
A Gram stain of a urethral discharge or a urethral smear that shows more than five leukocytes per high power field (× 1,000) and eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis (7) (LE: 3, GR: B). The Gram stain is the preferred rapid diagnostic test for evaluating urethritis. It is highly sensitive and specific for documenting urethritis and the presence or absence of gonococcal infection. A positive leukocyte esterase test or > 10 leucocytes per high power field (× 400) in the first voiding urine specimen is diagnostic. In all patients with urethritis, and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. If an amplification system is used for identifying the pathogens, the first voiding urine specimen can be taken instead of a urethral smear. Trichomonas sp. can usually be identified microscopically.
9.6  Therapy

9.6.1  Treatment of gonorrhoeal urethritis

The following guidelines for therapy comply with the recommendations of the US Centers for Disease Control and Prevention (8-10). The following antimicrobials can be recommended for the treatment of gonorrhoea:

As first-choice treatment
- ceftriaxone, 1 g intramuscularly (with local anaesthetic) as a single dose;
- azithromycin, 1 g orally as a single dose.

Alternative regimens
- ciprofloxacin, 500 mg orally as single dose;
- ofloxacin, 400 mg orally as single dose;
- levofloxacin, 250 mg orally as single dose.

Note that fluoroquinolones are contraindicated in adolescents (< 18 years) and pregnant women.

As a result of the continuous spread of fluoroquinolone-resistant N. gonorrhoeae, this class of antibiotics is no longer recommended for the treatment of gonorrhoea in the United States (11). In Europe, knowledge of local susceptibility patterns is mandatory for the correct treatment of gonorrhoeal urethritis.

Because gonorrhoeae is frequently accompanied by chlamydial infection, an active antichlamydial therapy should be added.

9.6.2  Treatment of non-gonorrhoeal urethritis

The following treatment has been successfully applied to non-gonorrhoeal urethritis:

<table>
<thead>
<tr>
<th>As first choice of treatment:</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>azithromycin, 1 g orally as single dose</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>doxycycline, 100 mg orally twice daily for 7 days</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>As second choice of treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin base, 500 mg orally four times daily for 14 days</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>erythromycin ethylsuccinate, 800 mg orally four times daily for 7 days</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>ofloxacin, 300 mg orally twice daily for 7 days</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>levofloxacin, 500 mg orally once daily for 7 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Doxycycline and azithromycin are considered to be equally effective in the treatment of chlamydial infections, however, infections with Myc. genitalium may respond better to azithromycin (12). Erythromycin is less effective and causes more side effects. In pregnant women, fluoroquinolones and doxycycline are contraindicated, therefore, besides erythromycin and azithromycin, a regimen with amoxicillin 500 mg three times daily for 7 days is also recommended.

If therapy fails, one should consider treating infections by T. vaginalis and/or Mycoplasma with a combination of metronidazole (2 g orally as single dose) and erythromycin (500 mg orally four times daily for 7 days). As in other STDs, the treatment of sexual partners is necessary.

9.7  Follow-up and prevention

Patients should return for evaluation if symptoms persist or recur after completion of therapy. Patients should be instructed to abstain from sexual intercourse until 7 days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV.

9.8  References


10. BACTERIAL PROSTATITIS

10.1 Summary and recommendations
Bacterial prostatitis is a disease entity diagnosed clinically and by evidence of inflammation and infection localised to the prostate. According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, when symptoms persist for at least 3 months. It is recommended that European urologists use the classification suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis with confirmed or suspected infection is distinguished from chronic pelvic pain syndrome (CPPS).

Acute bacterial prostatitis can be a serious infection. Parenteral administration of high doses of a bactericidal antibiotic is usually required, which may include a broad-spectrum penicillin, a third-generation cephalosporin, or a fluoroquinolone. All of these agents can be combined with an aminoglycoside for initial therapy. Treatment is required until there is defervescence and normalisation of infection parameters (LE: 3, GR: B). In less severe cases, a fluoroquinolone may be given orally for 10 days (LE: 3, GR: B).

In chronic bacterial prostatitis, and if infection is strongly suspected in CPPS, preferably a fluoroquinolone should be given for at least 4 weeks. In case of fluoroquinolones resistance or adverse reactions, trimethoprim can be given orally for a period of 4 to 12 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics only continued if pre-treatment cultures are positive and/or the patient has reported positive effects from the treatment. A total treatment period of 4-6 weeks is recommended (LE: 3, GR: B).

Patients with CPPS are treated empirically with numerous medical and physical modalities. The management of pain and other related symptoms are covered in the EAU Guidelines on Chronic Pelvic Pain (1).

10.2 Introduction and definition
Traditionally, the term prostatitis has included both acute and chronic bacterial prostatitis, in which an infective
origin is accepted, and the term prostatitis syndrome or, more recently, CPPS, in which no infective agent can be found and whose origin is multifactorial and in most cases obscure.

Prostatitis and CPPS are diagnosed by symptoms and evidence of inflammation and infection localised to the prostate (2). A causative pathogen, however, is detected by routine methods in only 5-10% of cases (3), and for whom antimicrobial therapy therefore has a rational basis. The remainder of patients are treated empirically with numerous medical and physical modalities. However, recent improvement in classification and application of modern methods, including molecular biology, should allow proper systematisation of treatment (4-6).

This chapter reviews documented or suspected bacterial infections of the prostate.

### 10.3 Diagnosis

#### 10.3.1 History and symptoms

According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, the latter being defined by symptoms that persist for at least 3 months (4-6). The predominant symptoms are pain at various locations and LUTS (Tables 10.2 and 10.3) (7-9). Chronic bacterial prostatitis is the most frequent cause of recurrent UTI in men (10).

#### Table 10.1: Classification of prostatitis and CPPS according to NIDDK/NIH (4-6)

<table>
<thead>
<tr>
<th>Type</th>
<th>Name and description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute bacterial prostatitis</td>
</tr>
<tr>
<td>II</td>
<td>Chronic bacterial prostatitis</td>
</tr>
<tr>
<td>III</td>
<td>Chronic abacterial prostatitis - CPPS</td>
</tr>
<tr>
<td>IIIA</td>
<td>Inflammatory CPPS (white cells in semen/EPS/VB3)</td>
</tr>
<tr>
<td>IIIB</td>
<td>Non-inflammatory CPPS (no white cells in semen/EPS/VB3)</td>
</tr>
<tr>
<td>IV</td>
<td>Asymptomatic inflammatory prostatitis (histological prostatitis)</td>
</tr>
</tbody>
</table>

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine 3 (urine following prostatic massage).

#### Table 10.2: Localisation of pain in patients with prostatitis like symptoms*

<table>
<thead>
<tr>
<th>Site of pain</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate/perineum</td>
<td>46%</td>
</tr>
<tr>
<td>Scrotum and/or testes</td>
<td>39%</td>
</tr>
<tr>
<td>Penis</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>6%</td>
</tr>
<tr>
<td>Lower back</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Adapted from Zermann et al. (6).

#### Table 10.3: LUTS in patients with prostatitis like symptoms*

- Frequent need to urinate
- Difficulty urinating, e.g. weak stream and straining
- Pain on urination, or that increases with urination

*Adapted from Alexander et al. (9).

#### 10.3.1.1 Symptom questionnaires

Symptoms appear to have a strong basis for use as a classification parameter in bacterial prostatitis as well as in CPPS (11). Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms (11,12). They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH (USA) (13).

Although the CPSI has been validated, to date, its benefit in clinical studies is still uncertain. The questionnaire contains four questions regarding pain or discomfort, two regarding urination, and three related to quality of life (see Appendix 16.5).

#### 10.3.2 Clinical findings

In acute prostatitis, the prostate may be swollen and tender on digital rectal examination (DRE). Prostatic
massage is contraindicated. Otherwise, the prostate is usually normal on palpation. An essential consideration in the clinical evaluation is to exclude prostatic abscesses. In case of lasting symptoms ("chronic prostatitis" symptoms) CPPS as well as other urogenital and ano-rectal disorders must be taken into consideration.

Symptoms of chronic prostatitis or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should be investigated for urogenital tuberculosis.

10.3.3 Urine cultures and expressed prostatic secretion
The most important investigations in the evaluation of the patient with acute prostatitis is mid-stream urine culture. In chronic bacterial prostatitis, a quantitative bacteriological localisation cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey (2) (see Appendix 16.6).

The Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in acute bacterial prostatitis (Table 10.4) (14). In chronic bacterial prostatitis, the spectrum of strains is wider. The significance of intracellular bacteria, such as *C. trachomatis*, is uncertain (15). In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis*, *Candida* sp. and rare pathogens, such as *Coccidioides immitis, Blastomyces dermatitidis*, and *Histoplasma capsulatum* (16). In case of suspected prostate tuberculosis, the urine should be investigated for *Mycobacterium* spp by PCR technique.

Table 10.4: Most common pathogens in prostatitis

<table>
<thead>
<tr>
<th>Aetiologically recognised pathogens*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
</tr>
<tr>
<td><em>Klebsiella</em> sp.</td>
</tr>
<tr>
<td><em>Prot. mirabilis</em></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organisms of debatable significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococci</em></td>
</tr>
<tr>
<td><em>Streptococci</em></td>
</tr>
<tr>
<td><em>Corynebacterium</em> sp.</td>
</tr>
<tr>
<td><em>C. trachomatis</em></td>
</tr>
<tr>
<td><em>U. urealyticum</em></td>
</tr>
<tr>
<td><em>Myc. hominis</em></td>
</tr>
</tbody>
</table>

*Adapted from Weidner et al. (3) and Schneider et al. (14).

10.3.4 Prostate biopsy
Perineal biopsies cannot be recommended as routine work-up and should be reserved only for research purposes. Transrectal prostate biopsy is not advisable in bacterial prostatitis (LE: 4; GR: C).

10.3.5 Other tests
Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles but is unreliable and cannot be used as a diagnostic tool in prostatitis (17).

10.3.6 Additional investigations
10.3.6.1 Ejaculate analysis
An analysis of the ejaculate is not recommended for microbiological investigation due to the low sensitivity and specificity compared to the 2- or 3-glass tests. Ejaculate analysis is however frequently involved as part of the investigation of a generalised male accessory gland infection (MAGI) and it provides information about sperm quality. The EAU working group believes that guidelines on prostatitis should not contain a set of differential diagnostic examinations. An experienced urologist should decide which investigations are relevant for each individual patient. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

10.3.6.2 Prostate Specific Antigen (PSA)
PSA is often increased in acute bacterial prostatitis and other urogenital infections. If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalise after antimicrobial treatment for 4
weeks in about 50% of patients (18). A delay of at least 3 months should be allowed before it can be assumed that a stable level of PSA has been reached. Measurement of free and total PSA adds no practical diagnostic information in prostatitis (19).

10.4 Treatment
10.4.1 Antibiotics
Antibiotics are life-saving in acute bacterial prostatitis and recommended in chronic bacterial prostatitis.

Acute bacterial prostatitis is a serious infection with fever, intense local pain, and general symptoms. Parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone, should be administered. For initial therapy, any of these antibiotics may be combined with an aminoglycoside. After defervescence and normalisation of infection parameters, oral therapy can be substituted and continued for a total of 2-4 weeks (20).

The recommended antibiotics in chronic bacterial prostatitis, together with their advantages and disadvantages, are listed in Table 10.7 (21). Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties (21) (LE: 2b, GR: B), their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including P. aeruginosa. In addition, levofloxacin is active against Gram-positive and atypical pathogens, such as C. trachomatis and genital mycoplasmas (LE: 2b, GR: B).

The duration of antibiotic treatment is based on experience and expert opinion and is supported by many clinical studies (22). In chronic bacterial prostatitis antibiotics should be given for 4-6 weeks after initial diagnosis. Relatively high doses are needed and oral therapy is preferred (21,22) (LE: 3, GR: B). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given (21,23) (LE: 2b, GR: B).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Favourable pharmacokinetics</td>
<td>Depending on the substance:</td>
<td>Recommend</td>
</tr>
<tr>
<td></td>
<td>Excellent penetration into the prostate</td>
<td>Drug interaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good bioavailability</td>
<td>Phototoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Equivalent oral and parenteral pharmacokinetics (depending on the substance)</td>
<td>Central nervous system adverse events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good activity against typical and atypical pathogens and P. aeruginosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In general, good safety profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Good penetration into prostate</td>
<td>No activity against Pseudomonas, some enterococci and some Enterobacteriaceae</td>
<td>Consider</td>
</tr>
<tr>
<td></td>
<td>Oral and parenteral forms available</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relatively cheap</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitoring unnecessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active against most relevant pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Cheap</td>
<td>No activity against P. Aeruginosa</td>
<td>Reserve for special indications</td>
</tr>
<tr>
<td></td>
<td>Oral and parenteral forms available</td>
<td>Unreliable activity against coagulase-negative staphylococci, E. coli, other Enterobacteriaceae, and enterococci</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good activity against Chlamydia and Mycoplasma</td>
<td>Contraindicated in renal and liver failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of skin sensitisation</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>Reasonably active against Gram-positive bacteria</td>
<td>Minimal supporting data from clinical trials</td>
<td>Reserve for special indications</td>
</tr>
<tr>
<td></td>
<td>Active against Chlamydia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good penetration into prostate</td>
<td>Unreliable activity against Gram-negative bacteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relatively non-toxic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Bjerklund Johansen et al. (21).
10.4.2 **Intraprostatic injection of antibiotics**

This treatment has not been evaluated in controlled trials and should not be considered (24,25).

10.4.3 **Drainage and surgery**

Approximately 10 per cent of men with acute prostatitis will experience urinary retention (26) which can be managed by suprapubic, intermittent or indwelling catheterisation. Suprapubic cystostomy placement is however generally recommended. The use of catheterisation without evidence of retention may increase the risk of progression to chronic prostatitis (27). Alpha-blocker treatment has also been recommended, but clinical evidence of benefit is poor.

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible (28). The size may matter. In one study conservative treatment was successful if the abscess cavities were smaller than 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage (29). Surgery should be avoided in the treatment of bacterial prostatitis.

10.5 **References**


11. EPIDIDYMITIS AND ORCHITIS

11.1 Summary and recommendations
Orchitis and epididymitis are classified as acute or chronic processes according to the onset and clinical course. The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis.

Epididymitis is almost always unilateral and relatively acute in onset. In young males it is associated with sexual activity and infection of the consort (LE: 3). The majority of cases in sexually active males aged < 35 years are due to sexually transmitted organisms, whereas in elderly patients, it is usually due to common urinary pathogens (LE: 3). Epididymitis causes pain and swelling, which begins in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information. The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria (LE: 3). A urethral swab and MSU should be obtained for microbiological investigation before antimicrobial therapy (GR: C). Antimicrobials should be selected on the empirical basis
that in young, sexually active men, *C. trachomatis* is usually causative, and that in older men, the most common uropathogens are involved. Fluoroquinolones with activity against *C. trachomatis* (e.g. ofloxacin and levofloxacin), should be the drugs of first choice. If *C. trachomatis* has been detected, treatment could also be continued with doxycycline, 200 mg/day, for a total of at least 2 weeks. Macrolides may be used as alternative agents (GR: C). Supportive therapy includes bed rest, up positioning of the testes and anti-inflammatory therapy. In case of *C. trachomatis* epididymitis, the sexual partner should also be treated (GR: C). Abscess-forming epididymitis or orchitis needs surgical treatment. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

### 11.2 Definition and classification

Epididymitis, inflammation of the epididymis, causes pain and swelling which is almost always unilateral and relatively acute in onset. In some cases, the testes are involved in the inflammatory process (epididymo-orchitis). On the other hand, inflammatory processes of the testicle, especially virally induced orchitis, often involve the epididymis.

Orchitis and epididymitis are classified as acute or chronic processes according to the onset and clinical course. Chronic disease with induration develops in 15% of acute epididymitis cases. In the case of testicular involvement, chronic inflammation may result in testicular atrophy and the destruction of spermatogenesis (1,2).

### 11.3 Incidence and prevalence

There are no new data available concerning the incidence and prevalence of epididymitis. According to older data, acute epididymitis has been a major cause for admission to hospitals of military personnel (2) (LE: 3). Acute epididymitis in young men is associated with sexual activity and infection of the consort (3) (LE: 3).

The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. The incidence depends upon the vaccination status of the population (4). Primary chronic orchitis is a granulomatous disease, and a rare condition with uncertain aetiology that has been reported in about 100 cases in the literature (5).

### 11.4 Morbidity

Complications in epididymo-orchitis include abscess formation, testicular infarction, testicular atrophy, development of chronic epididymal induration and infertility (2).

Epididymitis caused by sexually transmitted organisms occurs mainly in sexually active males aged < 35 years (2,6) (LE: 3). The majority of cases of epididymitis are due to common urinary pathogens, which are also the most common cause of bacteriuria (2,6) (LE: 3). Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection.

### 11.5 Pathogenesis and pathology

Typically, in epididymitis due to common bacteria and sexually transmitted organisms, the infection is spread from the urethra or bladder. In non-specific granulomatous orchitis, autoimmune phenomena are assumed to trigger chronic inflammation (5,7). Paediatric orchitis and mumps orchitis are of haematogenous origin (7).

Epididymo-orchitis is also seen in systemic infections such as tuberculosis, lues, brucellosis and cryptococcus disease.

### 11.6 Diagnosis

In acute epididymitis, the inflammation and swelling usually begin in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. All men with epididymitis that is caused by sexually transmitted organisms have a history of sexual exposure, and the organisms can lie dormant for months before the onset of symptoms. If the patient is examined immediately after undergoing urinalysis, urethritis and urethral discharge may be missed because WBC and bacteria have been washed out of the urethra during urination.

The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria. The presence of intracellular Gram-negative diplococci on the smear correlates with infection with *N. gonorrhoeae*. The presence of only WBC on a urethral smear indicates the presence of non-gonorrhoeal urethritis. *C. trachomatis* is isolated in approximately two-thirds of these patients (2,6) (LE: 3).

Ejaculate analysis according to WHO criteria including leukocyte analysis indicates persistent inflammatory activity. In many cases, transient decreased sperm counts and forward motility can be found. Azosperma due to complete obstruction of both epididymides is a rare complication (8). If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis. In about 20% of mumps orchitis cases, the disease occurs bilaterally in post-pubertal men with a risk of testicular
atrophy and azoospermia (3) (LE: 3).

11.6.1 Differential diagnosis
It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information, including the age of the patient, history of urethritis, clinical evaluation and Doppler (duplex) scanning of testicular blood flow.

11.7 Treatment
Only a few studies have measured the penetration of antimicrobial agents into the epididymis and testes in humans. Of these, the fluoroquinolones have shown favourable properties (9) (LE: 2a).

Antimicrobials should be selected on the empirical basis that in young, sexually active men, C. trachomatis is usually causative, and that in older men, with BPH or other micturition disturbances, the most common uropathogens are involved. Studies that have compared microbiological results from puncture of the epididymis and from urethral swabs as well as urine have shown very good correlation. Therefore, before antimicrobial therapy, a urethral swab and MSU should be obtained for microbiological investigation (GR: C).

Again, fluoroquinolones, preferably those with activity against C. trachomatis (e.g. ofloxacin and levofloxacin), should be the drugs of first choice, because of their broad antibacterial spectra and their favourable penetration into the tissues of the urogenital tract. If C. trachomatis has been detected as an aetiological agent, treatment could also be continued with doxycycline, 200 mg/day, for a total period of at least 2 weeks. Macrolides may be used as alternative agents (GR: C).

Supportive therapy includes bed rest, up-positioning of the testes and antiphlogistic therapy. In young men, epididymitis can lead to permanent occlusion of the epididymal ducts and thus to infertility, therefore, one should consider antiphlogistic therapy with methylprednisolone, 40 mg/day, and reduce the dose by half every second day (GR: C).

In case of C. trachomatis epididymitis, the sexual partner should also be treated (GR: C). If uropathogens are found as causative agents, a thorough search for micturition disturbances should be carried out to prevent relapse (GR: C). Abscess-forming epididymitis or orchitis also needs surgical treatment. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

11.8 References
12. FOURNIER’S GANCRENE

12.1 Summary of recommendations
1. Full, repeated surgical debridement should commence within 24 h of presentation (LE: 3; GR: B).
2. Treatment with broad-spectrum antibiotics should be started on presentation, with subsequently refinement according to culture and clinical response (LE: 3; GR: B).
3. Adjunctive treatment such as pooled immunoglobulin and hyperbaric oxygen are not recommended, except in the context of clinical trials (LE: 3; GR: C).

12.2 Background
Fournier’s gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway. Evidence regarding investigation and treatment is predominantly from case series and expert opinion (LE: 3/4).

12.3 Clinical presentation
Fournier's gangrene remains rare but its incidence is increasing with an ageing population and higher prevalence of diabetes, and emergence of multi-resistant pathogens. Typically there is painful swelling of the scrotum or perineum with severe sepsis. Examination shows a small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease. Risk factors include immuno-compromised patients, most commonly diabetes or malnutrition, or a recent history of catheterisation, instrumentation or perineal surgery. In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment. A high index of suspicion and careful examination, particularly of obese patients, is required.

12.4 Microbiology
Fournier's gangrene is typically a type 1 necrotising fasciitis that is polymicrobial in origin, including S. aureus, Streptococcus sp., Klebsiella sp., E. coli and anaerobs; involvement of Clostridium sp. is now less common. These organisms secrete endotoxins causing tissue necrosis and severe cardiovascular impairment. Subsequent inflammatory reaction by the host contributes to multi-organ failure and death if untreated.

12.5 Management
The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement is necessary to save the patient's life (LE: 3; GR: B). Disease specific severity scoring systems do not appear superior to generic critical illness scores and are therefore not recommended for routine use (LE: 3;GR: C). Computed tomography or MRI can help define para-rectal involvement, suggesting the need for colostomy (LE: 3, GR: C). Consensus from case series suggests that surgical debridement should be early (< 24 h) and complete, because delayed and/or inadequate surgery results in higher mortality (LE: 3; GR: B). Concurrent parenteral antibiotic treatment should be given that covers all causative organisms and can penetrate inflammatory tissue (LE: 3, GR: B). This can then be refined following surgical cultures. The benefit of pooled immunoglobulin therapy and hyperbaric oxygen remains uncertain and should not be used routinely (LE:3, GR: C). With aggressive early surgical and medical management, survival rates are > 70% depending upon patient group and availability of critical care (LE: 3). Following resolution, reconstruction using skin grafts is required.
12.6  Further reading

13.  SEXUALLY TRANSMITTED INFECTIONS

The classical bacteria that cause venereal diseases, e.g. gonorrhoea, syphilis, chancroid and inguinal granuloma, only account for a small proportion of all known sexually transmitted deceases (STDs) today. Other bacteria and viruses as well as yeasts, protozoa and epizoa must also be regarded as causative organisms of STD. Taken together, all STDs are caused by > 30 relevant pathogens. However, not all pathogens that can be sexually transmitted manifest genital diseases, and not all genital infections are exclusively sexually transmitted. At present, the reader is refered to the 2010 CDC STD Treatment Guidelines (1).

The human immunodeficiency virus (HIV) causes a disease of the immune system leading to a vast panorama of complications and complex medical conditions also called acquired immunodeficiency...
13.1 Reference

14. SPECIFIC INFECTIONS

Urogenital tuberculosis and bilharziasis are two infections that may affect the urogenital tract. Although not endemic in Europe, cases of urogenital tuberculosis are occasionally diagnosed in all communities. In a world of globalisation, travellers are regularly confronted with situations in which they may be infected. Guidelines on the diagnosis and management of these two infections have been published elsewhere. Following the abstract printed here, there is a direct link to these published guidelines, which can be consulted for free.

14.1 Urogenital tuberculosis
Nearly one third of the world’s population is estimated to be infected with M. tuberculosis. Moreover, tuberculosis is the most common opportunistic infection in AIDS patients. Urogenital tuberculosis is not very common but it is considered a severe form of extra-pulmonary tuberculosis. The diagnosis of urogenital tuberculosis is made based on culture studies by isolation of the causative organism; however, biopsy material on conventional solid media may occasionally be required. Drugs are the first-line therapy in urogenital tuberculosis. Treatment regimens of 6 months are effective in most patients. Although chemotherapy is the mainstay of treatment, surgery in the form of ablation or reconstruction may be unavoidable. Both radical and reconstructive surgery should be carried out in the first 2 months of intensive chemotherapy.

14.1.1 Reference

14.2 Urogenital schistosomiasis
More than 100 million people worldwide are affected by bilharziasis, which is caused by Schistosoma haematobium. For travellers, precautions are most important. For the population in endemic areas, an integrated approach including health education is necessary. Effective pharmacological treatment is available.

14.2.1 Reference

15. PERIOPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

15.1 Summary and recommendations
The aim of antimicrobial prophylaxis in urological surgery is to prevent infective complications that result from diagnostic and therapeutic procedures at the time of surgery and in the immediate post-operative period. However, evidence for the best choice of antibiotics and prophylactic regimens is limited (Table 15.1).

Before surgery, it is essential to categorise the patients in relation to (1):
- general health status according to American Society of Anesthesiology (ASA) score P1-P5;
- presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight;
- presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital...
infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;

- type of surgery and surgical field contamination burden;
- expected level of surgical invasiveness, duration and technical aspects.

Only transrectal core prostate biopsy (LE: 1b, GR: A) and TURP (LE: 1a, GR: A) are well documented. There is no evidence for any benefits of antibiotic prophylaxis in standard non-complicated endoscopic procedures and shockwave lithotripsy (SWL), although it is recommended in complicated procedures and patients with identified risk factors.

For open and laparoscopic surgery, the same rules as in abdominal and gynaecological surgery can be applied. No antibiotic prophylaxis is recommended for clean operations, whereas a single or 1-day dose is recommended in clean-contaminated. The approach in contaminated operations varies with the type of procedure, the level of surgical site contamination and level of difficulty. Opening of the urinary tract is considered as clean-contaminated surgery.

A single dose or a short course of antimicrobials can be given parenterally or orally. The administration route depends on the type of intervention and patient characteristics. Oral administration requires drugs that have good bioavailability. In a case of continuous close urinary drainage, prolongation of perioperative antibiotic prophylaxis is not recommended.

Many antibiotics are suitable for perioperative antibacterial prophylaxis, e.g. co-trimoxazole, second-generation cephalosporins, fluoroquinolones, aminopenicillins plus a beta-lactam inhibitor, and aminoglycosides. Broader-spectrum antibiotics including fluoroquinolones should be used cautiously and reserved for treatment. This applies also to the use of vancomycin.

The use of antimicrobials should be based on knowledge of the local pathogen profile and antibiotic susceptibility pattern. Best practice includes surveillance and an audit of infectious complications.

### Table 15.1: Level of evidence and grade of recommendation for standard urological procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LE</th>
<th>GR</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>1b</td>
<td>A</td>
<td>Low frequency of infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contradictory findings</td>
</tr>
<tr>
<td>Urodynamic study</td>
<td>1a</td>
<td>A</td>
<td>Low frequency of infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contradictory findings</td>
</tr>
<tr>
<td>Transrectal core biopsy of prostate</td>
<td>1b</td>
<td>A</td>
<td>High risk of infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Assess carefully risk factors</td>
</tr>
<tr>
<td>Diagnostic ureteroscopy</td>
<td>4</td>
<td>C</td>
<td>No available studies</td>
</tr>
<tr>
<td><strong>Therapeutic procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURB</td>
<td>2b</td>
<td>C</td>
<td>Poor data. No concern given to burden of tumour, i.e. size, multiplicity, necrosis</td>
</tr>
<tr>
<td>TURP</td>
<td>1a</td>
<td>A</td>
<td>Good documentation</td>
</tr>
<tr>
<td>SWL (standard, no risk factors such as the presence of a stent or nephrostomy tube)</td>
<td>1a/1b</td>
<td>A</td>
<td>Low frequency of infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contradictory findings</td>
</tr>
<tr>
<td>Ureteroscopy stone</td>
<td>2b</td>
<td>B</td>
<td>Literature does not distinguish between severity of stone management</td>
</tr>
<tr>
<td>Percutaneous stone management</td>
<td>2b</td>
<td>B</td>
<td>High risk of infection</td>
</tr>
<tr>
<td><strong>Open and laparoscopic surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean operations (no opening of urinary tract)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>3</td>
<td>C</td>
<td>SSI poorly documented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Catheter-related UTI</td>
</tr>
<tr>
<td>Scrotal surgery</td>
<td>3</td>
<td>C</td>
<td>Review studies contradictory</td>
</tr>
<tr>
<td>Prosthetic implants</td>
<td>3</td>
<td>B</td>
<td>Limited documentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regimen not well defined</td>
</tr>
<tr>
<td>Clean-contaminated (opening of urinary tract)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephroureterectomy</td>
<td>3</td>
<td>B</td>
<td>Poor documentation</td>
</tr>
<tr>
<td>Ureteropelvic junction repair</td>
<td>4</td>
<td>C</td>
<td>No studies detected</td>
</tr>
<tr>
<td>Total (radical) prostatectomy</td>
<td>2a</td>
<td>B</td>
<td>No RCT, poor documentation</td>
</tr>
<tr>
<td>Partial bladder resection</td>
<td>3</td>
<td>C</td>
<td>No specific RCT studies</td>
</tr>
</tbody>
</table>
Clean-contaminated/contaminated (opening of bowel, urine deviation)

Cystectomy with urine deviation | 2a | B | Limited documentation

SWL = extracorporeal shockwave lithotripsy; TURB = transurethral resection of the bladder; SSI = surgical site infection; TURP = transurethral resection of the prostate; RCT = randomised controlled trials.

15.2 Introduction

Antibiotic prophylaxis in urology has been controversial for many years. Most studies in the past have been poorly designed and lacked statistical power. There has been inconsistency concerning definitions and assessment of risk factors. Urological practice has changed particularly in the last decade and older studies are no longer relevant. Several surveys among urologists in Europe have revealed wide differences in regimens and choice of antibiotics for prophylaxis. Clearly, there is a need for evidence-based guidelines (2-6).

The present section aims to clarify the current state of knowledge and to propose practical recommendations based on clinical studies, expert opinion and professional consensus. The section also considers the recommendations of societies, such as the Paul Ehrlich Society for Chemotherapy, the corresponding working groups of the German Society of Urology (7), French Association of Urology (8) and of an international consensus working group (1).

One systematic review of antibiotic prophylaxis in urological surgery has been published (9). The results of the review strengthen the underlying documentation for the present recommendations.

A recent pan-European survey was carried out by the EAU Section for Infection in Urology (ESIU) in a large number of European countries, including > 200 urological services or units. The survey found that ≥10-12% of patients had a healthcare-associated UTI (10). Moreover, a review of antibiotic prophylaxis praxis showed large discrepancies in the use of antibiotic prophylaxis in all type of procedures and between countries, and low compliance to the guidelines (11). The surveys illustrate the need for a stringent antibiotic policy throughout Europe, and that recommendations for antibiotic prophylaxis should be included in the general antibiotic policy of each hospital.

The microbial development of resistance presents a challenge to the urological community for both treatment and prophylaxis. It is essential that the urologist is aware of the microbial pattern and resistance profile in his/her community and can assess the risk of each individual patient of harbouring resistant strains (see Section 1.2).

15.3 Goals of perioperative antibacterial prophylaxis

Antibiotic prophylaxis and therapy are two different issues. Antibiotic prophylaxis aims to prevent healthcare-associated infections that result from diagnostic and therapeutic procedures. Antibiotic prophylaxis is only one of several measures to prevent infections and can never compensate for poor hygiene and operative technique. In contrast, antibiotic therapy is the treatment of a clinically suspected or microbiologically proven infection.

There is a dilemma regarding the definition of infections. The US CDC have presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications (12). These definitions have also been used in the recent pan-European study on nosocomial UTI (10). Revision of definitions and recommendations are on-going in some countries (13). Table 15.2 illustrates the different types of infectious complications encountered in urological surgery.

Table 15.2: Main types of healthcare-associated infections encountered in urological practice

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Minor</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical wound</td>
<td>Superficial wound infection</td>
<td>Deep wound infection</td>
</tr>
<tr>
<td>Incision/surgical site infection (SSI)</td>
<td></td>
<td>Wound rupture (abdominal dehiscence)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deep abdominal or surgical site abscess</td>
</tr>
<tr>
<td>UTI or organ-specific infection</td>
<td>Asymptomatic bacteriuria (bacterial colonisation)</td>
<td>Febrile UTI</td>
</tr>
<tr>
<td></td>
<td>Symptomatic lower UTI</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peri-renal abscess</td>
</tr>
<tr>
<td>Blood stream</td>
<td>Bacteremia without signs of systemic response</td>
<td>SIRS or sepsis with signs of systemic response</td>
</tr>
<tr>
<td>Other urogenital sites</td>
<td>Epididymitis (Orchitis)</td>
<td>Acute bacterial prostatitis (type I)</td>
</tr>
<tr>
<td>Other sites</td>
<td></td>
<td>Septic embolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary bone infection</td>
</tr>
</tbody>
</table>
Surgical site infections are seen after open surgery and to some extent after laparoscopic surgery. Febrile and complicated UTIs are mainly complications of endoscopic surgery and the use of indwelling catheters and stents. They can also occur following open surgery of the urinary tract. Sepsis can be seen with all types of procedures.

The endpoints of perioperative prophylaxis in urology are debatable. It is generally agreed that its main aim is to prevent symptomatic, febrile urogenital infections such as acute pyelonephritis, prostatitis, epididymitis and urosepsis, as well as serious wound infections directly related to surgery (Table 15.2). This might be extended to asymptomatic bacteriuria and even minor wound infections, which could easily be treated on an outpatient basis. In some circumstances, even minor wound infections can have serious consequences, as in implant surgery. However, asymptomatic bacteriuria after TURP or other endourological procedures can disappear spontaneously and is usually of no clinical significance. Another question is whether perioperative prophylaxis should also be concerned with the prevention of non-urological infections, e.g. endocarditis and postoperative pneumonia. Perioperative antibacterial prophylaxis in urology must go beyond the traditional aim of prophylaxis in surgery, which is the prevention of wound infections.

15.4 Risk factors

Risk factors (Table 15.3 and 2.1) are underestimated in most trials. However, they are important in the preoperative assessment of the patient. They are related to:

- general health of the patient as defined by ASA score P1-P5;
- presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight;
- presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;
- type of surgery and surgical field contamination;
- expected level of surgical invasiveness, duration and technical aspects.

The traditional classification of surgical procedures according to Cruse and Foord (14) into clean, clean-contaminated, contaminated, and infected/dirty operations applies to open surgery but not to endourological interventions. It is still debated whether opening of the urinary tract (i.e. bladder surgery, radical prostatectomy, or surgery of the renal pelvis and ureter) should be classified as clean or clean-contaminated surgery in cases of negative urine culture. The same applies to endoscopic and transurethral surgery. However, members of the EAU Expert Group consider these procedures as clean-contaminated because urine culture is not always a predictor of bacterial presence, and the lower genitourinary tract is colonised by microflora, even in the presence of sterile urine (6,15,16).

Table 15.3: Generally accepted risk factors for infectious complications

<table>
<thead>
<tr>
<th>General risk factors</th>
<th>Special risk factors associated with an increased bacterial load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Long preoperative hospital stay or recent hospitalisation</td>
</tr>
<tr>
<td>Deficient nutritional status</td>
<td>History of recurrent urogenital infections</td>
</tr>
<tr>
<td>Impaired immune response</td>
<td>Surgery involving bowel segment</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Colonisation with microorganisms</td>
</tr>
<tr>
<td>Smoking</td>
<td>Long-term drainage</td>
</tr>
<tr>
<td>Extreme weight</td>
<td>Urinary obstruction</td>
</tr>
<tr>
<td>Coexisting infection at a remote site</td>
<td>Urinary stone</td>
</tr>
<tr>
<td>Lack of control of risk factors</td>
<td></td>
</tr>
</tbody>
</table>

The pan-European study on nosocomial UTI (10) has identified the three most important risk factors for infectious complications as:

- an indwelling catheter;
- previous urogenital infection;
- long preoperative hospital stay.

The risk of infection varies with the type of intervention. The wide spectrum of interventions further complicates the provision of clear-cut recommendations. Furthermore, the bacterial load, the duration and difficulty of the operation, the surgeon's skill, and perioperative bleeding may also influence the risk of infection (6).

15.5 Principles of antibiotic prophylaxis

Antibiotic prophylaxis aims at protecting the patient but not at the expense of promoting resistance. However,
there is good evidence that intelligent use of prophylaxis can lower the overall consumption of antibiotics (16,17). It is essential to individualise the choice of antibiotic prophylaxis according to each patient’s cumulative risk factors (18). Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection (19-21).

Unfortunately, the benefit of antibiotic prophylaxis for most modern urological procedures has not yet been established by well-designed interventional studies.

15.5.1 **Timing**

There is a given time-frame during which antibiotic prophylaxis should be administered. Although the following guidelines are based on research into skin wounds and clean-contaminated and contaminated bowel surgery, there is good reason to believe that the same findings apply to urological surgery. The optimal time for antibiotic prophylaxis is 1-2 h before instrumentation. Some studies on bowel surgery indicate similar results up to 3 h after the start of an intervention (22-24).

For practical purposes, oral antibiotic prophylaxis should be given approximately 1 h before the intervention. Intravenous antibiotic prophylaxis should be given at the induction of anaesthesia. These timings allow antibiotic prophylaxis to reach a peak concentration at the time of highest risk during the procedure, and an effective concentration shortly afterwards (25). It is worth noting that a bloodstream infection can develop in less than an hour (22).

15.5.2 **Route of administration**

Oral administration is as effective as the intravenous route for antibiotics with sufficient bioavailability. This is recommended for most interventions when the patient can easily take the drug 1 h before intervention. In other cases, intravenous administration is recommended. Local irrigation of the operating field with antibiotics is not recommended.

15.5.3 **Duration of the regimen**

For most procedures, duration of antibiotic prophylaxis has not yet been adequately addressed and rarely can a defined regimen be recommended. In principle, the duration of perioperative prophylaxis should be minimised; ideally to a single preoperative antibiotic dose. Perioperative prophylaxis should be prolonged only where there are significant risk factors (see Section 15.4).

15.5.4 **Choice of antibiotics**

No clear-cut recommendations can be given, as there are considerable variations in Europe regarding both bacterial spectra and susceptibility to different antibiotics. Antimicrobial resistance is usually higher in Mediterranean compared with Northern European countries; resistance is correlated with an up to fourfold difference in sales of antibiotics (26). Thus, knowledge of the local pathogen profile, susceptibility and virulence is mandatory in establishing local antibiotic guidelines. It is also essential to define the predominant pathogens for each type of procedure. When choosing an antimicrobial agent, it is necessary to consider the procedure-specific risk factors, contamination load, target organ, and the role of local inflammation.

In general, many antibiotics are suitable for perioperative antibacterial prophylaxis, e.g. co-trimoxazole, second-generation cephalosporins, aminopenicillins plus a BLI, aminoglycosides and fluoroquinolones. Broader-spectrum antibiotics should be used sparingly and reserved for treatment. Fluoroquinolones should be avoided as far as possible for prophylaxis. This applies also to the use of vancomycin.

15.6 **Prophylactic regimens in defined procedures**

All procedures are not alike. There is a large variation in invasiveness and risk for identical interventions. The empirical relationship between the level of invasiveness and risk for infective complications is illustrated in Figure 15.1. Moreover, a tentative classification of the urological procedures in relation to the surgical field contamination level is given in Table 15.5.a and 15.5.b.
The EAU/ESIU working group has suggested a distribution of the different common diagnostic and therapeutic urological procedures in relation to the categories of surgical site contamination after adaptation to the urological context (14,27). The recommendations for antibiotic prophylaxis in standard urological surgery are summarised in Table 15.4a and 15.4b (28,29).

15.6.1 Diagnostic procedures
Antimicrobial prophylaxis in core biopsy of the prostate is generally recommended (GR: A). However, the choice of regimens remains debatable. Most regimens used are effective, and recent studies have suggested that 1-day and even single doses are sufficient in low-risk patients (30-45) (LE: 1b, GR: A). The increase in fluoroquinolones resistance in the faecal flora has raised the question of appropriateness of the current recommendations (46,47). No clear-cut alternative is evidence-based. Each urologist must weigh the need for a prostate biopsy in relation to the risk, assess the individual risks factors including the risk of harbouring a resistant bacteria (i.e. ESBL) and consider the need for a rectal swab before the instrumentation.

The frequency of infectious complications after cystoscopy, urodynamic studies and diagnostic simple ureteroscopy is low. The use of antibiotic prophylaxis is still debated and the results are controversial. In view of the very large number of cystoscopic examinations and the potential adverse effect on bacterial sensitivity, antibiotic prophylaxis is not recommended in standard cases. However, bacteriuria, indwelling catheters, and a history of urogenital infection are risk factors that must be considered (48-62) (LE: 1b, GR: A).

15.6.2 Endourological treatment procedures (urinary tract entered)
There is little evidence for any benefit of antibiotic prophylaxis in TURB. However, antibiotic prophylaxis should be considered in patients with large tumours with a prolonged resection time, large necrotic tumours, and with risk factors (49,63,64) (LE: 2b, GR: C).

Transurethral resection of the prostate is the best-studied urological intervention. A meta-analysis of 32 prospective, randomised and controlled studies, including > 4,000 patients, showed a benefit of antibiotic prophylaxis with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively (16,65-67) (LE: 1a, GR: A). There is a difference between smaller resections in healthy patients and large resections in at-risk patients (Figure 15.1).

There have been few studies that have defined the risk of infection following ureteroscopy and percutaneous stone removal, and no clear-cut evidence exists (68). It is reasonable, however, to distinguish low-risk procedures, such as simple diagnostic and distal stone treatment, from higher-risk procedures, such as treatment of proximal impacted stones and intrarenal interventions (Figure 15.1) (5). Other risk factors (i.e. size, length, bleeding, and surgeon’s experience) also need to be considered in the choice of regimen (69-76) (LE: 2b, GR: B).

Shockwave lithotripsy is one of the most commonly performed procedures in urology. No standard prophylaxis is recommended. However, prophylaxis is recommended in cases of internal stent and treatment, due to the increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, or infectious stones) (77-86) (LE: 1a-1b, GR: A).

Most antibiotic groups have been evaluated, such as fluoroquinolones, BLIs, including cephalosporins, and co-trimoxazole, but comparative studies are limited.
15.6.3 Laparoscopic surgery
There has been a lack of sufficiently powered studies in laparoscopic urological surgery. However, it seems reasonable to manage laparoscopic surgical procedures in the same manner as the corresponding open procedures (LE: 4, GR: C).

15.6.4 Open or laparoscopic urological operations without opening of the urinary tract (clean procedures)
No standard antibiotic prophylaxis is recommended in clean operations (87-94) (LE: 3, GR: C).

15.6.5 Open or laparoscopic urological operations with open urinary tract (clean-contaminated procedures)
In cases of opening the urinary tract, a single perioperative parenteral dose of antibiotics is recommended (LE: 3, GR: C). This is valuable for standard procedures such as total (radical) prostatectomy (92-95). In open enucleation of prostatic adenoma, the risk of postoperative infection is particularly high (96) (LE: 2b, GR: B).

15.6.6 Open urological operations with bowel segment (clean-contaminated or contaminated procedures)
Antibiotic prophylaxis is recommended, as for clean-contaminated operations in general surgery. Single or 1-day dosage is recommended, although prolonged operation and other morbidity risk factors might support the use of a prolonged regimen, which should be < 72 h. The choice of antibiotic should focus on aerobic and anaerobic pathogens. Evidence is based on colorectal surgery (LE: 1a, GR: A), but experience is limited as for specific urological interventions (97-100) (LE: 2a, GR: B).

15.6.7 Postoperative drainage of the urinary tract
When continuous urinary drainage is left in place after surgery, prolongation of perioperative antibacterial prophylaxis is not recommended, unless a complicated infection that requires treatment is suspected. Asymptomatic bacteriuria (bacterial colonisation) should only to be treated before surgery or after removal of the drainage tube (LE: 3, GR: B).

15.6.8 Implantation of prosthetic devices
When infectious complications occur in implant surgery, they are usually problematic and often result in removal of the prosthetic device. Diabetes mellitus is considered a specific risk factor for infection. Skin-related staphylococci are responsible for most infections. The antibiotics used must be chosen to target these strains (101-104) (LE: 2a, GR: B).

Table 15.4a: Surgical Wound classes modified from (13) and adapted to urological surgery. Tentative classification of urological procedures in relation to the different levels of surgical field contamination. The risk of wound infection or SSI expressed in per cent (within brackets in left column) is that of classical wound infections without antibiotic prophylaxis and not bacteriuria or clinical UTI in urological surgery (Modified from Urogenital infections, EAU/ICUD, 2010, p 674-75). In this table some examples of open and laparoscopic procedures are given and the ABp basic principle.

<table>
<thead>
<tr>
<th>Surgical contamination</th>
<th>Description</th>
<th>Open or laparoscopic urological surgery (examples of procedures)</th>
<th>Antibiotic prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean (I) (1-4%)</td>
<td>Uninfected surgical site</td>
<td>Simple nephrectomy</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Urogenital tract not entered</td>
<td>Planned scrotal surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No evidence of inflammation</td>
<td>Vasectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No break in technique</td>
<td>Varicocoele</td>
<td></td>
</tr>
<tr>
<td>Clean-contaminated (UT) (IIA)</td>
<td>Urogenital tract (UT) entered with no or little (controlled) spillage. No break in technique</td>
<td>Pelvio-ureteric junction repair</td>
<td>Single dose prior to (oral) or at surgery (i.v.)</td>
</tr>
<tr>
<td>(Not well studied)</td>
<td></td>
<td>Nephroureterectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial cystectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total prostatectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder surgery, partial cystectomy</td>
<td></td>
</tr>
<tr>
<td>Level of surgical field contamination</td>
<td>Bacteriuria</td>
<td>Diagnostic procedures</td>
<td>TURB and TURP (similar cystoscopy)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------</td>
<td>-----------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Clean (I)</td>
<td>No</td>
<td>Cystoscopy</td>
<td>Small TURB/fulguration</td>
</tr>
<tr>
<td>Clean-contaminated (UT) (IIA)</td>
<td>No</td>
<td>Trans-perineal prostate biopsy</td>
<td>TURB large tumour (no history of UTI)</td>
</tr>
<tr>
<td>Contaminated (UT=IIIA)</td>
<td>Yes</td>
<td>Trans-perineal prostate biopsy (history of UTI)</td>
<td>TURB necrosis/ bacteriuria TURP in men with indwelling catheter or bacteriuria</td>
</tr>
<tr>
<td>Infected/Dirty (IV)</td>
<td>Yes</td>
<td>Prostate biopsy in men with catheter or UTI</td>
<td>Clinical UTI Drainage as required Emergency TURB, TURP</td>
</tr>
</tbody>
</table>

Table 15.4b: Tentative classification of the different diagnostic and therapeutic endoscopic urological procedures in relation to the level of surgical field contamination. Bacteriuria is a key factor to separate between clean-contaminated and contaminated surgical environment (modified from Urogenital infections EAU/ICUD, 2010, p 674-75).
Table 15.5: Recommendations for perioperative antibiotic prophylaxis in urology

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pathogens (expected)</th>
<th>Prophylaxis</th>
<th>Antibiotics</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic procedures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transrectal biopsy of the prostate</td>
<td>Enterobacteriaceae</td>
<td>All patients</td>
<td>Fluoroquinolones TMP ± SMX Metronidazole?¹</td>
<td>Single dose effective in low-risk patients. Consider prolonged course in high-risk patients</td>
</tr>
<tr>
<td></td>
<td>Anaerobes?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>Enterobacteriaceae</td>
<td>No</td>
<td>TMP ± SMX Cephalosporin 2nd generation</td>
<td>Consider in high-risk patients</td>
</tr>
<tr>
<td>Urodynamic examination</td>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteroscopy</td>
<td>Enterobacteriaceae</td>
<td>No</td>
<td>TMP ± SMX Cephalosporin 2nd generation</td>
<td>Consider in high-risk patients</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWL</td>
<td>Enterobacteriaceae</td>
<td>No</td>
<td>TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI¹</td>
<td>Risk patients</td>
</tr>
<tr>
<td>SWL with stent or nephrostomy tube</td>
<td>Enterococci</td>
<td>All patients</td>
<td>TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI¹</td>
<td>Risk patients</td>
</tr>
<tr>
<td></td>
<td>Staphylococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteroscopy for uncomplicated distal stone</td>
<td>Enterobacteriaceae</td>
<td>No</td>
<td>TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones</td>
<td>Consider in risk patients</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteroscopy of proximal or impacted stone and percutaneous stone extraction</td>
<td>Enterobacteriaceae</td>
<td>All patients</td>
<td>TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones</td>
<td>Short course Length to be determined Intravenous suggested at operation</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURP</td>
<td>Enterobacteriaceae</td>
<td>All patients</td>
<td>TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI</td>
<td>Low-risk patients and small-size prostate probably do not require prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUR of bladder tumour</td>
<td>Enterobacteriaceae</td>
<td>No</td>
<td>TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI</td>
<td>Consider in high-risk patients and large tumours</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Open or laparoscopic urological surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean operations</td>
<td>Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens</td>
<td>No</td>
<td></td>
<td>Consider in high-risk patients Short postoperative catheter requires no treatment</td>
</tr>
<tr>
<td>Clean-contaminated (opening of urinary tract)</td>
<td>Enterobacteriaceae Enterococci Staphylococci</td>
<td>Recommended Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI</td>
<td>Single perioperative course</td>
<td></td>
</tr>
<tr>
<td>Clean-contaminated/contaminated (use of bowel segments)</td>
<td>Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria</td>
<td>All patients Cephalosporin 2nd or 3rd generation Metronidazole</td>
<td>As for colonic surgery</td>
<td></td>
</tr>
<tr>
<td>Implant of prosthetic devices</td>
<td>Skin-related bacteria, e.g. staphylococci</td>
<td>All patients Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1No evidence for metronidazole in core biopsy of the prostate.
a = gram-negative bacteria excluding Pseudomonas aeruginosa.

15.7 References


## 16. APPENDICES

### 16.1 Criteria for the diagnosis of UTI, as modified according to IDSA/European Society of Clinical Microbiology and Infectious Diseases guidelines (1-3)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Clinical features</th>
<th>Laboratory investigations</th>
</tr>
</thead>
</table>
| 1        | Acute uncomplicated UTI in women; acute uncomplicated cystitis in women | Dysuria, urgency, frequency, suprapubic pain, no urinary symptoms in 4 weeks before this episode | > 10 WBC/mm³  
> 10³ cfu/mL* |
| 2        | Acute uncomplicated pyelonephritis | Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urological abnormalities (ultrasonography, radiography) | > 10 WBC/mm³  
> 10⁴ cfu/mL* |
| 3        | Complicated UTI | Any combination of symptoms from categories 1 and 2 above; one or more factors associated with a complicated UTI (see text) | > 10 WBC/mm³  
> 10⁵ cfu/mL* in women  
> 10⁴ cfu/mL* in men, or in straight catheter urine in women |
| 4        | Asymptomatic bacteriuria | No urinary symptoms | > 10 WBC/mm³  
> 10⁵ cfu/mL* in two consecutive MSU cultures  
> 24 h apart |
| 5        | Recurrent UTI (antimicrobial prophylaxis) | At least three episodes of uncomplicated infection documented by culture in past 12 months: women only; no structural/functional abnormalities | < 10³ cfu/mL* |

All pyuria counts refer to unspun urine.

*Uropathogen in MSU culture.

### 16.1.1 References

### 16.2 Recommendations for antimicrobial therapy in urology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Most frequent pathogen/species</th>
<th>Initial, empirical antimicrobial therapy</th>
<th>Therapy duration</th>
</tr>
</thead>
</table>
| **Cystitis acute, uncomplicated**  | • *E. coli*  
• Klebsiella  
• Proteus  
• Staphylococci  | • TMP-SMX\(^1\)  
• Nitrofurantoin  
• Fosfomycin trometamol  
• Pivmecillinam  
Alternative:  
• Fluoroquinolone\(^2,3\)  | 3 days  
(5-)7 days  
1 day  
(3-)5 days  
(1-)3 days |
| **Pyelonephritis acute, uncomplicated** | • *E. coli*  
• Proteus  
• Klebsiella  
• Other enterobacteria  
• Staphylococci  | • Fluoroquinolone\(^2\)  
• Cephalosporin (group 3a)  
Alternatives:  
• Aminopenicillin/BLI  
• Aminoglycoside  | 7-10 days |
| **UTI with complicating factors** | • *E. coli*  
• Enterococci  
• *Pseudomonas*  
• Staphylococci  | • Fluoroquinolone\(^2\)  
• Aminopenicillin/BLI  
• Cephalosporin (group 2)  
• Cephalosporin (group 3a)  
• Aminoglycoside  | 3-5 days after defervescence or control/elimination of complicating factor |
| **Nosocomial UTI** | • Klebsiella  
• Proteus  | In case of failure of initial therapy  
within 1-3 days or in clinically cases:  
Anti-*Pseudomonas* active:  
• Fluoroquinolone, if not used initially  
• Acylaminopenicillin/BLI  
• Cephalosporin (group 3b)  
• Carbapenem  
• ± Aminoglycoside  
In case of failure:  
• Fluconazole  
• Amphotericin B  | |
| **Pyelonephritis severe acute, complicated** | • *Enterobacter*  
• Other enterobacteria  
• *(Candida)*  | • Fluoroquinolone\(^2\)  
• Aminopenicillin/BLI  
• Cefepime (group 3a/b)  
• Carbapenem  
• ± Aminoglycoside  | |
| **Prostatitis acute, chronic** | • *E. coli*  
• Other enterobacteria  
• *Pseudomonas*  
• Enterococci  
• Staphylococci  
• *Chlamydia*  
• *Ureaplasma*  
• *E. coli*  
• Other enterobacteria  
After urological interventions - multi-resistant pathogens:  
• *Pseudomonas*  
• Proteus  
• *Serratia*  
• *Enterobacter*  | • Fluoroquinolone\(^2\)  
Alternative in acute bacterial prostatitis:  
• Cephalosporin (group 3a/b)  
In case of *Chlamydia* or *Ureaplasma*:  
• Doxycycline  
• Macrolide  
• Cephalosporin (group 3a/b)  
• Fluoroquinolone\(^2\)  
• Anti-*Pseudomonas* active  
• Aminopenicillin/BLI  
• Carbapenem  
• ± Aminoglycoside  | Acute:  
2-4 weeks  
Chronic:  
4-6 weeks or longer |
| **Epididymitis** | *Ureaplasma*:  
Acute  | | |
| **Urosepsis** | *E. coli*  
• Other enterobacteria  
• *Pseudomonas*  
• Enterococci  
• Staphylococci  
• *Chlamydia*  
• *Ureaplasma*  
• *E. coli*  
• Other enterobacteria  
After urological interventions and/or multi-resistant pathogens:  
• *Pseudomonas*  
• Proteus  
• *Serratia*  
• *Enterobacter*  | | 3-5 days after defervescence or control/elimination of complicating factor |

---

\(^1\) Only in areas with resistance rate < 20% (for *E. coli*).

\(^2\) Fluoroquinolone with mainly renal excretion (see text).

\(^3\) Avoid Fluoroquinolones in uncomplicated cystitis whenever possible.
### 16.3 Recommendations for antimicrobial prescription in renal failure

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mild (GFR 50-20)</th>
<th>Moderate (GFR 20-10)</th>
<th>Severe (GFR &lt; 10)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>normal dose every 12 h</td>
<td>normal dose every 24 h</td>
<td>50% of normal dose every 24 h</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Aciclovir po</td>
<td>normal</td>
<td>Herpes simplex: normal</td>
<td>Herpes simplex: 200 mg bid</td>
<td>Give post-HD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herpes zoster: 800 mg Total Dissolved Solids tds</td>
<td>Herpes zoster: 800 mg bd</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>5-6 mg/kg 12 h</td>
<td>3-4 mg/kg 24 h HD: 5 mg/kg post HD and monitor levels</td>
<td>2 mg/kg 24-48 h</td>
<td>Give post-HD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor pre- and 1 h post-dose levels</td>
<td>after 3rd dose and adjust dose as required</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin po</td>
<td>normal</td>
<td>normal</td>
<td>250 mg 8 h (normal)</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>(Liposomal + lipid complex)</td>
<td>Amphotericin is highly NEPHROTOXIC. Consider using liposomal/lipid complex amphotericin. Daily monitoring of renal function (GFR) essential.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin IV</td>
<td>normal</td>
<td>250-500 mg 6 h</td>
<td>250 mg 6 h</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>normal</td>
<td>75%</td>
<td>20-50% Max. 3.6 g/day (1.2 g qds)</td>
<td>Give post-HD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refer to microbiology for dosing in SBE</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>normal</td>
<td>normal</td>
<td>1 g stat then 50%</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Cefradine</td>
<td>normal</td>
<td>Normal</td>
<td>250 mg 6 h</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 g 12 h</td>
<td>1 g 24 h</td>
<td>500 mg 24 h (1 g 24 h)</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>normal</td>
<td>normal</td>
<td>normal Max. 2 g/day</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime IV</td>
<td>normal</td>
<td>750 mg-1.5 g 12 h</td>
<td>750 mg 24 h (750 mg 12 h)</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Ciprofloxin IV + po</td>
<td>normal</td>
<td>50%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin IV + po</td>
<td>normal</td>
<td>normal</td>
<td>50%</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Clindamycin IV + po</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav IV (Augmentin)</td>
<td>normal</td>
<td>1.2 stat then 50% 12 h (1.2 g 12 h)</td>
<td>1.2 stat then 50% 24 h (1.2 g stat then 600 mg 12 h)</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>Co-amoxiclav po (Augmentin)</td>
<td>normal</td>
<td>375-625 mg 12 h (375 mg 8 h)</td>
<td>375 mg 12 h (375 mg 8 h)</td>
<td>Give post-HD</td>
</tr>
<tr>
<td>*Co-trimoxazole IV</td>
<td>normal</td>
<td>Normal for 3/7 then 50%</td>
<td>50%</td>
<td>Give post-HD</td>
</tr>
</tbody>
</table>

*Note: HD refers to hemodialysis.*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Regimen</th>
<th>Normal Treatment</th>
<th>Abnormal Treatment</th>
<th>GFR 10-40 mL/min</th>
<th>GFR &lt; 10 mL/min</th>
<th>BOTH METHODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>Normal normal normal normal</td>
<td>All other tetracyclines contraindicated in renal impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin IV + po</td>
<td>normal normal normal normal Max. 1.5 g/day (500 mg qds)</td>
<td>GFR 10-40 mL/min</td>
<td>GFR &lt; 10 mL/min</td>
<td>BOTH METHODS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Ethambutol</td>
<td>normal 24-36 h 48 h</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitor levels if GFR &lt; 30mL/min (contact Mirco)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>normal normal normal 50%</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Give post-HD No adjustments in single-dose therapy required</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Flucytosine</td>
<td>50 mg/kg 12 h 50 mg/kg 24 h</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levels should be monitored predialysis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>normal normal normal normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Gentamicin</td>
<td>GFR 10-40 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONCE DAILY</td>
<td>3 mg/kg stat (max. 300 mg) Check pre-dose levels 18-24 h after first dose Redose only when level &lt; 1 mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Gentamicin</td>
<td>GFR &lt; 10 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONVENTIONAL</td>
<td>80 mg 12 h 80 mg 48 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR &lt; 10 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 mg 24 h HD: 1-2 mg/kg Post-HD: redose according to levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once daily: pre only Conventional: pre and 1 h post level required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg 8-12 h 250-500 mg bid</td>
<td>Risk of convulsions - use Meropenem: see below</td>
<td></td>
<td>Give post-HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>normal normal 200-300 mg 24 h</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>normal normal normal normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>500 mg stat then 250 mg bid** 500 mg stat then 125 mg bid** 500 mg stat then 125 mg od</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**Applies if full dose is 500 mg bid If full dose is 500 mg od, five reduced doses daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>normal normal normal normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>12 h 50% 12 h 50% 24 h</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meronidazole</td>
<td>normal normal 12 h (normal)</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Do NOT use in renal impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td>normal normal normal normal</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin/</td>
<td>4.5 g 8 h 4.5 g 12 h 4.5 g 12 h</td>
<td>Give post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tazobactam (Tazocin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>normal normal normal normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>normal normal normal 50-100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Teicoplanin</td>
<td>100% 48 h 100% 72 h 100% 72 h</td>
<td>Dose reduction after day 3 of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>See Doxycycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>normal</td>
<td>Normal for 3/7 then 50% 18 h</td>
<td>50% 24 h</td>
<td>Give post-HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g od</td>
<td>1 g 48 h Check pre-dose level before 3rd dose</td>
<td>1 g stat (or 15 mg/ kg, up to max. 2 g). Recheck level after 4-5 days ONLY give subsequent dose when level &lt; 12mg/L</td>
<td>Monitor pre-dose levels and adjust dose as required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinconazole</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Give post HD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| bid = twice daily; HD = haemodialysis; od = once daily; po = by mouth; qid = four times daily; SBE = subacute bacterial endocarditis; tds = total dissolved solids; qds = Quantum Dots. |
16.4  CPSI


NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort
1. In the last week, have you experienced any pain or discomfort in the following areas?
   a. Area between rectum and testicles (perineum)
      Yes □ 1  No □ 0
   b. Testicles
      □ 1  □ 0
   c. Tip of penis (not related to urination)
      □ 1  □ 0
   d. Below your waist, in your pubic or bladder area
      □ 1  □ 0

2. In the last week, have you experienced:
   a. Pain or burning during urination?
      Yes □ 1  No □ 0
   b. Pain or discomfort during or after sexual climax (ejaculation)?
      □ 1  □ 0

3. How often have you had pain or discomfort in any of these areas over the last week?
   □ 0 Never
   □ 1 Rarely
   □ 2 Sometimes
   □ 3 Often
   □ 4 Usually
   □ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?
   □ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10
   NO = PAIN AS BAD
   AS YOU CAN IMAGINE

Urination
5. How often have you had a sensation of not emptying your bladder completely after you finished urinating over the last week?
   □ 0 Not at all
   □ 1 Less than 1 time in 5
   □ 2 Less than half the time
   □ 3 About half the time
   □ 4 More than half the time
   □ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?
   □ 0 Not at all
   □ 1 Less than 1 time in 5
   □ 2 Less than half the time
   □ 3 About half the time
   □ 4 More than half the time
   □ 5 Almost always

Impact of Symptoms
7. How much have your symptoms kept you from doing the kinds of things you would usually do over the last week?
   □ 0 None
   □ 1 Only a little
   □ 2 Some
   □ 3 A lot

8. How much did you think about your symptoms, over the last week?
   □ 0 None
   □ 1 Only a little
   □ 2 Some
   □ 3 A lot

Quality of life
9. If you were to spend the rest of your life with your symptoms, just the way they have been during the last week, how would you feel about that?
   □ 0 Delighted
   □ 1 Pleased
   □ 2 Mostly satisfied
   □ 3 Mixed (about equally satisfied and dissatisfied)
   □ 4 Mostly dissatisfied
   □ 5 Unhappy
   □ 6 Terrible

Scoring the NIH-CPSI Prostatitis Symptom Index Domain

Pain:
Total of items 1a,1b,1c,1d,2a,2b,3 and 4  = __________

Urinary Symptoms:
Total of items 5 and 6  = __________

Quality of Life Impact:
Total of items 7,8, and 9  = __________

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16.5 Meares & Stamey localisation technique*

**MEARES AND STAMEY LOCALIZATION TECHNIQUE**

1. Approximately 30 minutes before taking the specimen, the patient should drink 400ml of liquid (two glasses). The test starts when the patient wants to void.
2. The lids of the sterile specimen containers, which are marked VB1, VB2, EPS and VB3, should be removed. Place the uncovered specimen containers on a flat surface and maintain sterility.
3. Hands are washed.
4. Expose the penis and retract the foreskin so that the glans is exposed. The foreskin should be retracted throughout.
5. Cleanse the glans with a soap solution, remove the soap with sterile gauze or cotton and dry the glans.
6. Urinate 10-15ml into the first container marked VB1.
7. Urinate 100-200ml into the toilet bowl or vessel and without interrupting the urine stream, urinate 10-15ml into the second container marked VB2.
8. The patient bends forward and holds the sterile specimen container (EPS) to catch the prostatic secretion.
9. The physician massages the prostate until several drops of prostatic secretion (EPS) are obtained.
10. If no EPS can be collected during massage, a drop may be present at the office of the urethra and this drop should be taken with a 10μl calibrated loop and cultured.
11. Immediately after prostatic massage, the patient urinates 10-15ml of urine into the container marked VB3.

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16.6 Antibacterial agents

<table>
<thead>
<tr>
<th>Groups</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulphonamide combinations</td>
<td>Trimethoprim, co-trimoxazole, co-tetroxoprime (trimethoprim plus sulfametrol)</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Group 1: Norfloxacin, pefloxacin</td>
</tr>
<tr>
<td></td>
<td>Group 2: Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Group 3: Levofloxacin</td>
</tr>
<tr>
<td></td>
<td>Group 4: Gatifloxacin, moxifloxacin</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td>Erythromycin, roxithromycin, clarithromycin, azithromycin</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>Doxycycline, minocycline, tetracycline</td>
</tr>
<tr>
<td><strong>Fosfomycin</strong></td>
<td>Fosfomycin sodium, fosfomycin trometamol&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Nitrofuran</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
<td>Benzylpenicillin, Penicillin G</td>
</tr>
<tr>
<td>Phenoxybenicillins</td>
<td>Penicillin V, propicillin, azidocillin</td>
</tr>
<tr>
<td>Isoxazolylpenicillins</td>
<td>Oxacillin, cloxacillin, dicloxacillin, flucloxacillin</td>
</tr>
<tr>
<td>Aminobenzylpenicillins&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Ampicillin, amoxycillin, bacampicillin</td>
</tr>
<tr>
<td>Aminopenicillins/BLI&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Ampicillin/sulbactam, amoxycillin/clavulanic acid&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
16.6.1 Penicillins
Penicillin G and the oral penicillins, penicillin V, propicillin and azidocillin, have a high intrinsic activity against streptococci and pneumococci. However, the resistance rate of pneumococci may vary considerably between countries. In Germany, penicillin resistance in pneumococci is still < 1%. Because of their narrow spectrum of activity, these penicillins do not have any role in the treatment of urogenital infections.

16.6.1.1 Aminopenicillins
Aminopenicillins, e.g. ampicillin and amoxycillin, have a broader spectrum of activity. Apart from streptococci and pneumococci, they cover enterococci, Haemophilus influenzae, Haemophilus parainfluenzae, Listeria sp., E. coli, Pr. mirabilis, and Salmonella and Shigella sp. However, resistance may occur.

Aminopenicillins are sensitive to β-lactamases. They are therefore not sufficiently active against certain species, such as staphylococci, Moraxella catarrhalis, Bacteroides fragilis and many enterobacteria. This gap in the spectrum of activity can be closed by the use of a BLI (clavulanic acid, or sulbactam). Amoxycillin/clavulanic acid and ampicillin/sulbactam are available on the market as fixed combinations. Indications for aminopenicillins and their combinations with a BLI are mild respiratory tract infections, UTIs, as well as infections of the skin and soft tissues.

16.6.1.2 Acylaminopenicillins
The acylaminopenicillins include apalcillin, azlocillin, mezlocillin and piperacillin. They are characterised by their high activity against enterococci, enterobacteria and Pseudomonas (weaker activity of mezlocillin). Acylaminopenicillins are hydrolyzed by β-lactamases and are therefore active only against β-lactamase-producing strains of staphylococci, B. fragilis, and if used in combination with a BLI, some of the enterobacteria. The acylaminopenicillin/BLI combination provides a broad spectrum of activity and may be used for a large number of indications, including complicated UTIs and urosepsis. A selection of free combinations with sulbactam is available, or there is the fixed combination of tazobactam and piperacillin, which has the advantages of being easy to use and a well-documented database drawn from qualified clinical studies.

16.6.1.3 Isoxazolylpenicillins
Isoxazolylpenicillins are available as parenteral drugs with oxacillin and flucloxacillin, and have a narrow

<table>
<thead>
<tr>
<th>Acylaminopenicillins</th>
<th>Mezlocillin, piperacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>±BLI</td>
<td>Piperacillin/tazobactam, sulbactam</td>
</tr>
</tbody>
</table>

Cephalosporins

| Group 1 (oral) | Cefalexin, cefadroxil, cefaclor |
| Group 2 (oral) | Loracarbef, cefuroxime axetile |
| Group 3 (oral) | Cefpodoxime proxetile, cefetamet pivoxil, ceftibuten, cefixime |
| Group 1 (parenteral) | Cefazolin |
| Group 2 (parenteral) | Cefamandole, cefuroxime, cefotiam |
| Group 3a (parenteral) | Cefodizime, cefotaxime, ceftriaxone |
| Group 3b (parenteral) | Cefoperazone, ceftazidime |
| Group 4 (parenteral) | Cefepime, cefpirome |
| Group 5 (parenteral) | Cefoxitin |

Monobactams

| Aztreonam |

Carbapenems

| Imipenem, meropenem, ertapenem |

Aminoglycosides

| Gentamicin, netilmicin, tobramycin, amikacin |

Glycopeptides

| Vancomycin, teicoplanin |

Oxazolidones

| Linezolid |

1Classification according to the Paul Ehrlich Society for Chemotherapy (1-3).
2Only in adults, except pregnant and lactating women.
3Only in acute, uncomplicated cystitis as a single dose.
4Contraindicated in renal failure and in newborns.
5In cases of resistance, the pathogen is most likely to be a β-lactamase producer.
6BLIs can only be used in combination with β-lactam antibiotics.
7In solution, storage instability.
spectrum of activity. Their indications are limited to infections caused by S. aureus. Due to their suboptimal pharmacokinetic parameters, isoxazolylpenicillins are preferably used in milder infections of the skin and soft tissues, and of the ear, nose and throat area. They play no role in the treatment of UTIs, but may be used for staphylococcal abscesses in the genital area.

16.6.2 Parenteral cephalosporins
According to the Paul Ehrlich Society for Chemotherapy (1), the parenteral cephalosporins have been classified into five groups, according to their spectrum of activity (Table 16.7.2).

16.6.2.1 Group 1 cephalosporins
Group 1 cephalosporins (cefazolin and cefazedone) are very active against streptococci and staphylococci (including penicillin-G-resistant strains). They have only weak activity against Gram-negative microorganisms. Like all cephalosporins, cefazolin is not active against enterococci and MRSA and methicillin-resistant coagulase-negative staphylococci (MRSE).

16.6.2.2 Group 2 cephalosporins
Compared with Group 1 cephalosporins, Group 2 cephalosporins, e.g. cefuroxime, cefotiam and cefamandole, exhibit markedly improved activity against Gram-negative pathogens and maintain high activity against staphylococci.

16.6.2.3 Group 3a cephalosporins
Group 3a cephalosporins have high activity against Gram-negative bacteria and less activity against staphylococci. They differ mainly in their pharmacokinetic characteristics.

16.6.2.4 Group 3b cephalosporins
Group 3b cephalosporins, e.g. ceftazidime and cefoperazone, have added high anti-pseudomonal activity. However, the activity of cefoperazone against P. aeruginosa is markedly inferior to that of the other substances in this group.

16.6.2.5 Group 4 cephalosporins
Group 4 cephalosporins, e.g. cefepime and cefpirome, have a comparable activity against Gram-negative bacteria, but are more stable against extended-spectrum β-lactamases, and a better activity against Gram-positive bacteria.

16.6.2.6 Group 5 cephalosporins
The Group 5 cephalosporins are characterised by their anti-anaerobic activity. These cephalosporins have superior activity against Gram-negative bacteria compared with Group 1 and 2 cephalosporins, but most of them are weaker than Group 3 drugs. At present, cefoxitin is the only drug of that group available on the market in some countries.
Table 16.6.2: Classification of parenteral cephalosporins (2)

<table>
<thead>
<tr>
<th>Group</th>
<th>Generic names</th>
<th>Features of the group</th>
</tr>
</thead>
</table>
| Group 1 (1st generation) | Cefazolin  Cefazedone | • Active against Gram-positive and partly against Gram-negative bacteria  
• Stable against staphylococcal penicillinases  
• Unstable against β-lactamases of Gram-negative bacteria |
| Group 2 (2nd generation) | Cefuroxime  Cefotiam  Cefamandole | • Activity against Gram-positive bacteria good, but weaker than Group 1  
• Activity against Gram-negative bacteria superior to that of Group 1  
• Stable against staphylococcal penicillinases  
• Limited stability against β-lactamases of Gram-negative bacteria |
| Group 3a (3rd generation) | Cefotaxime  Ceftriaxone  Cefitoxime  Cefmenoxime  Cefodizime | • Activity against Gram-negative bacteria clearly superior to that of Groups 1 and 2  
• Stable against numerous β-lactamases of Gram-negative bacteria  
• Microbiologically less active against staphylococci |
| Group 3b (3rd generation) | Ceftazidime  Cefoperazone | • Spectrum of antibacterial activity similar to that of Group 3a  
• Additional activity against P. aeruginosa |
| Group 4 | Cefepime  Cefpirome | • Spectrum of antibacterial activity similar to that of Group 3a  
• Additional activity against P. aeruginosa  
• Higher stability against beta-lactamases than group 3b  
• With anti-anaerobic activity  
• Superior activity against Gram-negative bacteria than Group 1 and 2  
• Weaker than Group 3 |
| Group 5 | Cefoxitin | |

16.6.3 Oral cephalosporins

Oral cephalosporins are classified into three groups, based on their spectrum of activity, according to the recommendations of the Paul Ehrlich Society for Chemotherapy (1) (Table 16.7.3).

Table 16.7.3: Classification of oral cephalosporins (1)

<table>
<thead>
<tr>
<th>Oral cephalosporins</th>
<th>Drug names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Cefalexin  Cefadroxil  Cefaclor</td>
</tr>
<tr>
<td>Group 2</td>
<td>Cefprozil  Loracarbef  Cefuroxime axetile</td>
</tr>
<tr>
<td>Group 3</td>
<td>Cefpodoxime proxetile  Cefetamet pivoxile  Ceftibuten  Cefixime</td>
</tr>
</tbody>
</table>

16.6.3.1 Group 1 oral cephalosporins

Group 1 oral cephalosporins include cefalexin, cefadroxil and cefaclor. They are mainly active against Gram-positive cocci with limited activity against *H. influenzae* (cefACLor). Their main indications are skin and soft tissue infections and, with limitations, respiratory tract infections. Their activity against enterobacteria is limited,
therefore, they can only be recommended for the treatment or prophylaxis of uncomplicated UTIs in children or pregnant women, for whom the use of other antibiotics is limited.

16.6.3.2 Group 2 oral cephalosporins
The activity of cefprozil against *S. aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *H. influenzae* and *Mor. catarrhalis* is somewhat higher than that of cefaclor. However, cefprozil is less active than cefaclor against *E. coli*, *Klebsiella pneumoniae* and *Pr. mirabilis*.

Loracarbef is structurally close to cefaclor. In contrast to cefaclor, it is stable in solution, has better pharmacokinetics and a broader antibacterial spectrum. However, its activity against staphylococci is lower than that of cefaclor. The main indications are respiratory tract, skin and soft-tissue infections and uncomplicated UTIs.

Cefuroxime axetile has a higher β-lactamase stability and thus a broader spectrum than others in this group. It can be used mainly for bacterial infections of the upper (including otitis media) and lower respiratory tract, for skin and soft-tissue infections, and UTIs.

16.6.3.3 Group 3 oral cephalosporins
Group 3 oral cephalosporins have a higher activity and a broader spectrum against enterobacteria than group 2 cephalosporins. In contrast, their activity against Gram-positive bacteria is lower. Against staphylococci, the activity of cefpodoxime proxetil is intermediate, whereas cefetamet pivoxil, ceftibuten and cefixime are inactive.

The main indications for the oral cephalosporins of group 3 are complicated infections of the respiratory tract (provided that staphylococci can be excluded) and infections due to enterobacteria, e.g. UTIs or infections in immunocompromised patients. Group 3 oral cephalosporins are also suitable for oral switch therapy, i.e. when initial parenteral therapy (using a parenteral group 3a cephalosporin) needs to be continued orally. In addition, cefixime is licensed also for treatment of gonorrhoea.

16.6.4 Monobactams
Among the monobactams, only aztreonam is available. It is active only against Gram-negative aerobes. In this respect, its spectrum and activity are similar to those of the parenteral group 3b cephalosporins.

16.6.5 Carbapenems
Carbapenems are broad-spectrum antibiotics with good activity against Gram-positive and Gram-negative bacteria, including anaerobes. They are preferably used in the treatment of mixed infections and in the initial therapy of life-threatening diseases, including urosepsis. Imipenem/cilastatin, meropenem and doripenem are also active against *P. aeruginosa*. However, ertapenem is not active against *P. aeruginosa*. Ertapenem has a longer half-life than imipenem/cilastatin and meropenem, and is therefore, suitable for once-daily dosing.

16.6.6 Fluoroquinolones
Non-fluorinated quinolones are no longer recommended because of their poor antibacterial activity. According to the Paul Ehrlich Society for Chemotherapy, the fluoroquinolones are classified into four groups, based on their spectrum of activity, their pharmacokinetics and indications (Table 16.6.4).

Table 16.6.4: Classification of fluoroquinolones, as modified according to the Paul Ehrlich Society for Chemotherapy (3)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name*/features of the group</th>
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### Group 3
Improved activity against Gram-positive and atypical pathogens

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### Group 4
Improved activity against Gram-positive and atypical pathogens and anaerobes

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* Listed according to increasing *in vitro* activity (minimum inhibitory concentration) against indicative pathogens.
** In France and other countries, pefloxacin is also available for systemic use.
*** Investigated in acute exacerbations of chronic bronchitis, UTIs, gonorrhoea and gastrointestinal infections.

#### 16.6.6.1 Group 1 fluoroquinolones

The indications for group 1 fluoroquinolones are limited to UTIs in some countries, e.g. Germany. In France and some other countries, pefloxacin is also used for systemic oral and parenteral use. Norfloxacin is not available as parenteral antibiotic.

#### 16.6.6.2 Group 2 fluoroquinolones

Group 2 fluoroquinolones includes fluoroquinolones for systemic use with a broad spectrum of indications. These include infections of the urinary tract, respiratory tract, skin and soft tissues, bones and joints, as well as systemic infections and even sepsis. Group 2 fluoroquinolones exhibit good activity against enterobacteria and *H. influenzae*, with less activity against staphylococci, pneumococci, enterococci and atypical pathogens, e.g. *Chlamydia, Legionella* and *Mycoplasma* sp. Their activity against *P. aeruginosa* varies, with ciprofloxacin being most active in vitro. In addition, ciprofloxacin, ofloxacin and fleroxacin are also available for parenteral use.

#### 16.6.6.3 Group 3 fluoroquinolones

The main difference in the spectra of activity of group 3 fluoroquinolones (levofloxacin) and group 4 fluoroquinolones (gatifloxacin and moxifloxacin) is that the former have a higher intrinsic activity against Gram-positive pathogens, such as staphylococci, streptococci, pneumococci and enterococci.

However, group 3 and group 4 fluoroquinolones have comparable activity against Gram-negative pathogens. In addition, they have improved activity against the so-called atypical pathogens, such as *Chlamydia, Mycoplasma* and *Legionella* sp. In addition, group 4 fluoroquinolones have improved anti-anaerobic activity.

The only group 3 fluoroquinolone available for parenteral use is levofloxacin; the left enantiomer of the ofloxacin racemate. The main indications for levofloxacin are respiratory tract infections, and, due to its high renal elimination rate, UTIs, as well as skin and soft-tissue infections.

Among group 4 fluoroquinolones, gatifloxacin (not on the market in Europe), moxifloxacin and trovafloxacin have been licensed. However, in June 1999, trovafloxacin was taken off the market because of severe side effects. Thus, to date, no parenteral fluoroquinolone of this group has been made available.

Apart from respiratory tract infections, these broad-spectrum fluoroquinolones are appropriate for treatment of skin, soft-tissue and intra-abdominal infections, and oral treatment of gynaecological infections. However, final judgement of their position in the treatment of these diseases is not yet possible. Gatifloxacin has the highest renal excretion (about 84%) after oral administration. It is therefore also the most suitable for the treatment of uncomplicated and complicated UTI. Urinary excretion of moxifloxacin after oral administration is only in the range of about 20%.

#### 16.6.7 Co-trimoxazole

The treatment of UTIs is the main indication for trimethoprim alone or in combination with a sulphonamide, e.g. sulphamethoxazole. Trimethoprim with or without sulphamethoxazole can also be used for the prophylaxis of recurrent cystitis. The resistance rate against *E. coli* can vary between countries. It is therefore not recommended for empirical therapy of acute uncomplicated cystitis or pyelonephritis, when the resistance rate in the area is > 10-20% (4). In complicated UTIs, co-trimoxazole should only be used in accordance with sensitivity testing. Trimethoprim, especially in combination with sulphamethoxazole, can lead to severe although rare adverse events, such as Lyell syndrome, Stevens-Johnson syndrome and pancytopenia.

#### 16.6.8 Fosfomycin

Fosfomycin is active against Gram-negative and Gram-positive bacteria. The sodium salt is only for parenteral use. Fosfomycin trometamol is licensed for single-dose (3 g) treatment of uncomplicated cystitis in women.
16.6.9 **Nitrofurantoin**

The antibacterial activity of nitrofurantoin is limited to the urinary tract because of its low serum concentrations. It is active against *E. coli*, *Citrobacter* and most strains of *Klebsiella* and *Enterobacter*, whereas *Providencia* and *Serratia* are mostly resistant. *Proteus, P. aeruginosa* and *Acinetobacter* are almost always resistant. It is active against Gram-positive cocci, e.g. enterococci and staphylococci.

It is suitable only for the treatment or prophylaxis of uncomplicated UTIs. Short-term therapy for this indication has not been proven in sufficiently large studies. Little development of resistance has been observed over many years. Treatment can lead to severe, though rare adverse events, such as chronic desquamative interstitial pneumonia with fibrosis.

16.6.10 **Macrolides**

Erythromycin is the only macrolide that is available for both oral and parenteral use. The newer macrolides, roxithromycin, clarithromycin and azithromycin, are better tolerated than erythromycin, but can only be administered orally. The macrolides have good activity against streptococci, pneumococci, *Bordetella pertussis*, and *Chlamydia, Mycoplasma* and *Legionella* sp. The macrolides are not active against Gram-negative rods, therefore, their use in the treatment of UTIs is limited to special indications, such as non-gonococcal urethritis due to *C. trachomatis*.

16.6.11 **Tetracyclines**

The resistance against doxycycline and tetracycline of pneumococci, streptococci, *H. influenzae* and *E. coli* shows marked regional differences. Tetracyclines are therefore only suitable for initial empirical therapy if the local resistance situation is sufficiently well known and justifies their use. As a result of their high activity against the so-called atypical pathogens (*Legionella, Chlamydia* and *Mycoplasma* sp.), they may be used as alternative antibiotics in infections caused by these microorganisms, e.g. in non-gonococcal urethritis due to *C. trachomatis*.

16.6.12 **Aminoglycosides**

Aminoglycosides are for parenteral use only. These drugs have a narrow therapeutic window. Their effective levels of activity are close to toxic borderline concentrations, making a strict therapeutic indication mandatory. With few exceptions (e.g. treatment of UTIs), aminoglycosides should only be used in combination with another appropriate antibiotic. Ideal partners are β-lactam antibiotics, because this combination has a marked synergistic effect against certain bacterial species. Streptomycin is one of the older aminoglycosides and is used only for the treatment of tuberculosis.

Newer aminoglycosides include netilmicin, gentamicin, tobramycin and amikacin. They have good activity against enterobacteria and *Pseudomonas* (especially tobramycin). Their activity against streptococci, anaerobes and *H. influenzae* is not satisfactory. Resistance data for tobramycin, gentamicin and netilmicin are almost identical, whereas the resistance situation is more favourable for amikacin against many enterobacteria.

16.6.13 **Glycopeptides**

The glycopeptides vancomycin and teicoplanin are active against Gram-positive pathogens, i.e. staphylococci (including oxacillin-resistant strains), streptococci, enterococci, *Clostridium difficile*, diphtheria bacteria and Gram-positive aerobes. They are inactive against Gram-negative pathogens. Their use is indicated:

- In infections caused by the above-mentioned pathogens in case of allergy against all other suitable antibiotics.
- In infections caused by ampicillin-resistant enterococci or oxacillin-resistant staphylococci, or multi-resistant corynebacteria.
- As an alternative, in oral form, to metronidazole for the treatment of pseudomembranous colitis. Due to the risk of selection of glycopeptide-resistant enterococci and staphylococci, the use of glycopeptides should be highly restricted. Similar to the aminoglycosides, glycopeptides have a narrow therapeutic window.

16.6.14 **Oxazolidinones**

The only substance of this group is linezolid, which can be administered parenterally and orally. It has good activity against Gram-positive cocci, such as staphylococci, including methicillin (oxacillin)-resistant strains, enterococci, including vancomycin-resistant strains, and streptococci.

16.6.15 **References**


16.7 Relevant bacteria for urological infections

Obligate intracellular bacteria
- Chlamydia
  - C. trachomatis

No cell wall
- Mycoplasma
  - M. hominis
  - M. genitalium
- Ureaplasma
  - U. urealyticum

Spirochetes
- Treponema
  - T. pallidum

Rods*
- Ziehl-Neelsen Positive
- Mycobacteria
  - M. tuberculosis
- Corynebacteria
  - C. urealyticum
  - Listeria
  - Bacilli

Gram-positive aerobic
- Enterobacteriaceae
  - Escherichia
  - Klebsiella
  - Citrobacter
  - Proteus
  - Serratia
  - Providencia
  - Enterobacter
  - Pantoea
  - Hafnia
  - Salmonella
  - Shigella

Non-Fermenter
- Pseudomonas
- Acinetobacter
- Xanthomonas
- Burgholderia

Parvobacteria
- Haemophilus
  - Gardnerella vaginalis

Gram-negative aerobic
- Neisseria
  - N. gonorrhoeae

Cocci*
- Streptococcus
  - α-haemolytic
    - S. viridans
  - β-haemolytic
    - S. pyogenes
      - group A
    - S. agalactiae
      - group B
  - non-hemolytic
    - Enterococcus
      - E. faecalis
    - E. faecium
    - others
  - Staphylococcus
    - S. aureus
    - S. epidermidis
    - S. saprophyticus

Mycoplasma
- M. hominis
- M. genitalium

Ureaplasma
- U. urealyticum

*Anaerobic bacteria not considered.
17. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

- **ABU**: asymptomatic bacteriuria
- **ACE**: angiotensin-converting enzyme
- **ADPKD**: adult dominant polycystic disease
- **APCKD**: adult polycystic kidney disease
- **BLI**: β-lactamase inhibitor
- **BPH**: benign prostatic hyperplasia
- **CPPS**: chronic pelvic pain syndrome
- **CPSI**: Chronic Prostatitis Symptom Index
- **CT**: computed tomography
- **CAUTIs**: catheter-associated urinary tract infections
- **DMSA**: dimercaptosuccinic acid
- **DTPA**: diethylenetriamine pentaacetate
- **EPS**: expressed prostatic secretion
- **EUCAST**: European Committee for Antimicrobial Susceptibility Testing
- **G6PD**: glucose-6-phosphate dehydrogenase
- **GFR**: glomerular filtration rate
- **IDSA**: Infectious Diseases Society of America
- **IL**: interleukin
- **IPCN**: International Prostatitis Collaborative Network
- **IVU**: intravenous urography
- **LUTS**: lower urinary tract symptom
- **MAG-3**: mercaptoacetyllyglycine
- **MRI**: magnetic resonance imaging
- **MRSA**: methicillin-resistant Staphylococcus aureus
- **MSU**: mid-stream sample of urine
- **NCCLS**: National Committee for Clinical Laboratory Standards
- **NIDDK**: National Institute of Diabetes and Digestive and Kidney Diseases
- **NIH**: National Institutes of Health
- **PCP**: Pneumocystis carinii pneumonia
- **PSA**: prostate-specific antigen
- **SIRS**: systemic inflammatory response syndrome
- **SMX**: sulphamethoxazole
- **SSI**: surgical site infection
- **STD**: sexually transmitted disease
- **SWL**: shockwave lithotripsy
- **TMP**: trimethoprim
- **TNF**: tumour necrosis factor
- **TRUS**: transrectual ultrasound
- **TURP**: transurethral resection of the prostate
- **US**: ultrasonography
- **UTI**: urinary tract infection
- **VB1**: first-voided urine
- **VB2**: mid-stream urine
- **VB3**: voided bladder urine-3
- **VCU**: voiding cystourethography
- **VUR**: vesicoureteric reflux
- **WBC**: white blood cells

**Conflict of interest**

All members of the Urological Infections Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. INTRODUCTION

Urinary incontinence (UI) is an extremely common complaint in every part of the world. It causes a great deal of distress and embarrassment, as well as significant costs, to both individuals and societies. Estimates of prevalence vary according to the definition of incontinence and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost.

These Guidelines from the European Association of Urology (EAU) Working Panel on Urinary Incontinence are written by urologists for urologists, and aim to provide sensible and practical evidence-based guidance on the clinical problem of UI rather than an exhaustive narrative review. Such a review is already available from the International Consultation on Incontinence (1), and so the EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of UI. The focus of these Guidelines is entirely on assessment and treatment reflecting clinical practice. The Guidelines also do not consider patients with UI caused by neurological disease, as this is covered by complementary EAU Guidelines (2).

The EAU Panel knew that they would find little evidence for some issues and a lot of evidence for others. This difference, to some extent, reflects the greater funding available for industry-sponsored trials of drugs, the results of which are required for licensing in Europe and the USA. The less stringent regulatory requirements for the introduction of new devices or surgical techniques means that there are far fewer high-quality studies regarding these interventions. Although the lack of high-quality evidence means that judgements about the worth of interventions are prone to bias, the panel took the view that clinicians still require some guidance concerning clinical practice. In these circumstances, we have summarised the available evidence and made recommendations, with uncertainty reflected by a lower grade of recommendation.

1.1 Methodology

The Panel decided to rewrite the existing EAU Guidelines on UI using a new methodological approach and to present them in a format that most closely reflected the approach to management of UI. The current Guidelines provide:

- A clear clinical pathway (algorithm) for common clinical problems. This can provide the basis for thinking through a patient’s management and also for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance on what to do or not to do, in most clinical circumstances. This should be particularly helpful in those areas of practice for which there is little or no high-quality evidence.

1.1.1 PICO questions

The ‘PICO’ (Population, Intervention, Comparison, Outcome) framework was used to develop a series of clinical questions that would provide the basis of presentation of the guidelines (3,4). There are four elements to each clinical question:

- population;
- intervention;
- comparison;
- outcome.

The wording of each PICO is important because it directs the subsequent literature research. For each element, the EAU Panel listed every possible wording variation.

In these Guidelines, the four traditional domains of urological practice are presented as separate chapters, namely assessment and diagnosis, conservative management, drug therapy and surgical treatments.

In this second edition of these new EAU Guidelines for Urinary Incontinence, the Panel has focused largely on the management of a ‘standard’ patient. The Panel has referred in places to patients with ‘complicated incontinence’, by which we mean patients with associated morbidity, a history of previous pelvic surgery, surgery for UI, radiotherapy and women with associated genitourinary prolapse. This second edition does not review the prevention of UI, or the management of fistula, but these issues will be fully addressed in future editions.

1.1.2 Search strategies

A number of significant narrative reviews, systematic reviews and guidance documents have been produced within the last few years. The Panel agreed that the literature searches carried out by these reviews would be accepted as valid. Thus, for each PICO question, a search was carried out with a start date that was...
the same as the cut-off date for the search associated with the most recent systematic review for the PICO topic. This pragmatic selection approach, while being a compromise and open to criticism, made the task of searching the literature for such a large subject area possible within the available resources. For each section, the latest cut-off date for the relevant search is indicated.

Thus, for each PICO, a subsequent literature search was carried out (confined to Medline and Embase and to English language articles), which produced an initial list of abstracts. The abstracts were each assessed by two Panel members, who selected the studies relevant to the PICO question, and the full text for these was retrieved (Table 1).

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Latest ‘cut-off’ date for search</th>
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<tr>
<td>Assessment and diagnosis</td>
<td>28 June 2012</td>
</tr>
<tr>
<td>Conservative therapy</td>
<td>28 June 2012</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>28 June 2012</td>
</tr>
<tr>
<td>Surgical therapy</td>
<td>9 July 2012</td>
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Each PICO was then assigned to a Panel member, who read the papers and extracted the evidence for incorporation into standardised evidence tables, which are maintained online as an evidence resource for the Panel. This resource will continue to be available and will be continuously updated with each repeated literature review.

The existing evidence from previous systematic reviews and new evidence were then discussed for each PICO in turn at a Panel meeting generating consensus conclusions. To help standardise the approach, modified process forms (data extraction and considered judgment) from the Scottish Intercollegiate Guidelines Network (SIGN) were used.

The quality of evidence for each PICO is commented on in the text, aiming to synthesise the important clinical messages from the available literature and is presented as a series of levels of evidence summaries in the EAU format (Table 2).

From the evidence summaries, the Panel then produced a series of action-based recommendations, again graded according to EAU standards (Table 3). These grades aim to make it clear what the clinician should or should not do in clinical practice, not merely to comment on what they might do.

The Panel has tried to avoid extensive narrative text. Instead, algorithms are presented for both initial and specialised management of men and women with non-neurogenic UI. Each decision node of these algorithms is clearly linked back to the relevant evidence and recommendations.

It must be emphasised that clinical guidelines present the best evidence available to the expert Panel at the time of writing. There remains a need for ongoing re-evaluation of the current guidelines by the Panel. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients; they aim to focus decisions. Clinical decisions must also take into account the patient’s personal values, preferences and specific circumstances.

1.1.3 Level of evidence and grade of recommendation

References used in the text have been assessed according to their level of scientific evidence (Table 2), which is a modification of the system used by the Oxford Centre for Evidence Based Medicine (CEBM). A similar modification has been used for the Guidelines’ recommendations. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. Diagnostic studies were assessed according to a similar modification of the CEBM evidence levels for diagnostic accuracy and prognosis.
Table 2: Level of evidence (LE)*

<table>
<thead>
<tr>
<th>LE</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (5)

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and grade of recommendation. The availability of randomised controlled trials (RCTs) may not necessarily translate into a Grade A recommendation if there are methodological limitations or a disparity in published results.

Alternatively, an absence of high-level evidence does not necessarily preclude a Grade A recommendation; if there is overwhelming clinical experience and consensus to support a high-level recommendation, then a Grade A recommendation can be given. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the clinician. Whenever this occurs, it has been clearly indicated in the text with an asterisk, as ‘upgraded based on Panel consensus’. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, personal values and preferences when a grade is assigned (6-8).

The EAU Guidelines Office does not perform cost assessments nor can they address local/national preferences in a systematic fashion.

Table 3: Grade of recommendation (GR)*

<table>
<thead>
<tr>
<th>GR</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (5).

1.2 Publication history

The complete update in 2009 was largely a synthesis of guidance by the International Consultation on Urological Diseases (ICUD) and the National Institute for Health and Clinical Evidence (NICE), as was the 2010 edition. In 2011, an addendum was added on the use of drugs, now incorporated in the full text under Chapter 4. The 2012 edition was also partly based on guidance from the ICUD and NICE, but new searches were conducted from June 2008 to 2011; these have now been updated with new searches up to September 2012.

Two separate addenda are provided on mixed urinary incontinence (MUI) and management of UI in the elderly (see Appendices A and B). We expect to update these Guidelines annually.

A quick reference guide, presenting the main findings of the Urinary Incontinence Guidelines, is also available, as well as two scientific publications in the journal of the EAU, European Urology (9,10). All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

1.3 References

http://www.icud.info/incontinence.html
1.4 Use in different healthcare settings and by healthcare professionals

The Guidelines have been written for urologists and for use in any healthcare setting in Europe. However, the Panel recognises that many different health professionals besides urologists use EAU Guidelines. The Panel also recognises that a patient’s first point of contact may not always be a urologist, and that the healthcare professional delivering treatment, e.g. physiotherapy, may also not be a urologist. For this reason, some healthcare professionals may find that the Guidelines do not explain a particular topic in enough detail for their needs, e.g. delivery modalities for pelvic floor muscle training (PFMT).

1.5 Terminology

Evidence summaries provide a succinct summary of what the currently available evidence tells us about an individual clinical question. They are presented according to the levels of evidence used by the EAU.

Recommendations have been deliberately written as ‘action-based’ sentences. The following words or phrases are used consistently throughout the Guidelines, as follows:

- **Consider** an action. This word is used when there is not enough evidence to say whether the action causes benefit or risk to the patient. However, in the opinion of the Panel, the action may be justified in some circumstances. Action is optional.

- **Offer** an action. This word is used when there is good evidence to suggest that the action is effective, or that, in the opinion of the Panel, it is the best action. Action is advisable.

- **Carry out (perform)** an action. **Do** something. This phrase is used when there is strong evidence that this is the only best action in a certain clinical situation. Action is mandatory.

- **Do not** perform (i.e. avoid) an action. This phrase is used when there is high-level evidence that the action is either ineffective or is harmful to the patient. Action is contraindicated.
2. ASSESSMENT AND DIAGNOSIS

2.1 History and physical examination
Taking a careful clinical history is fundamental to the clinical process. Despite the lack of formal evidence, there is universal agreement that taking a history should be the first step in the assessment of anyone with UI. The history should include details of the type, timing and severity of UI, associated voiding and other urinary symptoms. The history should allow the UI to be categorised into stress urinary incontinence (SUI), urge urinary incontinence (UUI) or mixed urinary incontinence (MUI). It should also identify patients who need rapid referral to a specialist. These include patients with associated pain, haematuria, a history of recurrent urinary tract infections (UTIs), pelvic surgery (particularly prostate surgery) or radiotherapy, constant leakage suggesting a fistula, voiding difficulty or suspected neurological disease. In women, an obstetric and gynaecological history may help to understand the underlying cause and identify factors that may impact on treatment decisions. The patient should also be asked about other ill health and for the details of current medications, as these may impact on symptoms of UI, or cause it.

Similarly, there is little evidence that carrying out a clinical examination improves care, but wide consensus suggests that it remains an essential part of assessment of people with UI. It should include abdominal examination, to detect an enlarged bladder or other abdominal mass, and perineal and digital examination of the rectum (prostate) and/or vagina. Examination of the perineum in women includes an assessment of oestrogen status and a careful assessment of any associated pelvic organ prolapse (POP). A cough test may reveal SUI if the bladder is sufficiently full and pelvic floor contraction can be assessed digitally.

2.2 Patient questionnaires
Questionnaires may be symptom scores, symptom questionnaires, condition-specific patient-reported outcome measures (PROMS) or generic health-related quality of life (HRQoL) measures. Questionnaires are widely used to record patients’ symptoms in a standardised way, including their severity and impact, and have been used to monitor the condition over time, e.g. in the context of changes related to treatment. During the last 10 years, many questionnaires have been developed and researched, including ones specifically designed for lower urinary tract symptoms (LUTS), POP, faecal incontinence and both condition-specific and generic quality of life (QoL).

Questionnaires should have been validated for the language in which they are being used, and all measures that are used for outcome evaluation must have been shown to be sensitive to change. Many questionnaires have been developed by commercial organisations; there is a risk that the way such questionnaires are developed could produce questionnaires sensitive to small changes of little clinical importance. The methodology for their development was reviewed in the 4th International Consultation on Incontinence in 2008 (1).

2.2.1 Questions
• In adults with UI, does assessment using either urinary symptom or QoL questionnaires improve the treatment outcome for UI?
• In adults with UI, does assessment of the patient perspective (concerns or expectations) improve patient outcomes, regarding either urinary symptoms or QoL, compared to no patient-reported assessment?

2.2.2 Evidence
Although many studies have investigated the validity and reliability of questionnaires and PROMs, most have taken place in adults without UI. This greatly limits the extent to which results and conclusions from these studies can be applied in adults with UI. There is low-level evidence that questionnaires may be more sensitive to change than a bladder diary. A randomised crossover study (2) suggested that web-based questionnaires may be more acceptable to patients than paper versions (3).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validated symptom scores may be used to assist in the differential diagnosis of UI.</td>
<td>4</td>
</tr>
<tr>
<td>Validated symptom scores may be used to measure the severity of UI.</td>
<td>3</td>
</tr>
<tr>
<td>Questionnaires may be used to measure current health status or to suggest change following treatment.</td>
<td>3</td>
</tr>
<tr>
<td>The use of either questionnaires or PROMs in the assessment of adults with UI may help predict the outcome of treatment.</td>
<td>2</td>
</tr>
</tbody>
</table>
2.2.3 Research priorities
There is a lack of knowledge about whether using questionnaires to assess urinary symptoms or QoL helps to improve outcomes in adults with UI. Further research is needed to compare the use of questionnaires to assess urinary symptoms and/or QoL in addition to standard clinical assessment versus clinical measures alone. Patients should be closely involved in the design of such studies.

2.2.4 References

2.3 Voiding diaries
Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of lower urinary tract dysfunction, including UI. Voiding diaries are a semi-objective method of quantifying symptoms, such as frequency of urinary incontinence episodes. They also quantify urodynamic variables, such as voided volume and 24-hour or nocturnal total urine volume. Voiding diaries are also known as micturition time charts, frequency/volume charts and bladder diaries.

Discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency or UI, can be useful in patient counselling. In addition, voided volume measurement can be used to support diagnoses, such as overactive bladder (OAB) or polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials as a semi-objective measure of treatment outcome.

In patients with severe UI, a bladder diary is unlikely to accurately report total urine output and the discrepancy between functional bladder capacity and total bladder capacity may be large.

2.3.1 Questions
• In adults with UI, what are the reliability, diagnostic accuracy and predictive value of a voiding diary compared to patient history or symptom score?
• How does the accuracy of a computerised voiding diary compare to a paper diary?

2.3.2 Evidence
Two recent articles have suggested a consensus has been reached in the terminology used in voiding diaries (1,2):
• Micturition time charts record only the times of micturitions for a minimum of 24 continuous hours.
• Frequency volume charts record voided volumes and times of micturitions for a minimum of 24 hours.
• Bladder diaries include information on incontinence episodes, pad usage, fluid intake, degree of urgency and degree of UI.

Several studies have compared patients’ preference for, and the accuracy of, electronic and paper voiding diaries in voiding dysfunction (3-7). Several studies have compared shorter (3 or 5 days) and longer diary durations (7 days) (8-14). The choice of diary duration appears to be based upon the possible behavioural therapeutic effect of keeping a diary rather than on validity or reliability.

Two studies have investigated the reproducibility of voiding diaries in both men and women (9,14). Further studies investigated the variability of diary data within a 24-hour period (15) and compared voided volumes recorded in diaries with those recorded on uroflowmetry (16). Other studies have investigated the correlation between data obtained from voided diaries and standard symptom evaluation (17-20).
One study investigated the effect of diary duration on the observed outcome of treatment of LUTS (21). Another study found that keeping a voiding diary had a therapeutic benefit (22).

In conclusion, voiding diaries give reliable data on lower urinary tract function. There remains a lack of consensus about how long a diary should be kept and how well diary data correlate with some symptoms.

### Evidence summary

<table>
<thead>
<tr>
<th>LE</th>
<th>Frequency volume charts of 3-7 days duration are a reliable tool for the objective measurement of mean voided volume, daytime and night-time frequency and incontinence episode frequency.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>Frequency volume charts are sensitive to change and are a reliable measure of outcome.</td>
</tr>
</tbody>
</table>

### Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th>Use a frequency volume chart to evaluate co-existing storage and voiding dysfunction in patients with urinary incontinence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Use a diary duration of between 3 and 7 days.</td>
</tr>
<tr>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

### References


Reagent strip ('dipstick') urinalysis may detect infection, proteinuria, haematuria and glycosuria:
- Nitrite and leukocyte esterase may indicate a UTI.
- Protein may indicate infection and/or renal disease.
- Blood may indicate malignancy (or infection).
- Glucose may indicate diabetes mellitus.

It is generally agreed that dipstick urinalysis provides sufficient screening information in both men and women with UI. Microscopy and other tests may be necessary to confirm any abnormalities identified on dipstick analysis. Urinalysis is usually carried out on a mid-stream urine specimen, but an analysis of initial voided and terminal urine samples may be required for the assessment of urethral and prostate infections.

### 2.4.1 Questions
- In adults with UI, what is the diagnostic accuracy of urinalysis for UTIs?
- What is the benefit for UI of treating UTIs?

### 2.4.2 Evidence
In both men and women with UI, the diagnosis of a UTI by positive leucocytes or nitrates using urine culture as the reference standard had a low sensitivity and very high specificity (3,4). A negative urine dipstick test in patients with UI therefore excludes a UTI with a high degree of certainty.

There is a consensus that urinalysis should be a standard part of the basic evaluation of UI, irrespective of sex, age or aetiology.
Evidence summary

<table>
<thead>
<tr>
<th>Evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no evidence that a UTI causes UI.</td>
<td>4</td>
</tr>
<tr>
<td>There is no evidence that treating a UTI cures UI.</td>
<td>4</td>
</tr>
<tr>
<td>The presence of a symptomatic UTI worsens symptoms of UI.</td>
<td>3</td>
</tr>
<tr>
<td>Elderly nursing home patients with established UI do not benefit from treatment of asymptomatic bacteriuria.</td>
<td>2</td>
</tr>
</tbody>
</table>

Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do urinalysis as part of the initial assessment of a patient with urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>In a patient with urinary incontinence, treat a symptomatic urinary tract infection appropriately (see ‘EAU Guidelines on Urological Infections’ (5)).</td>
<td>A</td>
</tr>
<tr>
<td>Do not treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.</td>
<td>B</td>
</tr>
</tbody>
</table>

2.4.3 References


2.5 Post-voiding residual volume

Post-voiding residual (PVR) volume (also known as residual urine, bladder residual) is the amount of urine that remains in the bladder after voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. It is important because it may worsen symptoms and, more rarely, may be associated with upper urinary tract dilatation and renal insufficiency. Both bladder outlet obstruction and detrusor underactivity contribute to the development of PVR. The presence of PVR may be associated with UI symptoms.

Post-voiding residual can be measured by catheterisation or ultrasound (US). The prevalence of PVR is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume.

2.5.1 Question

In adults with UI, what are the diagnostic accuracy and predictive value of measurements of PVR?

2.5.2 Evidence

Most studies investigating PVR have not included patients with UI. Although some studies have included women with UI and men and women with LUTS, they have also included children and adults with neurogenic UI. In general, the data on PVR can be applied with caution to adults with non-neurogenic UI. The results of studies investigating the best method of measuring PVR (1-6) have led to the consensus that ultrasound (US) measurement of PVR is better than measurement using catheterisation.

Several studies have evaluated PVR in different subjects and patient cohorts (7-17). In peri- and post-menopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL (9). A comparison of women with and without LUTS suggested that symptomatic women had a higher incidence of elevated PVR (11). In women with UUI, a PVR > 100 mL was found in 10% of cases (18). Other research has found that a high PVR is associated with POP, voiding symptoms and an absence of SUI (8,12,14,15).

In women with SUI, the mean PVR was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having a PVR > 100 mL (16). Overall, women with symptoms of lower urinary tract or pelvic floor dysfunction and POP have a higher rate of elevated PVR compared to asymptomatic subjects.
There is evidence to suggest that elevated PVR should be particularly looked for in patients with voiding symptoms (18-21). There is no evidence to define a threshold between normal and abnormal PVR values. Expert opinion has therefore been used to produce definitions of elevated PVR values (22-25), but unfortunately these differ from one another. There is a lack of evidence to support the routine measurement of PVR in patients with UI (26-30).

**Evidence summary**

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>US provides an accurate estimate of post-voiding residual.</td>
<td>1b</td>
</tr>
<tr>
<td>Lower urinary tract dysfunction is associated with a higher rate of post-voiding residual compared to asymptomatic subjects.</td>
<td>2</td>
</tr>
<tr>
<td>Elevated post-voiding residual is not a risk factor for poor outcome in the management of SUI.</td>
<td>2</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use ultrasound to measure post-voiding residual.</td>
<td>A</td>
</tr>
<tr>
<td>Measure post-voiding residual in patients with urinary incontinence who have voiding dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>Measure post-voiding residual when assessing patients with complicated urinary incontinence.</td>
<td>C</td>
</tr>
<tr>
<td>Post-voiding residual should be monitored in patients receiving treatments that may cause or worsen voiding dysfunction.</td>
<td>B</td>
</tr>
</tbody>
</table>

2.5.3 **Research priority**

Further research is required to evaluate whether combining non-invasive tests provides greater diagnostic accuracy and prognostic value than tests viewed in isolation.

2.5.4 **References**


2.6 Urodynamics

In clinical practice, ‘urodynamics’ is generally used as a collective term for all tests of bladder and urethral function. These Guidelines will review both non-invasive estimation of urine flow, i.e. uroflowmetry, and invasive tests, including multichannel cystometry, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry, Valsalva leak point pressure estimation and retrograde urethral resistance measurement.

Multichannel cystometry, ambulatory monitoring and video-urodynamics aim to observe the effects on intravesical and intra-abdominal pressures while reproducing a patient’s symptoms. Bladder filling may be artificial or physiological and voiding is prompted. Any incontinence observed may be categorised as SUI, detrusor overactivity (DO) incontinence, a mixture of SUI/DO incontinence, or, rarely, urethral relaxation incontinence. A test may fail to reproduce a patient’s symptoms because of poor diagnostic accuracy or because the symptoms are not directly attributable to an urodynamically measurable phenomenon.

Urodynamic testing is widely used as an adjunct to clinical diagnosis, to direct decisions about treatment and to provide prognostic information. When clinical diagnosis is difficult because of an unclear history or inconclusive examination, urodynamics may provide the only ‘diagnosis’ available. Although it is unlikely that carrying out a test, in itself, would alter the outcome of treatment, it remains possible that the test results would influence treatment decisions to such an extent that better outcomes were achieved. This has been the rationale for using urodynamics prior to surgery.

2.6.1 Question

In adults with UI, what is the diagnostic accuracy and predictive value of uroflowmetry, i.e. the measurement of maximum urinary flow rate ($Q_{\text{max}}$) and urodynamic testing?

2.6.2 Evidence

2.6.2.1 Repeatability

Although a recent study has suggested that test retest variability is acceptable (1), many older studies have shown a variability of up to 15% in different urodynamic parameters (2-9). No published studies on the reliability of ambulatory monitoring were found.

Various techniques are used to measure urethral profilometry. Individual techniques are generally reliable in terms of repeatability, but results may vary between different techniques, so that one type of test cannot be compared meaningfully to another (10-12).

The measurement of abdominal or Valsalva leak point pressures has not been standardised. It has not been possible to correlate consistently any method of measuring Valsalva leak point pressure with either UI severity or other measures of urethral function (13-18).

Studies of technical accuracy have included adults with LUTS, with or without UI. The studies used different equipment and lacked standardised techniques (19,20). As with all physiological investigation, results have shown a wide range of variability.

Inter-rater and intra-rater reliability of video-urodynamics for the severity and type of SUI is good (21).

2.6.2.2 Diagnostic accuracy

The diagnostic accuracy of urodynamics cannot be measured against a ‘gold standard’ since all incontinence diagnoses are defined in urodynamic terms. Ambulatory urodynamics may detect unexpected physiological variance from normal, more often than conventional cystometry, but the clinical relevance of this is uncertain (22,23).
Detrusor overactivity may be found in asymptomatic patients, while normal cystometry is found in patients who are clearly symptomatic. There have been many studies of variable quality, investigating the relationship between UI symptoms and subsequent urodynamic findings. For their UK-based guidance, NICE reviewed 11 studies (24), which investigated the relationship between clinical diagnosis and urodynamic findings and the diagnostic accuracy of urodynamic measurement, specifically in females. The Panel found that no new evidence has been published since 2005 up until September 2012.

There is a consensus that urodynamic tests should aim to reproduce the patient’s symptoms and should be performed with attention to technical and methodological detail. In clinical practice, urodynamic testing (cystometry) may help to provide, or confirm, a diagnosis, predict treatment outcome, or facilitate discussion during a consultation. It is unlikely that any test, in itself, would alter the outcome of treatment. However, it is possible that the way test results influence treatment choices may have an impact on this. For all these reasons, urodynamics is often performed prior to invasive treatment for UI.

2.6.2.3 Does urodynamics influence the outcome of conservative therapy?
A meta-analysis of 129 studies of diagnostic tests for incontinence, using economic modelling, concluded that urodynamics was not cost-effective in a primary care setting (25).

A recent Cochrane review included seven RCTs that examined the question of whether urodynamics influences the outcome of all therapy for UI. The review showed that urodynamic tests influenced clinical decision-making (increased likelihood of using drugs in two trials or to avoid surgery in three trials). However, there was not enough evidence to suggest that this altered the clinical outcome of treatment (26). Subanalysis of a RCT comparing fesoterodine to placebo, and another dose finding study of botulinum toxin (27) showed no predictive value, in terms of drug response, for the urodynamic diagnosis of DO (28).

2.6.2.4 Does urodynamics influence the outcome of surgery for SUI?
Post-hoc analysis of surgical RCTs has shown the risk of failure of SUI surgery is higher in women who have worse leakage or urodynamically demonstrable USI (29).

One high-quality RCT compared office evaluation alone to office evaluation and urodynamics in women with clinical demonstrable SUI about to undergo surgery for SUI. There was no difference in levels of UI or any secondary outcome at 12 months’ follow-up (30). Another similar RCT stopped recruitment early and was redesigned, but the outcomes of the second-phase study have not yet been published (31).

Various studies have examined the relationship between measures of poor urethral function, i.e. low maximal urethral closure pressure, low Valsalva leak point pressure, and subsequent failure of surgery. Some studies found a correlation between low urethral pressures and surgical failure, while other studies did not (32-35). A correlation, in itself, was not necessarily predictive.

2.6.2.5 Does urodynamics help to predict complications of surgery?
The presence of pre-operative DO has more consistently been associated with development of post-operative UUI. Post-hoc analysis of an RCT comparing the autologous fascial sling to Burch colposuspension showed inferior outcomes for women who suffered pre-operative urgency (44). However pre-operative urodynamics had failed to predict this outcome (45). Other case series, however, have shown there is a consistent association of poor outcomes with pre-operative DO, although the predictive value was not calculated (46,47).

2.6.2.6 Does urodynamics influence the outcome of surgery for DO?
No studies were found on the relationship between urodynamic testing and subsequent surgical outcome for DO. However, most studies reporting surgical outcomes for DO have included only patients with urodynamically proven DO or DO incontinence. Higher-pressure DO appears to be consistently associated with surgical failure and persistent or de novo urgency. As with other suggested ‘predictors’, the predictive value has not often been formally calculated (32,48,49). Pre-operative urgency was resolved in some patients (50,51).

2.6.2.7 Does urodynamics influence the outcome of treatment for post-prostatectomy UI in men?
There are no RCTs examining the clinical usefulness of urodynamics in post-prostatectomy UI. However, many case series have demonstrated the ability of urodynamics to distinguish between different causes of UI (52-54).
The ability of urodynamic testing to predict surgical outcome for post-prostatectomy UI is inconsistent (55, 56).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most urodynamic parameters show a high random immediate and short-term test-retest variability of up to 15% in the same subject.</td>
<td>2</td>
</tr>
<tr>
<td>Test-retest variability creates an overlap between ‘normal’ and ‘abnormal’ populations, which may make it more difficult to categorise urodynamic findings in a particular individual.</td>
<td>2</td>
</tr>
<tr>
<td>Different techniques of measuring urethral function may have good test/retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.</td>
<td>3</td>
</tr>
<tr>
<td>There is limited evidence that ambulatory urodynamics is more sensitive than conventional urodynamics for diagnosing SUI or DO.</td>
<td>2</td>
</tr>
<tr>
<td>There may be inconsistency between history and urodynamic results.</td>
<td>3</td>
</tr>
<tr>
<td>Preliminary urodynamics can influence the choice of treatment for UI, but does not affect the outcome of conservative therapy or drug therapy for SUI.</td>
<td>1a</td>
</tr>
<tr>
<td>Preliminary urodynamics in women with uncomplicated, clinically demonstrable SUI does not improve the outcome of surgery for SUI.</td>
<td>1b</td>
</tr>
<tr>
<td>There is conflicting low-level evidence that urodynamic tests of urethral function predict outcome of surgery for SUI in women.</td>
<td>3</td>
</tr>
<tr>
<td>There is consistent low-level evidence that pre-operative DO predicts poorer outcomes of mid-urethral sling surgery in women.</td>
<td>3</td>
</tr>
<tr>
<td>There is limited evidence for whether preliminary urodynamics predicts the outcomes of treatment for UI in men.</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(NB: These refer only to neurologically intact adults with urinary incontinence)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinicians carrying out urodynamics in patients with urinary incontinence should:</strong></td>
<td></td>
</tr>
<tr>
<td>• Ensure that the test replicates the patient’s symptoms.</td>
<td>C</td>
</tr>
<tr>
<td>• Interpret results in context of the clinical problem.</td>
<td></td>
</tr>
<tr>
<td>• Check recordings for quality control.</td>
<td></td>
</tr>
<tr>
<td>• Remember there may be physiological variability within the same individual.</td>
<td></td>
</tr>
<tr>
<td>Advise patients that the results of urodynamics may be useful in discussing treatment options, although there is limited evidence that performing urodynamics will alter the outcome of treatment for urinary incontinence.</td>
<td>C</td>
</tr>
<tr>
<td>Do not routinely carry out urodynamics when offering conservative treatment for urinary incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Perform urodynamics if the findings may change the choice of invasive treatment.</td>
<td>B</td>
</tr>
<tr>
<td>Do not routinely carry out urethral pressure profilometry.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.6.3 **Research priority**

Does any individual urodynamic test influence the choice of treatments or prediction of treatment outcome for UI?

2.6.4 **References**


2.7 Pad testing
A well-designed continence pad will contain any urine leaked within a period of time and this has therefore been used as a way of quantifying leakage. Although the International Continence Society has attempted to standardise pad testing, there remains variation in the duration of the test and the physical activity undertaken during the test.
2.7.1 **Question**
In adults with UI, what are the reliability, the diagnostic accuracy and predictive value of pad testing?

2.7.2 **Evidence**
The use of pad tests has been reviewed in the 4th International Consultation on Incontinence. Many studies have investigated the use of short-term and long-term pad tests to diagnose UI (1). Several other studies have investigated the correlation between pad test results and symptom scores for UI or LUTS (2-6). In addition, several studies have analysed the reproducibility of pad tests (2,7-11).

A few studies have tried to use pad testing to predict the outcome of treatment for UI with inconsistent results (12-14). Currently, pad tests are mostly used as objective outcomes in clinical trials. However, pad tests may be helpful in daily clinical practice, and most guidelines already include the use of pad testing to evaluate treatment outcome (15, 16). There is good evidence to show that repeat pad testing can detect change following treatment for UI (17-19).

### Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A pad test can diagnose UI accurately, is reproducible and correlates with patients’ symptoms.</td>
<td>1b</td>
</tr>
<tr>
<td>A pad test cannot differentiate between causes of UI.</td>
<td>4</td>
</tr>
<tr>
<td>An office-based pad test requires standardisation of bladder volume and a predefined set of exercises to improve diagnostic accuracy.</td>
<td>1b</td>
</tr>
<tr>
<td>Patient adherence to home pad testing protocols is poor.</td>
<td>1b</td>
</tr>
<tr>
<td>Home-based pad tests longer than 24 hours provide no additional benefit.</td>
<td>2b</td>
</tr>
<tr>
<td>Change in pad tests can be used to measure treatment outcome.</td>
<td>1b</td>
</tr>
</tbody>
</table>

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use a pad test when quantification of urinary incontinence is required.</td>
<td>C</td>
</tr>
<tr>
<td>Use repeat pad test after treatment if an objective outcome measure is required.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.7.3 **Research priority**

- Does the results of pad testing influence the choice of treatments or the prediction of the outcome of treatment for UI?
- Does the amount of physical activity influence the outcome of 24-hour pad testing leading to overestimation of the severity of incontinence?

2.7.4 **References**


2.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause UI. In clinical research, imaging is used to understand the relationship between conditions of the central nervous system (CNS) and of the lower urinary tract in causing UI, and to investigate the relationship between conditions of the lower urinary tract and treatment outcome.

Ultrasound and magnetic resonance imaging (MRI) have replaced X-ray imaging, as both procedures are safer and can provide both qualitative and quantitative data on the kidneys, bladder neck and pelvic floor. Ultrasound is preferred to MRI because of its ability to produce three-dimensional and four-dimensional (dynamic) images at lower cost and wider availability. The current lack of knowledge about the pathophysiology of UI makes it difficult to carry out research in the imaging of UI. Studies on lower urinary tract imaging in patients with UI often include an evaluation of surgical outcomes, making design and conduct of these trials particularly challenging.
2.8.1 Questions

- In adults with UI, what is the reliability and accuracy of imaging in the diagnosis of UI?
- In adults do the results of imaging influence the choice, help predict outcome or help evaluate outcome of treatments for UI?

2.8.2 Evidence

Several imaging studies have investigated the relationship between sphincter volume and function in women (1) and between sphincter volume and surgery outcome in men and women (2,3). Imaging of urethral anastomosis following radical prostatectomy has been used to investigate continence status (4). However, no imaging test has been shown to predict the outcome of treatment for UI.

Many studies have evaluated the imaging of bladder neck mobility by US and MRI, and concluded that UI cannot be identified by a particular pattern of urethrovesical movements (5). In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with de novo SUI (6).

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support structure (7). However, there is a large variation in MRI interpretation between institutions (8) and little evidence to support its clinical usefulness.

Studies have assessed the use of imaging to effect of mid-urethral sling insertion for SUI. One study suggested that mid-urethral sling placement decreased mobility of the mid-urethra but not mobility of the bladder neck (9). In addition, the position of mid-urethral slings with respect to the pubis has been associated with the cure of UI (10).

No studies were found which specifically addressed the PICO question for this section. Lower urinary tract imaging does not appear to provide any clinical benefit in patients with UI (11). Despite this, however, some experts continue to recommend imaging (12-15).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging can reliably measure bladder neck and urethral mobility, although there is no evidence of any clinical benefit in patients with UI.</td>
<td>2b</td>
</tr>
<tr>
<td>Imaging of the pelvic floor can identify levator ani detachment and hiatus, although there is little evidence of clinical benefit.</td>
<td>2b</td>
</tr>
<tr>
<td>Ultrasound can image mid-urethral slings, although more research is needed into the relationship between sling position and surgical outcome.</td>
<td>2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of uncomplicated stress urinary incontinence SUI in women.</td>
<td>A</td>
</tr>
</tbody>
</table>

2.8.3 References


3. CONSERVATIVE TREATMENT

In clinical practice, it is a convention that non-surgical therapies are tried first because they usually carry the least risk of harm.

The Guidelines Panel has grouped together simple clinical interventions, which are likely to be initiated by the healthcare professional at the first point of contact. These are followed by a series of treatments described as 'lifestyle interventions' because they are changes that a patient can make to improve symptoms. These are then followed by behavioural treatments, which require some form of training or instruction, and physical therapies, which require instruction and use some form of physical intervention. Drug treatment is described separately. The Panel recognises that in clinical practice a combination of these interventions may be recommended as a care package. Consequently, recommendations have been linked together in places where this reflects the way in which care is often 'packaged'.

3.1 Simple clinical interventions

3.1.1 Underlying disease/cognitive impairment

Urinary incontinence, especially in the elderly, can be worsened or caused by underlying diseases, especially conditions that cause polyuria, nocturia, increased abdominal pressure or CNS disturbances. These conditions include:

- cardiac failure (1)
- chronic renal failure
- diabetes (1,2)
- chronic obstructive pulmonary disease (3)
• neurological disorders
• stroke
• dementia
• multiple sclerosis
• general cognitive impairment
• sleep disturbances, e.g. sleep apnoea.

It is possible that correction of the underlying disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients often suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient’s UI.

3.1.1 Question
In adults with UI, does correcting an underlying disease or cognitive impairment improve UI compared to no correction of underlying disease?

3.1.1.2 Evidence
We found only one relevant study that showed no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life versus conventional treatment (4). This was despite the known benefit of close control of blood glucose levels on other known consequences of type 1 diabetes mellitus, including renal and visual impairment. A higher prevalence of UI was associated with an increase in age and body mass index in this study.

### Evidence summary LE

| Improved diabetic control does not improve UI. | 3 |

3.1.1.3 References

3.1.2 Adjustment of medication
Although UI is listed as an adverse effect of many drugs in many drug compendiums, e.g. British National Formulary, this mainly results from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of UI as a primary outcome or were powered to assess the occurrence of statistically significant UI or worsening rates against placebo. In most cases, it is therefore not possible to be sure that a drug causes UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidity or ageing on UI.

Although changing drug regimens for underlying disease may be considered as a possible early intervention for UI, there is very little evidence of benefit (1). There is also a risk that stopping or altering medication may result in more harm than benefit.

3.1.2.1 Question
In adults with UI, does adjustment of medication improve UI compared to no change in treatment?
3.1.2.2 Evidence

A structured narrative review found there was only weak evidence for a causative effect for most medications associated with the adverse effect of new, or worsening, UI (2). A case-control study found that women with hypertension treated with alpha-blockers were more likely to develop UI than untreated controls (3).

Several case series have suggested a link between drugs with a CNS site of action and UI (2). A secondary analysis of a large observational database of elderly Italians found a higher risk of UI among those taking benzodiazepines. In addition, a retrospective analysis of a large Dutch database of dispensed prescriptions found that patients started on a selective serotonin re-uptake inhibitor were more likely to require a subsequent prescription of antimuscarinic drugs or absorbent urinary pads, suggesting the development of UI (4). Although one would expect that diuretic therapy would increase UI in the same way as polyuria, limited evidence in men suggests that this is not the case (2).

Systemic oestrogen therapy for post-menopausal women was shown by a meta-analysis (5) to be associated with the development and worsening of UI. Systemic oestrogen, compared to placebo, worsened symptoms of UI, both in women who had undergone a hysterectomy, and in those who had not (5). In addition, data from a single large RCT (6) showed that previously continent women treated with systemic oestrogen were more likely to develop symptoms of UI compared to women given a placebo. These more recent analyses have superseded conflicting results from earlier and smaller studies of the effect of oestrogen replacement therapy on UI. However, the number of women who gain relief from UI through stopping systemic oestrogen replacement is likely to be small since there has been a decline in the use of oestrogen replacement therapy by post-menopausal women, due to concerns about the development of cancer and the association of oestrogen replacement therapy with UI.

Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-blockers used to treat hypertension in women may cause or exacerbate UI, and stopping them may relieve UI.</td>
<td>3</td>
</tr>
<tr>
<td>Individuals taking drugs acting on the CNS may experience UI as a side effect.</td>
<td>3</td>
</tr>
<tr>
<td>Diuretics in elderly patients does not cause or worsen UI.</td>
<td>3</td>
</tr>
<tr>
<td>Systemic oestrogen replacement therapy in previously continent women increases the risk of developing UI.</td>
<td>1b</td>
</tr>
<tr>
<td>Systemic oestrogen replacement therapy worsens UI in women with pre-existing UI.</td>
<td>1a</td>
</tr>
</tbody>
</table>

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take a drug history from all patients with urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>Inform women with urinary incontinence that begins or worsens after starting systemic oestrogen replacement therapy that it may cause urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>Review any new medication associated with the development or worsening of urinary incontinence.</td>
<td>C</td>
</tr>
</tbody>
</table>

3.1.2.3 References

3.1.3 **Constipation**

Several studies have shown strong associations between constipation, UI and OAB. Constipation can be improved by behavioural and medical treatments.

### 3.1.3.1 Question

Does treatment for constipation improve UI?

### 3.1.3.2 Evidence

One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc., reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both (1).

An observational study comparing women with UI and women with POP to controls found that a history of constipation was associated with both prolapse and UI (3). Two, large, cross-sectional population-based studies (4,5) and two longitudinal studies (6,7) showed that constipation was a risk factor for LUTS.

In conclusion, constipation appears to be associated with LUTS. However, there is no evidence to show whether or not treating constipation improves LUTS, although both constipation and UI appear to be improved by certain behavioural interventions.

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a consistent association between a history of constipation and the development of UI and pelvic organ prolapse.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that treatment of constipation improves UI.</td>
<td>4</td>
</tr>
<tr>
<td>Multimodal behavioural therapy improves both constipation and UI in the elderly.</td>
<td>1b</td>
</tr>
</tbody>
</table>

**Recommendation**

For adults with urinary incontinence, treat co-existing constipation.

### 3.1.3.3 Research priority

Does the normalisation of bowel habit improve urinary UI in patients who are constipated?

### 3.1.3.4 References


### 3.1.4 **Containment**

Although initiation of assessment and treatment of UI should be the main priority for healthcare professionals, containment is of great practical importance to many patients with UI. Absorbent pads are predominantly used to absorb or collect leakage. However, if these are inadequate, an indwelling urethral or suprapubic catheter may then be used after taking into account the complications associated with catheter use, e.g. infection, pain, and stone formation.
3.1.4.1 Question
In adults with UI, does urinary containment improve patient outcomes, regarding either urinary symptoms or QoL, compared to no containment?

3.1.4.2 Evidence
There was a lack of consistency in the evidence reviewed. There have been two consensus statements in the 4th International Consultation on Incontinence (1) and one RCT comparing conservative treatment with urinary pads (2). There have been Cochrane reviews of devices (3) and pads (4), and three small trials of devices with differing outcomes (5-7). Few studies have been carried out in urinary catheterisation; these included an RCT comparing condom catheters with indwelling urinary catheters (8). A small open crossover RCT (9) evaluated different penile clamps and showed that none completely controlled urine leakage, but penile blood flow was reduced. Another crossover RCT compared penile sheaths to absorbent pads in incontinent (10) men. Penile sheaths are only useful if they can be applied easily and independently.

Two RCTs have shown that the use of a vaginal pessary is equivalent to bladder training (BT) for the treatment of SUI (6,11).

### Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pads are not effective as a treatment for UI.</td>
<td>1b</td>
</tr>
<tr>
<td>Different pads have different advantages and disadvantages.</td>
<td>1b</td>
</tr>
<tr>
<td>Intermittent catheterisation carries a lower risk of UTI and bacteriuria than indwelling catheterisation.</td>
<td>1b</td>
</tr>
<tr>
<td>Containment devices are better than no treatment.</td>
<td>4</td>
</tr>
<tr>
<td>Penile sheaths offer better containment, and higher QoL, than absorbent products in men with UI.</td>
<td>1b</td>
</tr>
<tr>
<td>Penile sheaths are safer than indwelling catheters if no residual urine is present.</td>
<td>1b</td>
</tr>
</tbody>
</table>

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer pads when containment of urinary incontinence is needed.</td>
<td>B</td>
</tr>
<tr>
<td>Adapt the choice of pad to the type and severity of urinary incontinence and the patient’s needs.</td>
<td>A</td>
</tr>
<tr>
<td>Offer catheterisation to manage urinary incontinence when no other treatments can be considered.</td>
<td>B</td>
</tr>
<tr>
<td>Offer condom catheters to men with urinary incontinence without significant residual urine.</td>
<td>A</td>
</tr>
<tr>
<td>Offer to teach intermittent catheterisation to manage urinary incontinence associated with retention of urine.</td>
<td>A</td>
</tr>
<tr>
<td>Do not routinely offer intravaginal devices as treatment for urinary incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Do not use penile clamps for control of urinary incontinence in men.</td>
<td>A</td>
</tr>
</tbody>
</table>

3.1.4.3 Research priority
How does a simple intravaginal device compare to conventional conservative treatment in the cure or sustained improvement of UI?

3.1.4.4 References


http://www.ncbi.nlm.nih.gov/pubmed/20960307


3.2 Lifestyle interventions

Examples of lifestyle factors that may be associated with incontinence include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI.

3.2.1 Caffeine reduction

Many drinks contain caffeine, particularly tea, coffee and cola. The pharmacological actions of caffeine include CNS stimulation, diuresis and smooth muscle relaxation. Anecdotal evidence of urinary symptoms being aggravated by excessive caffeine intake has focused attention on whether caffeine reduction may improve UI. However, a cross-sectional population survey found no statistical association between caffeine intake and UI (1). A lack of knowledge about the caffeine content of different drinks has made the role of caffeine reduction in alleviating UI more complex.

3.2.1.1 Question

In adults with UI, does caffeine reduction improve UI or QoL compared to no caffeine reduction?

3.2.1.2 Evidence

Four studies were found on the effect of caffeine reduction on UI (2-5). They were of moderate quality and the results were inconsistent. The studies were mainly in women, so results can only be cautiously generalised to men. There were two RCTs investigating caffeine reduction (3,4). One RCT showed that reducing caffeine intake resulted in reduced urgency but not reduced UI (3). However, the study was not powered for UI and compared the interventions of BT and caffeine reduction against BT alone. Another RCT found that reducing caffeine had no benefit for UI (4). An uncontrolled study suggested that people with OAB and high caffeine intake were more likely to show DO on filling during conventional cystometry (2). A further interventional study in the elderly showed borderline significance for the benefit of reducing caffeine intake on UI (5). In a large prospective cohort study there was no evidence that caffeine reduction reduced the risk of progression of urinary incontinence over 2 years (6).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of caffeine intake does not improve UI.</td>
<td>2</td>
</tr>
<tr>
<td>Reduction in caffeine intake may improve symptoms of urgency and frequency.</td>
<td>2</td>
</tr>
</tbody>
</table>

3.2.1.3 References


### 3.2.2 Physical exercise

Regular physical activity may strengthen the pelvic floor musculature and possibly decrease the risk of developing UI, especially SUI. However, it is also possible that heavy physical exercise may aggravate UI.

#### 3.2.2.1 Question

Does physical exercise cause, improve or exacerbate UI in adults?

#### 3.2.2.2 Evidence

The association between exercise and UI is unclear. Four studies (1-4) in differing populations concluded that strenuous physical exercise increases the risk of SUI during periods of physical activity. There is also consistent evidence that physically active females and elite athletes experience higher levels of SUI than control populations (5-10). On the other hand, the presence of UI may prevent women from taking exercise (11). There is no evidence that strenuous exercise predisposes athletes to the development of SUI later in life (12). Lower levels of UI have been observed in cohorts of women who undertake moderate exercise, but it remains unclear whether taking exercise can prevent development of UI (13,14).

### The elderly

Three RCTs in the elderly confirmed that exercise, as a component of a multidimensional regime including PFMT and weight loss, was effective in improving UI in women. It is not clear which component of such a scheme is most important (1-3).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female athletes may experience UI during intense physical activity but not during common activities.</td>
<td>3</td>
</tr>
<tr>
<td>Strenuous physical activity does not predispose to UI for women later in life.</td>
<td>3</td>
</tr>
<tr>
<td>Moderate exercise is associated with lower rates of UI in middle-aged or older women.</td>
<td>2b</td>
</tr>
</tbody>
</table>

#### References


### 3.2.3 Fluid intake

It is generally assumed that a reduction in total volume of fluid intake may be beneficial for UI. Fluid restriction is a widely used, inexpensive and non-invasive intervention. It is usually advised that fluid intake and output is monitored using a frequency volume chart. Daily urine output should not be less than 1500 mL and not more than 3000 mL. The restriction of fluid intake may have adverse effects, including a predisposition to
UTI, dehydration, urinary tract stone formation and constipation. The cause of a high fluid intake should be investigated.

3.2.3.1 Question
In adults with UI, what is the effect of modifying fluid intake compared to not modifying fluid intake on symptoms and QoL?

3.2.3.2 Evidence
The few RCTs provide inconsistent evidence. In most studies, the instructions for fluid intake were individualised and it is difficult to assess participant adherence to protocol. All available studies were in women.

Two RCTs of limited quality due to high drop-out rates and small sample size (1,2) produced conflicting results regarding recommendations for fluid intake. One study found that increased fluid intake improved symptoms, while the other study, which was limited to patients with DO, found that decreased fluid intake improved QoL. A more recent RCT (3) showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI. An observational study also addressed fluid intake as part of a behavioural regime (4).

Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving antimuscarinics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice (5).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is conflicting evidence on whether fluid modification changes symptoms of UI and QoL.</td>
<td>2</td>
</tr>
</tbody>
</table>

3.2.3.3 References

3.2.4 Obesity and weight loss
In most developed countries, nearly one-quarter to more than one-third of adults is obese. Obesity and UI are serious health problems, adversely affecting QoL. Obesity has been identified as a risk factor for UI in many epidemiological studies (1,2). There is evidence that the prevalence of both UUI and SUI increases proportionately with rising body mass index. A significant proportion of patients who undergo surgery for incontinence are overweight or obese. In 2009, the 4th International Consultation on Incontinence recommended that the role of obesity in UI should be a research priority.

3.2.4.1 Question
In adults with UI, does weight loss lead to an improvement in symptoms of UI or QoL?

3.2.4.2 Evidence
All the available evidence relates to women. The prevalence of UI in overweight individuals is well established (1,2). Obesity appears to confer a four-fold increased risk of UI (3).

Two systematic reviews concluded that weight loss was beneficial in improving symptoms of UI (4,5). Five further RCTs reported a similar benefit beneficial effect on incontinence following surgical weight reduction programmes (6-9) (10).
Two large studies in diabetic women, for whom weight loss was the main lifestyle intervention showed UI did not get better but there was a lower subsequent incidence of UI among those who lost weight (6,11). There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese (12-19). For example, in a longitudinal cohort study, a weight loss of 5-10% was associated with a significant reduction in UI measured by pad test (20).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity is a risk factor for UI in women.</td>
<td>1b</td>
</tr>
<tr>
<td>Weight loss (&gt; 5%) in obese women improves UI.</td>
<td>1b</td>
</tr>
<tr>
<td>Weight loss in obese adults with diabetes mellitus reduces the risk of developing UI</td>
<td>1b</td>
</tr>
</tbody>
</table>

3.2.4.3 References


3.2.5 Smoking
Smoking cessation is now a generalised public health measure. Smoking, especially if > 20 cigarettes per day, is considered to intensify UI.

3.2.5.1 Question
In adults with UI, does smoking cessation improve patient outcomes regarding either urinary symptoms or QoL compared to continued smoking?

3.2.5.2 Evidence
Seven published articles were found, all in women, on whether smoking cessation improved patient outcome. There was no RCT, but several population studies were found, including a study including 83,500 people. The studies only provided a comparison of smoking rates between different populations and did not examine the role of smoking cessation.

Four of these studies, totalling more than 110,000 subjects, found an association between smoking and UI, for people smoking > 20 cigarettes per day (1-4). Both former and current cigarette smoking was positively associated with frequent and severe UI, with a stronger relationship in women who were current smokers (1). Other studies involving similar large populations have not shown an association. The effect of smoking cessation on UI was described as uncertain in a Cochrane review (5).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no consistent evidence that smokers are more likely to suffer from UI.</td>
<td>3</td>
</tr>
<tr>
<td>There is some evidence that smoking may be associated with more severe UI, but not mild UI.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that smoking cessation will improve the symptoms of UI.</td>
<td>4</td>
</tr>
</tbody>
</table>

3.2.6 Recommendations for lifestyle interventions

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encourage obese women suffering from any urinary incontinence to lose weight (&gt; 5%).</td>
<td>A</td>
</tr>
<tr>
<td>Advise adults with urinary incontinence that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Patients with abnormally high or abnormally low fluid intake should be advised to modify their fluid intake appropriately.</td>
<td>C</td>
</tr>
<tr>
<td>Counsel female athletes experiencing urinary incontinence with intense physical activity that it will not predispose to urinary incontinence in later life.</td>
<td>C</td>
</tr>
<tr>
<td>Patients with urinary incontinence who smoke should be given smoking cessation advice in line with good medical practice although there is no definite effect on urinary incontinence.</td>
<td>A</td>
</tr>
</tbody>
</table>
3.2.7 **Research priority**

Which lifestyle modifications are effective for the cure or sustained improvement of UI?

3.2.8 **References**


3.3 **Behavioural therapy/scheduled voiding**

Behavioural therapies include all those interventions initiated by the sufferer themselves but which require some form of training or supervision at their outset. These include bladder training (BT), scheduled voiding (prompted voiding and timed voiding). Almost always in clinical practice, these will be introduced as part of a package of care including lifestyle changes and possibly physical therapies as well. The detail is likely to depend on differences in healthcare systems as much as proven efficacy. The variation in these packages of care make any comparison between studies increasingly difficult and it is unusual to find trials that have evaluated only a single component.

Scheduled voiding is a treatment programme designed to gradually increase a person’s control over voiding function and urgency and to reduce episodes of UI. It is also known as bladder drill, bladder discipline, bladder re-education, or bladder training. The programme also aims to increase a person’s self-confidence in bladder function, though this can take months to achieve and may not persist long term unless the programme is maintained.

Different strategies may be used since no single regimen has yet been proven ideal. As well as following a voiding pattern, the patient is instructed on bladder function and fluid intake, including caffeine restriction and bowel habits. Patients may be asked to void according to a fixed voiding schedule. Alternatively, patients may be encouraged to follow a schedule established by their own bladder diary/voiding chart (habit training). ‘Timed voiding’ is voiding initiated by the patient, while ‘prompted voiding’ is voiding initiated by the caregiver. Timed and habit voiding are recommended to patients who can void independently.

3.3.1 **Prompted voiding**

Prompted voiding is the giving of positive reinforcement for requesting toileting assistance, either spontaneously or following verbal prompts from a caregiver. A high-quality systematic review from Flanagan et al. (1) examined the effectiveness of prompted voiding as an intervention for elderly people with UI, who are living in an assisted care setting, such as a nursing home. The review included nine RCTs, which all showed a positive effect on continence outcomes of prompted voiding in comparison to standard care using intervals of 1, 2, or 3 hours (1).

Both the Flanagan et al. review (1) and a further Cochrane review (2) included five RCTs that consistently showed that the behaviour modification programme known as “Functional Incidental Training (FIT)” (which included prompted voiding) improved continence in addition to activities of daily living (ADL). The review by Flanagan et al (1) also included another two RCTs that showed no added clinical benefit for incontinence from oxybutinin or oestrogen combined with prompted voiding.

There was only one RCT of timed voiding which showed inconsistent improvement in continence compared with standard care in cognitively impaired adults (timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. An assisted toileting
programme is included for those unable to undertake independent toileting). Overall, the findings were consistent with previous systematic reviews (3,4).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people</td>
<td>1b</td>
</tr>
<tr>
<td>The inclusion of prompted voiding in behavioural modification programmes improves continence in elderly, care-dependent people</td>
<td>1b</td>
</tr>
<tr>
<td>Timed voiding reduces leakage episodes in cognitively impaired men and women.</td>
<td>1b</td>
</tr>
</tbody>
</table>

For recommendations, see section 3.4.5.

3.3.2 **Bladder training**

Bladder training can be offered to any patient with any form of UI, as a first-line therapy for at least a short period of time. The ideal form or intensity of a BT programme for UI is unclear. It is also unclear whether or not BT can prevent the development of UI.

3.3.3 **Questions**

- Is BT better than no treatment for cure or improvement of UI?
- Is BT better than other conservative treatments for cure or improvement of UI?
- Is BT useful as an adjunct to other conservative treatments for UI?
- Are the benefits of BT durable in the longer term?
- Are there any patient groups for whom BT is more effective?

3.3.4 **Evidence**

There have been four systematic reviews covering the effect of BT compared to standard care (5-8). Two key RCTs, which compared BT with no intervention, found that UI was improved, but not cured, by timed bladder voiding at intervals of between 2.5 and 4 hours (9,10). However, it is unclear whether these findings also applied to specific groups of individuals with UI. However, another two RCTs reported inconsistent findings regarding treatment adherence (11).

Bladder training has been compared with other treatments for UI in a number of other RCTs. Bladder training alone is as effective in controlling UUI and nocturnal incontinence as oxybutynin, tolterodine and solifenacin (12-17).

Studies have shown that the addition of BT to antimuscarinic therapy provides no added benefit for an improvement in UI compared with antimuscarinic treatment alone (12, 13, 17). However, BT combined with antimuscarinic therapy does provide a greater benefit in reducing urinary frequency and nocturia (17, 18). Bladder training does not improve an individual’s capacity to discontinue drug therapy and maintain improvement of UUI (12). However, the addition of BT to antimuscarinic drugs may increase patient satisfaction with pharmacological treatment (19), including in patients previously dissatisfied with the antimuscarinic treatment (20).

Bladder training combined with PFMT is better than standard care for controlling UI in elderly women living in institutions (21). However, BT alone is inferior to a high-intensity programme of PFMT to improve SUI in elderly women (22). Bladder training is better than intravaginal pessaries to control SUI, although the improvement may only be short term.

Whatever the method of training used, any benefit of BT on UI is likely to be of short duration unless the BT programme is practised repeatedly. No adverse events have been reported with BT.

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited evidence that behavioural interventions are better than no treatment in women with UI</td>
<td>1b</td>
</tr>
<tr>
<td>The effectiveness of bladder training diminishes after the treatment has ceased.</td>
<td>2</td>
</tr>
<tr>
<td>There is inconsistent evidence to show whether bladder training is better than drug therapy.</td>
<td>2</td>
</tr>
<tr>
<td>The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI but may have other benefits.</td>
<td>1b</td>
</tr>
<tr>
<td>Bladder training is better than pessary alone.</td>
<td>1b</td>
</tr>
</tbody>
</table>

For recommendations see section 3.4.5.
References


http://www.springerlink.com/content/p75435j280072j72/


3.4 Physical therapies

3.4.1 Pelvic floor muscle training (PFMT)

Pelvic floor muscle training is used to increase the strength and durability of contraction of the pelvic floor muscles. This increases urethral closure pressure and stabilises the urethra, preventing downward movement during moments of increased activity. Patients are sometimes taught to perform ‘the knack’ of contracting the pelvic floor at moments when predictable UI is likely to occur. Otherwise regular training aims to increase pelvic floor muscle strength. There is some evidence that increasing pelvic floor strength may help to inhibit bladder contraction in patients with an OAB.

Traditionally, following vaginal examination and pelvic floor assessment by a trained professional, patients are taught to contract their pelvic floor muscles, as hard as they can and for as long as they can, and to repeat these exercises a number of times every day. This training can be delivered in many ways, including women teaching themselves (e.g. using an information leaflet), group training in classes, or intensive one-to-one supervision from a highly trained physical therapist. Pelvic floor muscle training may be used to prevent UI, e.g. in childbearing women before birth, in men about to undergo radical prostatectomy, or as part of a planned recovery programme after childbirth or surgery. Most often, PFMT is used to treat existing UI, and may be augmented with biofeedback, electrical stimulation or vaginal cones. Additional techniques, such as kinseitherapy (1), proprioception training (2) and trunk stabilisation (3) have been proposed, but the benefits are unclear.

3.4.1.1 Methods used to augment PFMT

Biofeedback increases patient awareness of the pelvic floor muscles, using visual, tactile or auditory stimuli, e.g. vaginal manometry or electromyography, and is used to help teach patients to exercise their pelvic floor muscles more effectively. However, there is no guarantee that the signals recorded come from the pelvic floor and digital palpation or US may provide better reassurance of correct contraction. Biofeedback can be used at home or in an office setting.

In electrical stimulation, surface electrodes supply electrical current to stimulate the pelvic floor muscles via their nerve supply. Electrodes are available in several formats, including vaginal, anal, or skin. Electrical stimulation is often used to help patients recognise their pelvic floor muscles though there is no evidence supporting this concept. It is also used to exercise muscles in the hope of increasing pelvic floor strength. Electrical stimulation can also be used to inhibit overactive detrusor contractions.

Weighted vaginal cones are cone-shaped vaginal inserts of graduated weights. A woman learns first to insert the lightest cone and retain it using pelvic floor contraction. Gradually, she is able to hold increasingly heavy cones as her pelvic floor muscles become stronger.
3.4.1.2 Question
In adult men and women suffering from UI, does treatment with PFMT (given either alone or augmented with biofeedback, electrical stimulation or vaginal cones) improve or cure UI or improve QoL, compared to no treatment, sham treatment or other conservative treatments, e.g. bladder training, electrical stimulation or vaginal cones?

3.4.1.3 Evidence
Although there have been many randomised trials of PFMT, the trials vary widely in terms of quality, mode of delivery, intensity and duration of treatment, and the details of contractions and repetitions. In a recent UK Health Technology Appraisal (HTA), the role of PFMT in the care of women with SUI was analysed in direct comparisons of treatments and a mixed treatment comparison model, which compared different ‘packages’ of care (4). This extensive meta-analysis reviewed data from 37 interventions and 68 direct comparisons, while the mixed treatment comparisons examined combinations of 14 different types of intervention from 55 separate trials. The mixed treatment comparison used both indirect and direct comparisons and has probably provided more accurate estimates of effect. Where relevant, the Technology Appraisal has influenced the evidence and recommendations in these Guidelines. The Agency for Healthcare Research and Quality (AHRQ) review of non-surgical treatment of UI in adult women also included indirect comparison methods as well as conventional meta-analysis (5).

3.4.1.4 Efficacy of PFMT in SUI, UUI and MUI in women
This question has been addressed by several systematic reviews (4-6), all report inconsistency between studies because of poor reporting of technique and different outcome measures. Meta-analysis showed that PFMT achieved cure or improvement of incontinence more often compared to no treatment and the magnitude of effect is large. The most recent Cochrane review compares different approaches to delivery of PFMT. From 21 RCTs, they were able to conclude only that increasing contact with the health professional delivering the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions (7). No other consistent differences between techniques were found.

With regard to the durability of PFMT, another RCT reported 15-year follow-up outcomes of an earlier RCT, showing that long-term adherence to treatment was poor. Half of patients had progressed to surgery, though the functional outcomes in those who had undergone surgery were less satisfactory than those who did not have surgery (8).

Augmentation of PFMT and comparison with other techniques
The AHRQ review concluded from two RCTs that the addition of BT to PFMT provided no additional benefit compared to BT alone in terms of curing UI (5).

The addition of biofeedback to PFMT was reviewed by Herderschee on the basis of 24 studies (9) and concluded that biofeedback may provide additional benefit. However, the AHRQ review (5) arrived at an opposite conclusion. Thus, although the addition of biofeedback may appear to add to the effectiveness of PFMT, it is not clear whether this effect is caused by feedback (e.g. from exposure to a health professional) or the ‘bio’ component. When the UK HTA reviewed the addition of electrical stimulation to PFMT (4), they found no difference in continence outcomes.

Comparison of PFMT to other treatments was extensively reviewed by both AHRQ and the 2010 UK HTA (4,5), which considered additional non-randomised data as part of a mixed treatment comparison. The UK HTA resulted in a number of different findings from those based solely on direct comparisons. In conclusion, the HTA, using a revised methodology, supported the general principle that greater efficacy was achieved by adding together different types of treatment and by increasing intensity.

3.4.1.5 Efficacy of PFMT in childbearing women
The Cochrane review in 2008 (10) reviewed 16 RCTs in pregnant or postpartum women, which included PFMT in one arm of the trial. Five trials were in postpartum women who had developed UI. Eight trials reported mixed treatment and prevention groups. Treatment of UI with PFMT in the postpartum period increased the chances of continence at 12 months’ postpartum.

3.4.1.6 PFMT in the elderly
An RCT assessing PFMT versus BT in women aged more than 65 years showed that PFMT was significantly better at improving and curing SUI. However, the use of pad tests to quantify leakage limited the clinical usefulness of the comparison (11).
In a study of Japanese women aged ≥ 70 years with UI, PFMT with general fitness training was effective for cure and improvement of UI after a 3-month period of supervised exercise (12).

A programme of supervised education and skill building around PFMT and BT for women aged ≥ 65 years was effective in decreasing the impact of UI, but there was no change in overall QoL compared with no intervention (13).

3.4.1.7 Efficacy of PFMT in men with SUI following radical prostatectomy
A Cochrane review of conservative management for post-prostatectomy urinary incontinence (PPI) (up to Nov 2009) concluded that the benefits of conservative treatment of PPI were uncertain (14). There have been further RCTs which create uncertainty about whether or not PFMT leads to earlier recovery of continence (15-17). Two additional RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT (18, 19). One RCT found that PFMT was helpful in men who had been incontinent for years after radical prostatectomy, and who had had no previous therapy (20).

3.4.1.8 Preventive value of PFMT in childbearing women and post-radical prostatectomy men
The Cochrane review by Hay Smith (10) reviews five RCTs in which PFMT was started in continent pregnant women. A number of other trials included both prevention and treatment groups in their comparisons. PFMT was found to reduce the risk of incontinence in late pregnancy and up to 6 months’ postpartum.

Ten RCTs of variable quality compared the preventative effect of PFMT prior to radical prostatectomy versus various different types of control treatments. These were generally small studies, which were difficult to compare with each other because of different times of delivery and different outcomes (21-29). However, one study was well designed and provided level 2 evidence confirming that pre-operative PFMT speeds up the recovery of continence post-operatively (30).

<table>
<thead>
<tr>
<th>PFMT as monotherapy</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFMT is better than no treatment for reducing episodes of UI and improving QoL in women with SUI and MUI. There is no evidence that PFMT is better than no treatment in providing a cure.</td>
<td>1</td>
</tr>
<tr>
<td>Higher-intensity regimes, or the addition of biofeedback, confer greater benefit, but differences are not sustained long term.</td>
<td>1</td>
</tr>
<tr>
<td>A taught/supervised programme of PFMT is more effective than self-taught PFMT.</td>
<td>1</td>
</tr>
<tr>
<td>Group-based PFMT is as effective as treatment delivered individually.</td>
<td>1</td>
</tr>
<tr>
<td>Short-term benefits of intensive PFMT are not maintained at 15 years’ follow-up.</td>
<td>2</td>
</tr>
<tr>
<td>PFMT appears effective for improvement of UI in elderly women</td>
<td>1b</td>
</tr>
<tr>
<td>PFMT does not result in measurable improvement in quality of life.</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFMT compared with other conservative treatments</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFMT results in better reduction in leakage episodes than training using vaginal cones, but no difference in self-reported cure or improvement.</td>
<td>1</td>
</tr>
<tr>
<td>PFMT results in fewer incontinence episodes than electrical stimulation.</td>
<td>1</td>
</tr>
<tr>
<td>PFMT is better than bladder training for improvement of leakage and quality of life, in women with SUI.</td>
<td>2</td>
</tr>
<tr>
<td>Intensive PFMT is more effective than bladder training in older women with SUI</td>
<td>1</td>
</tr>
<tr>
<td>PFMT is as effective as duloxetine in women with SUI and has fewer side effects.</td>
<td>2</td>
</tr>
<tr>
<td>PFMT is better tolerated than oxybutynin for UUI.</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFMT for UI in childbearing women</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFMT commencing in early pregnancy reduces the risk of incontinence in late pregnancy, and up to 6 months postpartum.</td>
<td>1</td>
</tr>
<tr>
<td>PFMT commencing in the early postpartum period improves UI in women for up to 12 months.</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFMT for post-prostatectomy UI</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised PFMT does not cure UI in men post prostatectomy.</td>
<td>1b</td>
</tr>
<tr>
<td>There is conflicting evidence whether men undergoing some form of PFMT, before or after radical prostatectomy, achieve continence more quickly than untreated men.</td>
<td>2</td>
</tr>
<tr>
<td>Men with post-prostatectomy UI, who have had no behavioural intervention, may still benefit from starting behavioural therapy, even years after surgery.</td>
<td>2</td>
</tr>
<tr>
<td>There is conflicting evidence on whether the addition of electrical stimulation or biofeedback or supervised training increases the effectiveness of PFMT alone.</td>
<td>2</td>
</tr>
<tr>
<td>There is no evidence that pre-operative PFMT prevents UI following radical prostatectomy. As with post-operative PFMT, it appears to lead to earlier recovery of continence.</td>
<td>2</td>
</tr>
</tbody>
</table>

For recommendations see section 3.4.5.
3.4.1.9 Research priorities

- What is the comparative effectiveness of different regimens for PFMT?
- What is the long-term durability of PFMT?
- What is the effectiveness of augmenting PFMT by the addition of electrical stimulation or vaginal cones?

3.4.1.10 References


3.4.2 **Electrical stimulation (surface electrodes)**

Electrical stimulation with surface electrodes can be delivered vaginally, anally or with skin electrodes on the perineum or suprapubic region. Stimulation parameters vary considerably from one study to another. Generally, low-intensity levels are used in home-based, self-administered therapy and high-intensity levels in clinic-based settings. Maximal stimulation under general anaesthesia has been described. The treatment regimes (number and frequency of sessions) vary considerably.
Electrical stimulation can also be combined with other forms of conservative therapy, e.g. PFMT and biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their pelvic floor muscles.

3.4.2.1 Question
In adults with UI, does treatment with electrical stimulation improve or cure symptoms of UI or QoL compared to no treatment or sham treatment?

3.4.2.2 Evidence
Most evidence on electrical stimulation refers to women. Five recent systematic reviews of electrical stimulation were found (1-5), although there was no specific Cochrane review. The five reviews included analysis of 15 RCTs, of which eight were comparisons to no treatment or sham treatment. Seven of the studies were comparisons to other physical or behavioural therapies and a further eight studies were comparisons of electrical stimulation combined with other therapies, usually PFMT. There were no new studies identified in 2011/12.

The studies were considered to be of generally low quality, with small sample size and a variety of stimulation parameters, treatment regimes and outcome parameters. In addition, most of the studies lacked detail of the statistical methods used, e.g. power calculation. Due to the lack of consistency in the parameters used for electrical stimulation and in the outcome measures, it has not been possible to compare or pool data from most of these studies.

The role of electrical stimulation is uncertain due to a lack of knowledge of how it might work in UI.

Physiotherapists have used electrical stimulation to help women identify and contract pelvic floor muscles during PFMT. It has been suggested that electrical stimulation probably targets the pelvic floor directly in SUI and the detrusor muscle or pelvic floor muscle or afferent innervation in UUI.

**Evidence summary LE**

<table>
<thead>
<tr>
<th>The evidence is inconsistent for whether electrical stimulation alone can improve UI.</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical stimulation is no more effective than antimuscarinic therapy for improvement of patients with UUI.</td>
<td>1</td>
</tr>
</tbody>
</table>

For recommendations see section 3.4.5.

3.4.2.3 References

3.4.3 Magnetic stimulation
(Extracorporeal) magnetic stimulation stimulates the pelvic floor musculature and/or the sacral roots in a non-invasive way. The patient is seated over a magnetic field generator. This produces a steep gradient magnetic field, which may stimulate the pelvic floor muscles and sphincters. Magnetic stimulation can also be given via a portable electromagnetic device. Magnetic stimulation may be effective in SUI and UUI. The mechanism of action is not understood.
3.4.3.1 Question
In adults with SUI or UUI or MUI, what is the clinical effectiveness of magnetic stimulation versus sham treatment?

3.4.3.2 Evidence
Eight RCTs and two cohort studies have investigated the question of whether magnetic stimulation is effective in UI. The RCTs were mostly of poor quality. The technique of electromagnetic stimulation was poorly standardised and involved different devices, mode of delivery, and stimulation parameters. Blinding was difficult to achieve and this resulted in a high risk of bias in some trials.

Three RCTs induced magnetic stimulation in women with UI, using a coil placed over the sacral foramina. Two were poor-quality RCTs, with a short follow-up and an inconclusive effect in SUI and UUI or OAB (1,2). The third better-quality RCT observed no improvement in UUI or OAB after a longer 12-week follow-up and did not recommend treatment with magnetic stimulation (3).

A portable device (Pulsegen) was compared in two RCTs to sham treatment in women with UI. Inconclusive effects were obtained. Both trials were poor quality with a short follow-up (4,5).

In adult women with SUI, an RCT using the NeoControl chair found no improvement (6). A cohort study for 6 weeks, but with a follow-up of 2 years, showed a moderate improvement in UI measured by pad test (7), while another cohort study found no improvement (8). A further poor-quality RCT using the NeoControl chair also found no benefit in women with UUI or OAB (9). No clinical benefits were reported when magnetic stimulation using the NeoControl chair was also compared to functional electrical stimulation with surface electrodes (10) or to conventional PFMT (11).

The negative or inconclusive effects obtained from the reviewed literature were considered to be consistent and generally applicable to adult women with SUI or UUI. There was a lack of evidence in men with UI.

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic stimulation does not cure or improve UI.</td>
<td>2a</td>
</tr>
<tr>
<td>There are no reports of adverse events for magnetic stimulation.</td>
<td>1b</td>
</tr>
</tbody>
</table>

For recommendations see section 3.4.5.

3.4.3.3 References


3.4.4 Posterior (percutaneous) tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Commonly, the PTNS is stimulated with a fine, 34-G, needle, which is inserted just above the medial aspect of the ankle (equivalent to the SP6 acupuncture point). Transcutaneous stimulation is also available. Treatment cycles typically consist of 12-weekly treatments of 30 minutes. PTNS may be effective in patients with UUI.

3.4.4.1 Question
In adults suffering from UUI, what is the clinical effectiveness of PTNS compared to sham treatment or antimuscarinic drug treatment?

3.4.4.2 Evidence
The reviewed studies included two RCTs of PTNS against sham treatment (1,2) and one comparing PTNS to tolterodine in patients with UUI (3). A further RCT compared transcutaneous PTNS to standard treatment with PFMT in older women (4).

The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results suggest that PTNS improves UUI in women who have had no benefit from antimuscarinic therapy or who are not able to tolerate these drugs. However, there is no evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women. In men there is insufficient evidence to make a conclusion about efficacy.

In patients who initially respond to PTNS, the improvement is maintained in some patients at 2 years with continued treatment (approximately monthly) (5).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
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<tbody>
<tr>
<td>PTNS is effective for improvement of UUI, in women who have had no benefit from antimuscarinic medication.</td>
<td>1b</td>
</tr>
<tr>
<td>PTNS is no more effective than tolterodine for improvement of UUI in women.</td>
<td>2b</td>
</tr>
<tr>
<td>No serious adverse events have been reported for PTNS in UUI.</td>
<td>3</td>
</tr>
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</table>

3.4.5 Recommendations for behavioural and physical therapies

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Offer supervised PFMT, lasting at least 3 months, as a first-line therapy to women with stress urinary incontinence or mixed urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>PFMT programmes should be as intensive as possible.</td>
<td>A</td>
</tr>
<tr>
<td>Offer PFMT to elderly women with urinary incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Consider using biofeedback as an adjunct in women with stress urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>Offer supervised PFMT to continent women in their first pregnancy to help prevent incontinence in the postnatal period.</td>
<td>A</td>
</tr>
<tr>
<td>Offer instruction on PFMT to men undergoing radical prostatectomy to speed recovery of incontinence.</td>
<td>B</td>
</tr>
</tbody>
</table>
Offer bladder training as a first-line therapy to adults with urge urinary incontinence or mixed urinary incontinence.

Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of urinary incontinence.

Do not offer magnetic stimulation for the treatment of incontinence or overactive bladder in adult women.

Do not offer PTNS to women or men who are seeking a cure for urge urinary incontinence.

Offer, if available, PTNS as an option for improvement of urge urinary incontinence in women, but not men, who have not benefitted from antimuscarinic medication.

Support other healthcare professionals in use of rehabilitation programmes including prompted voiding for care of elderly care-dependent people with urinary incontinence.

PFMT = pelvic floor muscle training; PTNS = posterior tibial nerve stimulation.

3.4.6 Research priorities

• Which aspect of behavioural modification is effective for the cure or sustained improvement of UI?
• Which method of delivering PFMT is most effective for the cure or sustained improvement of UI?
• Is PTNS effective in treatment of UI in men?

3.4.7 References


4. DRUG TREATMENT

4.1 Antimuscarinic drugs

Antimuscarinic drugs (also commonly referred to as anticholinergic drugs) are currently the mainstay of treatment for UUI. They act by blocking muscarinic receptors in the bladder wall. This reduces detrusor contractility and also alters sensation. Antimuscarinic agents differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action, in their pharmacokinetic properties, e.g. lipid solubility and half-life, and in their formulation, e.g. immediate release (IR), extended release (ER) or transdermal.

The evaluation of cure or improvement of UI using oxybutynin and tolterodine IR formulations is made harder by the lack of a standard definition of improvement and the failure to use cure as a primary outcome. Meta-analysis of the published evidence is therefore not always possible.

In general, these reviews noted that the treatment effect of drugs is usually small, while the treatment effect of other conservative therapies is large.

Dry mouth is the commonest side effect, though others include constipation, blurred vision, fatigue and cognitive dysfunction. When people have a dry mouth, they may be inclined to drink more, but it is not clear
whether this adversely influences the effect of the drug.

The 2012 edition of these Guidelines separated out IR antimuscarinics from ER preparations. The 2012 AHRQ review did a detailed evaluation of all antimuscarinic drugs up to December 30th 2011, but did not review IR preparations separately.

The IR formulation of oxybutynin is the prototype drug in the treatment of UUI. Oxybutynin IR provides maximum dosage flexibility, including an off-label ‘on-demand’ use. Immediate-release drugs have a greater risk of side effects than ER formulations because of their higher plasma peak levels. A transdermal delivery system (TDS) and gel developed for oxybutynin has improved its side effect profile while still maintaining efficacy.

4.1.1.1 Question
In adults with UI, how do antimuscarinic drugs, compare to placebo for improvement or cure of UI and for the risk of adverse effects?

4.1.1.2 Evidence
Five systematic reviews of individual antimuscarinic drugs versus placebo were reviewed by the Guidelines Panel for this section (1-5). As well as the studies included in these reviews, the Panel have examined studies published since these reviews up until September 2012. Most studies included patients with OAB, with a mean age of 55-60 years. Because most patients in the studies were women, the results can be generalised to women, but not to men. The reported rates for improvement or cure of UUI were only for short-term treatment (up to 12 weeks). The evidence reviewed was consistent, indicating that ER and IR formulations of antimuscarinics offer clinically significant short-term cure and improvement rates for UUI.

The Guidelines Panel considered that the most important outcome for this section was the cure of UI, and that the risk of adverse events was best represented by withdrawal from a trial because of adverse events. Table 4 shows a summary of the findings from the most recent systematic review (5). In summary, every drug where this data was available shows superiority compared to placebo in achieving UI, but the absolute effect is small.

Table 4. Summary of cure rates and discontinuation rates of antimuscarinic drugs from RCTs which reported these outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Studies</th>
<th>Patients</th>
<th>Relative risk (95% CI)</th>
<th>Number needed to treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure of incontinence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>2</td>
<td>2465</td>
<td>1.3 (1.1-1.5)</td>
<td>8 (5-17)</td>
</tr>
<tr>
<td>Oxybutynin (includes IR)</td>
<td>4</td>
<td>992</td>
<td>1.7 (1.3 – 2.1)</td>
<td>9 (6-16)</td>
</tr>
<tr>
<td>Propiverine (includes IR)</td>
<td>2</td>
<td>691</td>
<td>1.4 (1.2-1.7)</td>
<td>6 (4-12)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5</td>
<td>6304</td>
<td>1.5 (1.4-1.6)</td>
<td>9 (6-17)</td>
</tr>
<tr>
<td>Tolterodine (includes IR)</td>
<td>4</td>
<td>3404</td>
<td>1.2 (1.1-1.4)</td>
<td>12 (8-25)</td>
</tr>
<tr>
<td>Trospium (includes IR)</td>
<td>4</td>
<td>2677</td>
<td>1.7 (1.5-2.0)</td>
<td>9 (7-12)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darifenacin</td>
<td>7</td>
<td>3138</td>
<td>1.2 (0.8-1.8)</td>
<td></td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>4</td>
<td>4433</td>
<td>2 (1.3-3.1)</td>
<td>33 (18-102)</td>
</tr>
<tr>
<td>Oxybutynin (includes IR)</td>
<td>5</td>
<td>1483</td>
<td>1.7 (1.1-2.5)</td>
<td>16 (8-86)</td>
</tr>
<tr>
<td>Propiverine (includes IR)</td>
<td>2</td>
<td>1401</td>
<td>2.6 (1.4-5)</td>
<td>29 (16-27)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>7</td>
<td>9808</td>
<td>1.3 (1.1-1.7)</td>
<td>78 (39-823)</td>
</tr>
<tr>
<td>Tolterodine (includes IR)</td>
<td>10</td>
<td>4466</td>
<td>1 (0.6-1.7)</td>
<td></td>
</tr>
<tr>
<td>Trospium (includes IR)</td>
<td>6</td>
<td>3936</td>
<td>1.5 (1.1-1.9)</td>
<td>56 (30-228)</td>
</tr>
</tbody>
</table>

Darifenacin
The cure rates for darifenacin were not included in the AHRQ review. Two RCTs compared darifenacin to placebo, comparing cure rates, involving 838 patients (681 women). One study only included patients older than 65 years (6,7). Continence rates were 29-33% for darifenacin compared to 17-18% for placebo.

Transcutaneous oxybutynin
Randomised controlled trials of transdermal oxybutynin versus placebo and other oral formulations have shown a significant improvement in the number of incontinence episodes and micturitions per day but incontinence
was not reported as an outcome.

Oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured (8,9).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin IR and transdermal, tolterodine IR, and propiverine IR provide a significantly better rate of cure or improvement of UI compared to placebo.</td>
<td>1a</td>
</tr>
<tr>
<td>Trospium IR provides a significantly better reduction in incontinence episodes than placebo.</td>
<td>1a</td>
</tr>
<tr>
<td>ER formulations of antimuscarinic agents are effective for improvement and cure of UUI.</td>
<td>1b</td>
</tr>
<tr>
<td>ER formulations of antimuscarinic agents result in higher rates of dry mouth compared to placebo.</td>
<td>1b</td>
</tr>
</tbody>
</table>

4.1.1.3 References


4.2 Comparison of antimuscarinic agents

Head-to-head comparison trials of the efficacy and side effects of different antimuscarinic agents can help clinicians and patients to decide on the best initial agent to use, and the most appropriate second-line agent to try if the initial agent provides little benefit or has troublesome side effects.

4.2.1 Question

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI, and/or a greater improvement in QoL, and/or a lesser likelihood of adverse effects compared to an alternative antimuscarinic drug?

4.2.2 Evidence

There is a considerable body of evidence covering this question, comprising over 40 RCTs and five systematic reviews that address this question (1-5). Nearly all the primary studies have been funded and sponsored by the manufacturer of the newer drug under evaluation, which forms the experimental arm of the RCT. It was noted
that upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm.

In general, these studies have been designed for regulatory approval. They have short treatment durations of typically 12 weeks and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. It is therefore difficult to use the results from these trials in daily clinical practice to select the best first-line drug or second-line alternative following the failure of initial treatment. A quality assessment carried out as part of one systematic review (3) found that all the trials were of low or moderate quality.

The 2012 AHRQ review included a specific section addressing comparisons of antimuscarinic drugs. Table 5 shows the results of these comparisons.

Table 5: Comparison of antimuscarinic drugs as reviewed in the 2012 AHQR review (3)

<table>
<thead>
<tr>
<th>Experimental drug versus standard drug</th>
<th>No. of studies</th>
<th>Patients</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fesoterodine vs. tolterodine ER (continence)</td>
<td>2</td>
<td>3312</td>
<td>1.1 (1.04-1.16)</td>
</tr>
<tr>
<td>Oxybutynin ER vs. tolterodine ER (improvement)</td>
<td>3</td>
<td>947</td>
<td>1.11 (0.94-1.31)</td>
</tr>
<tr>
<td>Solifenacin vs. tolterodine ER</td>
<td>1</td>
<td>1177</td>
<td>1.2 (1.08-1.34)</td>
</tr>
<tr>
<td>Trospium vs. oxybutynin</td>
<td>1</td>
<td>357</td>
<td>1.1 (1.04-1.16)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solifenacin vs. tolterodine ER</td>
<td>3</td>
<td>2755</td>
<td>1.28 (0.86-1.91)</td>
</tr>
<tr>
<td>Trospium vs. oxybutynin</td>
<td>2</td>
<td>2015</td>
<td>0.75 (0.52 -1.1)</td>
</tr>
<tr>
<td>Fesoterodine vs. tolterodine</td>
<td>4</td>
<td>4440</td>
<td>1.54 (1.21-1.97)</td>
</tr>
</tbody>
</table>

There was no evidence that any one antimuscarinic agent improved QoL more than another agent (3).

Dry mouth is the most prevalent and most studied adverse effect of antimuscarinic agents. Good evidence indicates that, in general, ER formulations of both short-acting drugs and longer-acting drugs are associated with lower rates of dry mouth than IR preparations (3,4). Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin, 15 mg daily (3,4). Overall, oxybutynin ER has resulted in higher rates of dry mouth than tolterodine ER, but generally oxybutynin did not have higher rates for moderate or severe dry mouth. Transdermal oxybutynin was associated with a lower rate of dry mouth than oxybutynin IR and tolterodine ER, but had an overall higher rate of withdrawal due to an adverse skin reaction (3). Solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER (3). Fesoterodine, 8 mg daily, had a higher rate of dry mouth than tolterodine, 4 mg daily (6,7). In general, discontinuation rates were similar for each treatment arm in comparative RCTs, irrespective of differences in the occurrence of dry mouth.

In conclusion, there is no consistent evidence for the superiority of one antimuscarinic agent over another the size of effect. There is good evidence that ER, once daily, and transdermal preparations, are associated with lower rates of dry mouth than ER preparations, although discontinuation rates are similar.
Evidence summary

There is no consistent evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI.

1a

The ER formulation of oxybutynin is superior to the ER and IR formulations of tolterodine for improvement of UUI.

1b

Solifenacin is more effective than tolterodine IR for improvement of UUI.

1b

Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI but with a higher risk of side effects.

1b

ER and once-daily formulations of antimuscarinic drugs are generally associated with lower rates of dry mouth than IR preparations, although discontinuation rates are similar.

1b

Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.

1b

Oxybutynin IR or ER shows higher rates of dry mouth than the equivalent formulation of tolterodine.

1a

There is no evidence that any particular antimuscarinic agent is superior to another for improvement in QoL.

1a

4.2.3 References


4.3 Antimuscarinic drugs versus non-drug treatment

The choice of drug versus non-drug treatment of UUI is an important question for many clinicians. Especially in less economically developed countries, conservative treatment remains a cheap, effective alternative treatment to drug therapy, with a low risk of side effects.

4.3.1 Question

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI and/or greater improvement in QoL, and/or lesser likelihood of adverse effects compared to an alternative non-drug treatment?

4.3.2 Evidence

There is a large body of evidence comparing non-drug and drug treatment, including more than 100 RCTs and several, recently published, high-quality reviews (1-5). Most of these studies were not funded by the pharmaceutical industry, whose main focus is on drug treatment rather than on conservative treatment. The subject has also been considered by a Cochrane review (6).

The US HTA found that trials were of low- or moderate-quality with none categorised as high quality. The main focus of the review was to compare the different drugs used to treat UUI. Non-drug treatments were mentioned only in the evidence tables for the treatment of UUI. This review included studies comparing behavioural and
pharmacological treatments. Nine studies, including one prospective cohort study and eight RCTs, provided
direct comparisons between behavioural and pharmacological treatment arms. The behavioural approaches
included bladder training, multicomponent behavioural approaches and electrical stimulation. Only one of these
studies showed superiority for behavioural therapy. In one study, multicomponent behavioural modification
produced significantly greater reductions in incontinence episodes compared to oxybutynin and higher patient
satisfaction for behavioural versus drug treatment.

The HTA included a comparison between procedural and pharmaceutical treatments, including one RCT that
showed a substantial benefit for sacral neuromodulation compared with medical therapy (7).

In men with storage LUTS, one RCT compared oxybutynin to behavioural therapy, finding no difference in
efficacy (8). Another RCT showed that adding BT to solifenacin in women with OAB conferred no additional
benefit in terms of continent (9).

Two older RCTs (10, 11), in only small patient groups, reported a similar improvement in subjective parameters
with either transcutaneous electrical nerve stimulation or Stoller afferent nerve stimulation. However, only
oxybutynin-treated patients showed significant improvements in objective urodynamic parameters (capacity).
The oxybutynin-treated group had more side effects. Two studies compared antimuscarinics to electrical
stimulation finding no difference in UI outcomes (12). One underpowered RCT found that the addition of PTNS
to tolterodine ER improved UI and QoL (13).

In conclusion, there is no consistent evidence for the superiority of antimuscarinic drugs over non-drug
treatments, especially behavioural treatment. More side effects have been reported for drug therapy compared
to non-drug treatment. Electrical stimulation appears to be inferior to other treatment alternatives. Several trials
have suggested that a combination of drug and behavioural therapy produce the best results, including in the
long term.

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no consistent evidence to show superiority of drug therapy over behaviour therapy for treatment of UUI.</td>
<td>1b</td>
</tr>
<tr>
<td>Behavioural treatment results in increased patient satisfaction versus drug treatment alone.</td>
<td>1b</td>
</tr>
<tr>
<td>There is no consistent evidence to show superiority of drug therapy over PFMT for treatment of UUI.</td>
<td>1b</td>
</tr>
</tbody>
</table>

4.3.3 **References**


5. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults:


   Jun;183(4 Suppl):e585.
   http://download.journals.elsevierhealth.com/pdfs/journals/0022-5347/PIS0022534710026248.pdf


4.4 Antimuscarinic agents: adherence and persistence

Most studies on antimuscarinic medication provide information only about short-term outcomes (12 weeks), with a smaller number of trials providing longer-term follow-up data. However, it is recognised that in clinical practice many patients stop taking their medication rather more readily than tends to occur in RCTs, where the methodology tends to enhance adherence to allocated medication.

4.4.1 Question
Do patients with UUI adhere to antimuscarinic drug treatment and persist with prescribed treatment in everyday clinical practice?

4.4.2 Evidence

Thirteen papers have been published on adherence/persistence to antimuscarinic medication in everyday clinical practice (1-13). Ten papers used established pharmaco-epidemiological parameters (2,4,6-13), including: two recent open-label extensions of RCTs of fesoterodine 8m show adherence rates at 2 years from 49-84%, depending on populations (14, 15).

- Persistence. This is calculated from the index date until the patient discontinues treatment or is lost to follow-up, or the maximum follow-up period has ended, whichever occurs first.
- Medication possession rate (MPR). This is the total days of medication dispensed, except for the last refill, divided by the number of days between the first date on which medication was dispensed and the last refill date.
- Adherence ratio (MPR ≥ 0.8). This is the percentage of patients with MPR ≥ 0.8.

One study was in an open-label extension population (3). One study used only self-reports of patients and did not follow patients from the start of treatment (5). Most of the data was not derived from RCTs, but from pharmacy refill records. Pharmacy records are likely to overestimate adherence and persistence, because it is often not clear whether patients have been monitored from the start of treatment or whether monitoring (for the purpose of the study) was started in patients already taking the drug for some time and therefore defined as persistent users.

The main drugs studied in adherence/persistence trials were oxybutynin IR and ER and tolterodine IR and ER. These reviews demonstrated high non-persistence rates for tolterodine at 12 months, and particularly high rates (68-95%) for oxybutynin (7-10,13).

Five articles reported ‘median days to discontinuation’ as between < 30 days and 50 days (7,9,10,12,13), with one study reporting 273 days in a military health system (which provides patients with free medication) (9).

Only one RCT (3) included solifenacin, darifenacin and trospium. The only open-label extension study included in the review also studied solifenacin, darifenacin and trospium. However, determining adherence/persistence in an open-label extension population is not the preferred methodology, as these patients will not have been
monitored from the start of treatment and are therefore self-selected as persistent patients.

Several of the RCT trials tried to identify the factors associated with a lower, or low, adherence or persistence of antimuscarinic agents (4,6,9,10). These were identified in order of importance as:

- low level of efficacy (41.3%)
- adverse events (22.4%)
- cost (18.7%), as most adherence measures were higher in populations, which did not pay for medication, e.g. patients with health insurance (9).

Other reasons for poor adherence included:

- IR versus ER formulations
- age, with persistence lower among younger adults
- unrealistic expectations of treatment
- gender distribution, because adherence/persistence was better in studies that include relatively more female patients
- ethnic group because African-Americans and other minorities were more likely to discontinue or switch treatment
- effectiveness of treatment because in Campbell et al. only 52% were somewhat satisfied to very satisfied with treatment (6).

In addition, the source of data influenced the adherence figures.

### Evidence summary

<table>
<thead>
<tr>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than half of patients will stop antimuscarinic agents within the first 3 months because of ineffectiveness, adverse events and cost.</td>
</tr>
</tbody>
</table>

4.4.3 References

http://www.ncbi.nlm.nih.gov/pubmed/16161387


4.5 Antimuscarinic agents, the elderly and cognition
Although the prevalence of UI increases with age, this is not reflected by research targeted to elderly people with UI. Drug trials usually exclude patients with several comorbidities and those taking multiple medications. However, the mechanisms underlying UI in the elderly are more likely to be multifactorial than in younger patients. The elderly are also likely to be taking medications that may affect the efficacy or adverse effects of a new drug.

Muscarinic receptors exist throughout the body and are involved in many physiological processes. Most anticholinergics used to treat OAB are directed against the M2 and M3 receptors. The M1 receptor is involved in memory processes. The specificity of a drug for one or another receptor and the degree of penetration into the CNS through the blood-brain barrier may have an impact on cognitive function. In recent years, the effects of antimuscarinic agents on cognition have been studied in more detail.

4.5.1 Question
What is the comparative efficacy, and risk of adverse effects, particularly the cognitive impact, of treatment with antimuscarinic medication in elderly men and women with UUI compared to younger patients?

4.5.2 Evidence
There have been two systematic reviews of antimuscarinic agents in elderly patients (1,2). One review was confined to evidence on nursing home residents with UUI (2). A community-based cohort study on the burden of antimuscarinic drugs in an elderly population (n = 372) found a high incidence of cognitive dysfunction (3). Other systematic reviews have included sections on the efficacy and safety of antimuscarinics in elderly patients (4,5).

A systematic review in 2012 included nine studies in which the cognitive impact of antimuscarinics was tested but the evidence was found to be inconclusive (6).

There have been very few trials specifically investigating the cognitive changes that might occur with the use of antimuscarinic agents. Most trials have been done in healthy volunteers of different age groups and only for a short period (varying from a single dose to 12 weeks). Other publications describe post-hoc analyses of other trials or reviewed only a number of selected publications. In general, these trials have measured CNS side effects in a non-specific way that does not allow the impact on cognition to be considered in a particular patient population (7,8). Meta-analyses have been limited by study heterogeneity, dosing inconsistency and reporting bias. There is a need for more detailed, standardised measurement of age-stratified CNS outcomes in clinical trials to provide better information to patients and clinicians about the CNS risks associated with antimuscarinic agents.

Studies on antimuscarinic effects have been done in elderly persons (9), and in people with dementia with UUI (10). There have been no specific studies in vulnerable patient populations who are likely to have cognitive dysfunction and might suffer deterioration of their cognitive function due to using antimuscarinic medication.
Although there have been no RCTs specifically designed to examine the impact of antimuscarinic medication on elderly patients compared with younger patients, it is possible to extract relevant evidence from several RCTs, which have provided outcomes for specific age groups, and other studies of the risks/benefits of antimuscarinic agents in an elderly population. There are many case studies that report adverse effects of antimuscarinic agents in elderly patients, particularly those with serious cognitive dysfunction. It should be noted that the definition of an elderly patient and the exclusion criteria vary from study to study.

4.5.2.1 Oxybutynin

There is substantial evidence that oxybutynin IR may cause or worsen cognitive dysfunction in adults (7,9,11).

A crossover RCT in elderly volunteers given oxybutynin IR reported increased cognitive dysfunction. A short-term safety RCT of oxybutynin ER in elderly women with cognitive dysfunction observed no increase in delirium (12) but secondary analysis revealed no change in incontinence (13). Two studies in the elderly demonstrated additional benefit from oxybutynin IR combined with scheduled voiding versus scheduled voiding alone. Another study found no differences between oxybutynin ER and IR in elderly patients, although the study did not reach its recruitment target (14).

A large observational study (n = 3536) suggested that more rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction (15). However, the nature of the interaction with cholinesterase inhibitors is unclear. No general conclusions can be made, but caution is advised in prescribing these combinations.

4.5.2.2 Solifenacin

One pooled analysis from several RCTs (16) has shown that solifenacin has good efficacy and does not increase cognitive impairment in the elderly. Another RCT found no age-related differences in the pharmacokinetics of solifenacin between elderly, middle-aged or younger patients. One post-marketing surveillance study reported more frequent adverse events in subjects over 80 years old. Another study on healthy elderly volunteers showed no cognitive effect (11). In a subanalysis of a large trial, solifenacin 5-10 mg appeared effective for improvement in symptoms and QoL in people aged older than 75 years who had not responded to tolterodine (17).

4.5.2.3 Tolterodine

Pooled data from RCTs showed no change in efficacy or side effects related to age, but reported a higher discontinuation rate for both tolterodine and placebo in elderly patients (7). Two RCTs of tolterodine specifically designed in the elderly found that tolterodine showed a similar efficacy and side effect profile, as in younger patients. Post-hoc analysis from other RCTs has shown little effect on cognition. One trial showed lower rates of depression amongst elderly participants treated with tolterodine ER compared to oxybutynin IR (18).

4.5.2.4 Darifenacin

Two RCTs carried out specifically in the elderly population (one RCT in patients with UUI and the other RCT in volunteers) concluded that darifenacin was effective and the risk of cognitive change, measured as memory scanning tests, were no different to placebo (19,20). Another comparison between darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in patients receiving oxybutynin ER (9).

4.5.2.5 Trospium chloride

Trospium is a quaternary amine compound that does not cross the blood-brain barrier in healthy individuals, so theoretically is less likely to have an impact on cognitive function compared to other antimuscarinic agents. Two (EEG) studies in healthy volunteers showed no effect from trospium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes (21, 22).

No published evidence was found regarding the comparative efficacy and side effect profiles of trospium in the elderly compared with younger patients. However, there is some evidence that trospium does not impair cognitive function (10, 23, 24) and that it is effective compared to placebo in this group (25).

4.5.2.6 Fesoterodine

There is no evidence comparing the efficacy and side effects of fesoterodine in elderly and younger patients. Two separate pooled analyses of the same two RCTs of fesoterodine in the elderly confirmed the efficacy of the 8 mg but not the 4 mg dose in over-75 year olds. Adherence was lower in the over-75 year-old group but the effect on mental status was not reported (26, 27).
4.5.2.7 Applicability of evidence to general elderly population

It is not clear how much the data from pooled analyses and subgroup analyses from large RCTs can be extrapolated to a general ageing population. The community-based studies of the prevalence of antimuscarinic side effects in this age group may be the most helpful (3).

When starting anticholinergic medication in patients at risk of worsening cognitive function, it has been suggested that mental function is assessed objectively and monitored to detect any significant changes during treatment (28).

**Evidence summary**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin IR may worsen cognitive function.</td>
<td>1b</td>
</tr>
<tr>
<td>Trospium chloride has not been reported to affect cognitive function.</td>
<td>1b</td>
</tr>
<tr>
<td>Oxybutynin ER, 5 mg/day, does not cause delirium in the short term in cognitively impaired elderly women.</td>
<td>1b</td>
</tr>
<tr>
<td>Oxybutynin IR is less effective in people with impaired orientation, cerebral cortical underperfusion and reduced bladder sensation.</td>
<td>2</td>
</tr>
<tr>
<td>Solifenacin, tolterodine and darifenacin have not been shown to impair cognitive function in healthy elderly people.</td>
<td>3</td>
</tr>
<tr>
<td>The effectiveness and risk of adverse events of solifenacin, tolterodine and darifenacin for people with UUI do not differ with patient age.</td>
<td>3</td>
</tr>
</tbody>
</table>

**Recommendations for antimuscarinic drugs**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer IR or ER formulations of antimuscarinic drugs as initial drug therapy for adults with urge urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>If IR formulations of antimuscarinic drugs are unsuccessful for adults with urge urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.</td>
<td>A</td>
</tr>
<tr>
<td>Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.</td>
<td>B</td>
</tr>
<tr>
<td>Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urge urinary incontinence (&lt; 30 days).</td>
<td>A</td>
</tr>
<tr>
<td>When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of cognitive side effects, especially in those receiving cholinesterase inhibitors.</td>
<td>C</td>
</tr>
<tr>
<td>Avoid using oxybutynin IR in patients who are at risk of cognitive dysfunction.</td>
<td>A</td>
</tr>
<tr>
<td>Consider use of trospium chloride in patients known to have cognitive dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>Use antimuscarinic drugs with caution in patients with cognitive dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>Do an objective assessment of mental function before treating patients whose cognitive function may be at risk.</td>
<td>C</td>
</tr>
<tr>
<td>Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction.</td>
<td>C</td>
</tr>
</tbody>
</table>

*IR = immediate release; ER = extended release.*

4.5.3 Research priority

- All drug trials should report ‘dry’ rates for urinary incontinence based on a bladder diary.
- What is the relative incidence of cognitive side effects of antimuscarinic drugs?

4.5.4 References


4.6 Adrenergic drugs for UI

Previous trials of adrenergic drugs have focused on the effect of alpha-adrenoceptors in increasing the closure pressure of the urethral continence mechanism in women as a means of improving SUI. More recently, research has focused on beta-adrenoceptor stimulation as a means of increasing detrusor relaxation and therefore improving urine storage in people with overactive bladder and UUI.

A Cochrane review updated to 2010 (1) found 22 trials of adrenergic drugs for the treatment of women with predominant SUI in comparison to placebo or PFMT. Eleven of these trials involved phenylpropanolamine, which has since been withdrawn in some countries because of an increased risk of haemorrhagic stroke. The review found weak evidence that these drugs are better than placebo at improving UI in women. Comparative trials with PFMT gave inconsistent results. No new trials were published between 2007 and 2010 and the review is therefore currently categorised as stable. At present, these drugs are not licensed for use in UI and are not part of the standard treatment algorithm.

A review of relevant literature and web-based resources (2) identified conference abstracts of two RCTs on the use of mirabegron ER, a beta-adrenoceptor agonist, for the treatment of patients with overactive bladder and UUI (3,4). The use of mirabegron ER (50 and 100 mg) resulted in modest reduction (improvement) in episodes of UUI compared to placebo. Adverse effects were similar to placebo, although mirabegron ER use was associated with an average rise in pulse rate of 2 beats per minute and 4% of participants withdrew due to adrenergic side effects. The European-Australian study (3) included tolterodine 4 mg ER as a comparative arm, but the results were not reported in the abstract. The North American trial (4) has now been published in full (5). Mirabegron ER has been approved for use in people with OAB and UUI at a dose of 25 mg and 50 mg in both the USA and Japan and is under consideration by the European Medicines Agency (EMA) and NICE in the UK.

**Evidence summary**

| LE | Mirabegron ER is more effective than placebo for improvement of UUI. |
| 4b | Adrenergic-mediated side effects of mirabegron appear mild and not clinically significant. |

**Recommendation**

Offer mirabegron extended release to people with urge urinary incontinence depending on local licensing arrangements.
4.7 Duloxetine

Duloxetine inhibits the presynaptic re-uptake of the neurotransmitters, serotonin (5-HT) and norepinephrine (NE) leading to an increase in levels of these neurotransmitters in the synaptic cleft. In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurones, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

4.7.1 Questions

- In adults with SUI, does duloxetine cure or reduce UI and/or improve QoL compared to no treatment?
- In adults with SUI, does duloxetine result in a greater cure or improvement of UI, or a greater improvement in QoL or a lesser likelihood of adverse effects, compared to any other intervention?

4.7.2 Evidence

Duloxetine was evaluated as a treatment for female SUI or MUI in two systematic reviews (6,7) including 10 RCTs (8-17) and one subsequent RCT (10). The typical dose of duloxetine was 80 mg daily, with dose escalation up to 120 mg daily allowed in one study (9), over a period of 8-12 weeks. One RCT extended the observation period up to 36 weeks and used the Incontinence Quality of Life (I-QoL) score as a primary outcome (12).

The studies provided reasonably consistent results demonstrating improvement in UI compared to placebo. There were no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients (8). An improvement in I-QoL was not found in the study using I-QoL as a primary endpoint (12). A further study compared duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo (18). Duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment.

The long-term effect of duloxetine in controlling SUI was evaluated by two open-label studies with a follow-up of 1 year or more (19,20). However, the studies had high rates of discontinuation.

Duloxetine, 80 mg daily, which could be increased up to 120 mg daily, was investigated in a 12-week study in patients, who had OAB but not SUI (21). Episodes of UUI were also significantly reduced by duloxetine.

One study (22) compared PFMT + duloxetine versus PFMT + placebo, for 16 weeks, followed by 8 weeks of PFMT alone in males with post-prostatectomy incontinence. Duloxetine + PFMT significantly improved UI, but the effect did not last to the end of the study, indicating that duloxetine only accelerates cure and does not increase the percentage of patients cured.

In general, all studies had a high patient withdrawal rate of about 20-40% of patients in short-term studies and up to 90% in long-term studies. The high withdrawal rate was caused by a combination of a lack of efficacy and a high incidence of adverse events, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue.

**Evidence summary**

<table>
<thead>
<tr>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine does not cure UI.</td>
</tr>
<tr>
<td>Duloxetine, 80 mg daily, can improve SUI and MUI in women.</td>
</tr>
<tr>
<td>Duloxetine causes significant gastrointestinal and CNS side effects leading to a high rate of treatment discontinuation.</td>
</tr>
<tr>
<td>Duloxetine, 80 mg daily, can improve SUI in men.</td>
</tr>
<tr>
<td>Duloxetine 80mg - 120mg daily can improve UUI in women.</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine should not be offered to women or men who are seeking a cure for their incontinence.</td>
</tr>
<tr>
<td>Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms.</td>
</tr>
<tr>
<td>Duloxetine should be initiated using dose titration because of high adverse effect rates.</td>
</tr>
</tbody>
</table>
References


4.8 Intravaginal oestrogen
Oestrogen treatment for UI can be given orally, vaginally or even intravesically. Systemic oestrogen has been shown to worsen UI. Topical oestrogen treatment has less systemic effect and is not associated with an increased risk for cancer or thromboembolism. Topical treatment is used to treat urogenital disorders in post-menopausal women.

4.8.1 Question
In women with UI, does intravaginal oestrogen cure or improve UI compared to no treatment?

4.8.2 Evidence
A recent Cochrane systematic review including 33 trials looked at the use of oestrogen therapy in post-menopausal women (1) given local oestrogen therapy. There is also a more recent narrative review of oestrogen therapy in urogenital diseases (2). However, since the Cochrane review, no new RCTs have been published up to September 2012.

Local oestrogen therapy can be given as conjugated equine, oestril or oestradiol in vaginal pessaries, vaginal rings or creams. Besides improving vaginal atrophy (4), local oestrogen therapy reduces UI and frequency and urgency in OAB. Local oestrogens were more effective than placebo at improving or curing UI and reducing frequency (1). The current data do not allow differentiation among the various types of oestrogens or delivery methods. Moreover, the ideal duration of this type of therapy and the long-term effects have been poorly studied. One RCT compared oestradiol ring pessary with treatment with oxybutynin ER showing no difference in outcomes (5).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
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<tbody>
<tr>
<td>Local oestrogen therapy in post-menopausal women may improve or cure UI.</td>
<td>1a</td>
</tr>
<tr>
<td>There is no evidence available on the neoadjuvant or adjuvant use of local oestrogens at the time of surgery for UI.</td>
<td>1a</td>
</tr>
</tbody>
</table>

Recommendations
Offer post-menopausal women with urinary incontinence local oestrogen therapy, although the ideal duration of therapy and best delivery method are unknown.

4.8.3 References


4.9 Desmopressin
Desmopressin is a synthetic analogue of vasopressin (also known as antidiuretic hormone), which increases water re-absorption in the renal collecting ducts without increasing blood pressure. It can be taken orally, nasally or by injection. Desmopressin is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis.

4.9.1 Questions
• In adults with nocturnal UI, does desmopressin cure or reduce nocturnal UI and/or improve QoL compared to no treatment?
• In adults with nocturnal UI, does desmopressin result in a greater cure or improvement in nocturnal UI, or a greater improvement in QoL or a lesser likelihood of adverse effects, compared to any other intervention?

4.9.2 Evidence
4.9.2.1 Improvement of incontinence
Most studies of desmopressin in UI have been designed to investigate its effect on nocturia. Few studies have examined the use of desmopressin exclusively for the treatment of UI. Only two RCTS have compared desmopressin to placebo with UI as an outcome measure. A pilot RCT study (n = 128) in women demonstrated improved incontinence during the first 4 hours after taking desmopressin (1). An RCT in men and women with OAB concluded that continuous use of desmopressin improved frequency and urgency, but did not improve UI (2). There is no published evidence reporting desmopressin cure rates for UI and no evidence that compares desmopressin with other non-drug treatments for UI.

4.9.2.2 Monitoring for hyponatraemia
 Importantly, the use of desmopressin carries a risk of developing hyponatraemia (12%) (3). Elderly patients started on this drug should have their serum sodium checked regularly, beginning in the first few days after starting treatment.

Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
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</thead>
<tbody>
<tr>
<td>The risk of UI is reduced within 4 hours of taking oral desmopressin, but not after 4 hours.</td>
<td>1b</td>
</tr>
<tr>
<td>Continuous use of desmopressin does not improve or cure UI.</td>
<td>1b</td>
</tr>
<tr>
<td>Regular use of desmopressin may lead to hyponatraemia.</td>
<td>3</td>
</tr>
</tbody>
</table>

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer desmopressin to patients requiring occasional short-term relief from urinary incontinence and inform them that this drug is not licensed for this indication.</td>
<td>B</td>
</tr>
<tr>
<td>Do not use desmopressin for long-term control of urinary incontinence.</td>
<td>A</td>
</tr>
</tbody>
</table>

4.9.3 References


5. SURGICAL TREATMENT

Surgery for the treatment of UI is usually considered as an option in pathways of care only after the failure of conservative therapy or drug treatment, although the emergence of minimally invasive procedures with low rates of adverse effects may modify this principle in the future. The aim of all operations for UI is to make patients continent, usually by allowing them to store urine normally. However, the mechanisms for achieving this vary widely.

Some generic principles apply to good surgical practice. Any operation for UI should be preceded by a discussion with the patient and/or carers, about the purpose of the operation, the likely benefits and possible risks. It is also important to explain when there are alternative approaches, even if these procedures are not available locally. Surgeons performing operations for UI should be properly trained and perform an adequate number of procedures to maintain expertise. Most importantly, they should be able to demonstrate their competence by being aware of the outcomes of individual operations in their own hands, and should share this information with their patients.

Some newer surgical interventions can be very costly. The Panel is well aware that the availability of devices varies from one healthcare system to another. We have tried to recognise this in the recommendations by suggesting that procedures should be offered ‘when available’.

The section considers surgical options for the following situations:

- Women with uncomplicated SUI. This means no history of previous surgery, no neurological LUTD, no bothersome genitourinary prolapse, and not considering further pregnancy.
- Women with complicated SUI. Neurogenic LUTD is reviewed in the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction (1).
- Associated genitourinary prolapse has not been included in these Guidelines, but will be reviewed for 2013.
- Men with SUI, mainly in men with post-prostatectomy incontinence without neurological disease affecting the lower urinary tract.
- Patients with refractory DO incontinence.

It is inevitable that very few studies will be found which compare a surgical treatment to sham operation (the surgical equivalent of placebo control) since this is both hard to justify and usually impossible to blind to surgeon or patient. Consequently most evidence for surgery derives either from large cohort studies or from trials that compare an experimental technique to an established, gold standard, procedure.

New devices, and modifications to existing procedures, are emerging all the time. Some of these are introduced into the market, and to clinical practice, on the basis of very little clinical evidence. It is impossible, in the context of a guideline, to recognise every permutation of design that might be considered important by those who introduce it. The Panel has tried to acknowledge emerging techniques as they think appropriate and have made a strong recommendation (section 5.1.5.2) that new devices are only used as part of a structured research programme.

5.1 Women with uncomplicated SUI

5.1.1 Open and laparoscopic surgery for SUI

The open ‘Burch’ colposuspension aims to approximate the lateral tissues of the vaginal vault to the pectineal ligament by means of insertion of several, interrupted, non-absorbable sutures. The operation has been much modified over the years, most notably as the vagino-obturator shelf procedure. This has provided less elevation of the vaginal wall by inserting suspensory sutures into the obturator fascia instead of the pectineal ligament.

Autologous fascial slings have been used for many years to provide support or elevation to the mid- or proximal urethra. Again, there have been many different descriptions of this technique.

For decades, open colposuspension has been considered the gold standard surgical intervention for SUI, and has often been used as the comparator in RCTs of new, less invasive, surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

Although the outcome of open and laparoscopic procedures should be considered in absolute terms, it is also important to consider any associated complications, adverse events and costs. The outcome parameters used to evaluate surgery for SUI have included:
• continence rate and number of incontinence episodes;
• general and procedure-specific complications;
• generic, specific (UI) and correlated (sexual and bowel) QoL.

The large number of RCTs available for standard review and meta-analysis suggest that the evidence can be generalised to all women with SUI. There is also a good degree of consistency between the different RCTs.

5.1.1.1  Question
In women with SUI, what is the effectiveness of open and laparoscopic surgery, compared to no treatment or compared to other surgical procedures, measured in terms of cure or improvement of incontinence or QoL, or the risk of adverse events?

5.1.1.2  Evidence
Four systematic reviews were found, which covered the subject of open surgery for SUI, including 46 RCTs (1-4), but no RCTs comparing any operation to a sham procedure.

Open colposuspension
The Cochrane review (5) included 46 trials (4738 women) having open colposuspension. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Consequently, for this review we have only considered the absolute effect of colposuspension but have not reviewed all of these comparisons. No additional trials have been reported since this review.

Within the first year, complete continence rates of approximately 85-90% were achieved for open colposuspension, while failure rates for UI were 17% up to 5 years and 21% over 5 years. The re-operation rate for UI was 2%. Colposuspension was associated with a higher rate of development at 5 years of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocele was similar in colposuspension (37%) and with TVT (41%).

Seven trials, covered by the review, compared open colposuspension to needle suspension. These trials found similar levels of effectiveness at 85-90% and lower rates of failure at 5 years for the Marshall Marchetti Krantz procedure.

Open colposuspension was compared with conservative treatment in one small study (6). One trial compared open colposuspension with antimuscarinic treatment, while another compared it with periurethral injection of bulking agents. Colposuspension resulted in superior outcomes, but had significantly higher rates of adverse events.

Four trials compared Burch colposuspension to the Marshall Marchetti Krantz procedure and one trial evaluated Burch colposuspension with paravaginal repair in both cases showing fewer surgical failures up to 5 years but otherwise similar outcomes.

Anterior colporrhaphy
Anterior colporrhaphy is now mainly considered to be an obsolete operation for UI. In a Cochrane review (3), 10 trials compared anterior colporrhaphy (385 women) with colposuspension (627 women). The failure rate for UI at follow-up of up to 5 years was worse for anterior colporrhaphy with a higher requirement for re-operation for incontinence.

Autologous fascial sling
The Cochrane review (3,7) described 26 RCTs, including 2284 women undergoing autologous sling procedure in comparison to other operations. The trials did not identify those women undergoing repeat surgery for recurrent UI. No further studies have been reported.

There were seven trials of autologous fascial sling versus colposuspension. Except for one very high-quality study (8), most of the studies were of variable quality, with a few very small studies, and a short follow-up. The meta-analysis showed that fascial sling and colposuspension had a similar efficacy at 1 year. Colposuspension had a lower risk of voiding difficulty and UTIs, but a higher risk of bladder perforation.

In 12 trials of autologous fascial sling versus mid-urethral synthetic slings, the procedures showed similar efficacy. However, use of the synthetic sling resulted in shorter operating times and lower rates of complications, including voiding difficulty. Six trials compared autologous fascial slings with other materials.
of different origins, with results favouring traditional autologous fascial slings. There were no trials compared traditional suburethral slings with anterior colporrhaphy, laparoscopic retropubic colposuspension or the artificial urinary sphincter device.

**Laparoscopic colposuspension**

The Cochrane review (2) identified 22 RCTs, of which 10 trials compared laparoscopic colposuspension to open colposuspension. No other trials have been identified. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were less good for laparoscopic colposuspension. However, laparoscopic colposuspension had a lower risk of complications and shorter duration of hospital stay.

In eight RCTs comparing laparoscopic colposuspension to self-fixing slings, the subjective cure rates were similar, while the objective cure rate favoured the mid-urethral sling at 18 months. Complication rates were similar for the two procedures and operating times were shorter for the mid-urethral sling.

<table>
<thead>
<tr>
<th>Evidence summary</th>
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<tbody>
<tr>
<td>Anterior colporrhaphy has lower rates of cure for UI especially in the longer term.</td>
<td>1a</td>
</tr>
<tr>
<td>Open colposuspension and autologous fascial sling are similarly effective for cure of SUI in women.</td>
<td>1b</td>
</tr>
<tr>
<td>Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of SUI and a similar risk of voiding difficulty or de novo urgency.</td>
<td>1a</td>
</tr>
<tr>
<td>Laparoscopic colposuspension has a lower risk of other complications and shorter hospital stay than open colposuspension.</td>
<td>1a</td>
</tr>
<tr>
<td>Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and post-operative UTI.</td>
<td>1b</td>
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</tbody>
</table>

5.1.1.3 **References**


5.1.2 **Mid-urethral slings**

The description of tension-free support for mid-urethra using a synthetic sling was an important new concept in the treatment of women with urodynamic SUI, which led to the development of synthetic mesh materials and devices to allow minimally invasive insertion (1). Early clinical studies identified that slings should be made from monofilament, non-absorbable material, typically polypropylene, and constructed as a 1-2 cm wide mesh with a relatively large pore size (macroporous). Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.
5.1.2.1  Questions
In women with SUI, what is the effectiveness in curing SUI and adverse effects at 1 year of:

• mid-urethral synthetic sling insertion compared to Burch colposuspension?
• one method of insertion of a mid-urethral synthetic sling compared to another method?
• one direction of insertion of a mid-urethral synthetic sling compared to another direction of insertion?

5.1.2.2  Evidence
For the purpose of these guidelines, a new meta-analysis was performed.

**Mid-urethral sling insertion compared to colposuspension**

Thirteen RCTs (n = 1037) compared mid-urethral sling (retropubic) and colposuspension (open and laparoscopic). The meta-analysis found no difference in patient-reported cure rates at 12 months (2-15). The overall patient-reported cure rate was 75%. There was weak evidence of higher clinician-reported cure rates at 12 months after mid-urethral sling (83%) compared to colposuspension (78%) (2,7,9-15). However, longer-term follow-up for up to 5 years reported no difference in effectiveness, though the numbers of participants lost to follow-up was high (2,6,16). Voiding dysfunction was more likely for colposuspension (relative risk 0.34, 95% CI 0.16-0.7) whilst bladder perforation was higher for the mid-urethral sling (15% vs. 9%, and 7% vs. 2%, respectively) (4,5,7,17,18).

A single, randomised trial, comparing the mid-urethral sling (transobturator) with open colposuspension, reporting similar rates of patient-reported and clinician-reported cure and no evidence of differential harms (19).

In all the trials, operative time and duration of hospital stay was shorter for women randomised to insertion of the mid-urethral synthetic sling.

**Transobturator route versus retropubic route**

The EAU panel meta-analysis identified thirty-four RCTs (5786 women) comparing insertion of the mid-urethral sling by the retropubic and transobturator routes. There was no difference in cure rates at 12 months in either patient-reported or clinically reported cure rates (77% and 85%, respectively) (20). Voiding dysfunction was less common (4%) following transobturator insertion compared to retropubic insertion (7%), as was the risk of bladder perforation (0.3%) or urethral perforation (5%). Similarly, the risks of de novo urgency and vaginal perforation were 6% and 1.7%, respectively. Chronic perineal pain at 12 months after surgery was reported by 21 trials and meta-analysis of these data showed strong evidence of a higher rate in women undergoing transobturator insertion (7%) compared to retropubic insertion (3%).

**Insertion using a skin-to-vagina direction versus a vagina-to-skin direction**

A Cochrane systematic review and meta-analysis found that the skin-to-vagina direction (outside in) for retropubic insertion of mid-urethral slings was less effective than the vagina-to-skin (inside out) direction and was associated with higher rates of voiding dysfunction, bladder perforation and vaginal erosion (21). A further systematic review and meta-analysis found that the skin-to-vagina (outside in) direction of transobturator insertion of mid-urethral slings was equally effective compared to the vagina-to-skin route (inside out) using direct comparison. However, indirect comparative analysis gave weak evidence for a higher rate of voiding dysfunction and bladder injury (22). These differences in adverse effects were not found in the Cochrane review, which only used the limited amount of direct head-to-head comparative data and found no differences in effectiveness or adverse effects (21).

**Generalisability of evidence to adult women with SUI**

Analysis of the heterogeneity of trials in this meta-analysis suggests that the evidence is generalisable to women, who have predominantly SUI, and no other clinically severe lower genitourinary tract dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI.

The results of the EAU Panel meta-analysis (20) were consistent with those of the Cochrane systematic review (21), except that in the EAU Panel meta-analysis the objective cure rates appeared slightly higher for retropubic (88%) compared to transobturator insertion (84%). The EAU Panel finding is consistent with an additional systematic review and meta-analysis (23) and the difference may result from the Panel’s decision to only consider trial data with at least 12 months of follow-up. The cure rates at 12 months in our meta-analysis for mid-urethral slings were similar to those calculated in the meta-analysis for the American Urological Association guidelines (24). In addition, our results and recommendations are consistent with those of the Society of Obstetricians and Gynaecologists of Canada (25) and those of NICE in the UK (26).
Sexual function after mid-urethral tape surgery
A systematic review concluded there was a lack of RCTs addressing the effects of incontinence surgery on sexual function but noting a reduction in coital incontinence (27). One recent RCT (28) and another cohort study (29) have shown that overall sexual activity improves after sling surgery, although the cohort study also recorded a small group (6/79) who became sexually inactive. A further small RCT comparing sling techniques showed no difference between pre- and post-operative sexual function nor between any of the techniques used (30).

SUI surgery in the elderly
There are no RCTs comparing surgical treatment in older versus younger women, although subgroup analyses of some RCTs have included a comparison of older with younger cohorts. Definitions of “elderly” vary from one study to another so no attempt was made to define the term here. Instead, the panel attempted to identify those studies which have addressed age difference as an important variable.

An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 (31). An RCT assessing risk factors for the failure of TVT versus transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at 1 year (32). In a subanalysis of the SISTER trial cohort of 655 women at 2 years’ follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urge UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to post-operative normal voiding (33).

Another RCT comparing immediate TVT versus delayed TVT in older women confirmed significant efficacy in women undergoing surgery, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) (34).

A cohort study of 256 women undergoing inside-out transobturator tape reported similar efficacy in older versus younger women, but found a higher risk of de novo urgency in older patients (35).

<table>
<thead>
<tr>
<th>Evidence summary</th>
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<tbody>
<tr>
<td>Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling gives equivalent patient-reported cure of SUI at 12 months.</td>
<td>1a</td>
</tr>
<tr>
<td>Compared to colposuspension, the transobturator insertion of a mid-urethral synthetic sling gives equivalent patient-reported outcome at 12 months.</td>
<td>2</td>
</tr>
<tr>
<td>Mid-urethral synthetic sling inserted by either the transobturator or retropubic route gives equivalent patient-reported outcome at 12 months.</td>
<td>1a</td>
</tr>
<tr>
<td>The skin-to-vagina (top-down) direction of retropubic insertion of mid-urethral sling is less effective than a vagina-to-skin (bottom-up) direction.</td>
<td>1a</td>
</tr>
<tr>
<td>Mid-urethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.</td>
<td>1a</td>
</tr>
<tr>
<td>The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.</td>
<td>1a</td>
</tr>
<tr>
<td>The transobturator route of insertion is associated with a higher risk of chronic pain at 12 months than the retropubic route.</td>
<td>1a</td>
</tr>
<tr>
<td>The skin-to-vagina (top-down) direction of both retropubic and transobturator insertion is associated with a higher risk of post-operative voiding dysfunction.</td>
<td>1b</td>
</tr>
<tr>
<td>Older women benefit from surgical treatment for UI.</td>
<td>1</td>
</tr>
<tr>
<td>The risk of failure from surgical repair of SUI, or suffering adverse events, appears to increase with age.</td>
<td>2</td>
</tr>
<tr>
<td>There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.</td>
<td>4</td>
</tr>
<tr>
<td>In women undergoing surgery for SUI, coital incontinence is likely to improve.</td>
<td>3</td>
</tr>
<tr>
<td>Overall, sexual function is unlikely to deteriorate following SUI surgery.</td>
<td>3</td>
</tr>
<tr>
<td>There is no consistent evidence that the risk of post-operative sexual dysfunction differs between midurethral sling procedures.</td>
<td>3</td>
</tr>
</tbody>
</table>
5.1.2.3 References


5.1.3 Single-incision slings
There is continued innovation to reduce the invasiveness of procedures for SUI. Single-incision mid-urethral slings have been introduced on the basis of providing mid-urethral support, using a variety of modifications to a short macroporous polypropylene tape. These modifications allow the tape to be fixed to the retropubic tissues, endopelvic fascia or obturator fascia, while avoiding the troublesome complications of obturator nerve injury or passage through the gracilis muscle or skin of the inner thigh, or through the retropubic space. These procedures are usually performed as day cases under local anaesthesia.

5.1.3.1 Questions
• In women with SUI, do ‘single-incision’ slings cure UI or improve QoL, or cause adverse outcomes?
• How does a ‘single-incision’ sling compare to other surgical treatments for SUI?

5.1.3.2 Evidence
Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in design between devices and it may be misleading to make general statements about them as a class of operations. It should also be noted that the TVTS device has now been withdrawn from the market, however, much of the evidence on single incisions slings applies to this device.

One systematic review has been published (1), which included RCTs and quasi-RCTs, comparing single-incision slings to either retropubic or transobturator mid-urethral slings. The literature search included non-English trials and unpublished studies. A further systematic review is currently being undertaken by the Cochrane centre (2).

The nine RCTs in the Abdel Fattah current Cochrane review included 758 participants, who were followed up for a mean of 9.5 months. There was poor reporting of allocation concealment, as well as poorly reported randomisation, resulting in a high risk of bias. One centre provided several of the studies. Seven studies included only patients with tension-free vaginal tape secure (TVTS). The remaining two studies include only patients with a Miniarc® device.

Meta-analysis showed that the outcome of single-incision sling insertion was consistently worse compared with mid-urethral slings in terms of patient-reported cure of UI. Single-incision techniques had a shorter operating time, lower blood loss and and lower pain levels compared to a standard mid-urethral sling. One RCT found no difference in effectiveness between two different methods of insertion of the TVTS device with 12 months’ follow-up (3). One RCT designed to compare the TVTS device to a standard retropubic mid-urethral sling in 280 women found a significantly lower objective cure at 2 months for TVTS and a higher complication rate and was terminated early (4). Another RCT (5) compared the TVTS device to a standard transobturator mid-urethral sling but was underpowered to show a statistical difference between the techniques. A small, three-treatment arm, phase II RCT compared standard transobturator mid-urethral sling to TVTS and Miniarc® devices (6). The results suggested that cure rates were lower for TVTS but no statistical analysis was presented.

A more recent RCT comparing the TVTS device to standard transobturator mid-urethral sling, not included in the Cochrane review, demonstrated a lower objective cure rate and lower pain levels for the TVTS device (7).

Another recent non-randomised study compared the TVTS to the Curemesh® device showed no difference
in outcomes at a minimum of 15.5 months (8). Similarly, a quasi-RCT comparing a standard transobturator midurethral sling to a Contasure® device found no difference in cure of UI or adverse events (9).

Another recent RCT compared in 80 women a transobturator tape against the single incision sling Tissue Fixation System (TFS). Cure rates were significantly higher with the TFS tape (84% vs. 90%, respectively) (10).

There are a number of case series with a minimum of 12 months’ follow-up, including five series using the Miniarc device (11-16), two series using the TVTS device (14, 17) and one series using the Minitape® device (18). The 12-month outcomes range from 52% objective cure to 92% subjective cure. Results from one study reporting outcome at 2 years found that only 10% of included participants remained cured (18). One study reported a 24% rate of de novo urgency, but generally there were few reported adverse effects (14).

The Ajust® device is a self-fixing single incision sling that allows adjustment of tension during insertion. A short-term RCT compared Ajust to obturator tape in 137 women with similar efficacy but lower pain levels and earlier return to normal activity (19). A single cohort study reported an 80% success rate (patient’s global impression of improvement) in 90 women after 12 months of follow-up (19).

There are no RCTs relating to the Solyx® device. There is one retrospective review of 63 women with short-term follow-up (20), and one report of 12 months’ follow-up of the Ophira® device 176 women (21). These studies did not report outcomes of interest for these Guidelines.

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-incision mid-urethral slings are as effective as other mid-urethral slings in improving SUI in women in the short term.</td>
<td>1b</td>
</tr>
<tr>
<td>Operation times for insertion of single-incision mid-urethral slings are shorter than for standard retropubic slings.</td>
<td>1b</td>
</tr>
<tr>
<td>Blood loss and immediate post-operative pain are lower for insertion of single-incision slings compared with standard mid-urethral slings.</td>
<td>1b</td>
</tr>
<tr>
<td>TVT Secur is less effective than other mid-urethral slings at medium-term follow-up*.</td>
<td>1b</td>
</tr>
<tr>
<td>There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with standard mid-urethral slings.</td>
<td>1b</td>
</tr>
</tbody>
</table>

*NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVTS) device.

5.1.3.3 References


5.1.4 **Adjustable sling**

Voiding dysfunction is an adverse effect of anti-incontinence procedures and may require further intervention, such as clean intermittent self-catheterisation. One possible cause is overcorrection of the anatomical...
deformity by the sling. Adjustable slings seek to overcome this problem because they enable the tension of the newly implanted sling to be increased or decreased, either during or shortly after the operation. An adjustable sling aims to optimise the balance between correcting the SUI, while allowing normal voiding to continue. However, this concept has not been adequately tested. There is still no evidence to show that being able to adjust the tension of a sling has a beneficial effect on outcome.

5.1.4.1 Questions
• In women with SUI, does an adjustable sling cure SUI and improve QoL or does it cause adverse outcome(s)?
• How does an adjustable sling compare to other surgical treatments for SUI?

5.1.4.2 Evidence
There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There is limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definition. Few studies include sufficient numbers of patients or have a long enough follow-up to provide useful evidence. The available devices have differing designs, making it difficult to use existing data to make general conclusions about adjustable slings as a class of procedure. Three adjustable sling devices were reviewed: Remeex®, Safyre®, Ajust®. The latter is an adjustable single-incision sling.

Remeex®
Two cohort studies included a total of 155 patients and had more than 22 months’ follow-up (1,2). The results showed that at least 86% of women had objective cure of SUI, with re-adjustment of the device required in up to 16% of women. Include data from Kaplan abstract.

Saffyre®
Two cohort studies included a total of 208 patients with a minimum of 12 months follow-up (3). The reported cure rate was up to 92% with adverse effects of late vaginal erosion in 8% and dyspareunia in 11% (4).

A non-randomised comparison of adjustable tape and transobturator tape in a single centre suggested fewer obstructive voiding symptoms in women receiving an adjustable tape though objective voiding parameters were no different (5).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of SUI in women.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that adjustable slings are superior to standard mid-urethral slings.</td>
<td>4</td>
</tr>
</tbody>
</table>

5.1.4.3 References

5.1.5 Bulking agents
Injection of a bulking agent into the submucosal tissues of the urethra is thought to increase the coaptation of the urethral walls, in turn leading to increased urethral resistance and improved continence. Whether
this is achieved through causing obstruction or improving the mucosa-to-mucosa sealing is unknown. The recommended site of injection varies with the bulking agent and numerous materials have been developed for this use over 20 years (see below). They are injected transurethrally or paraurethrally under urethroscopic control, or alternatively using a purpose-made device (implacer), which reliably positions the needle-tip under local anaesthetic at the required position in the urethral wall.

5.1.5.1 Question
In women with SUI, does injection of a urethral bulking agent cure SUI or improve QoL, or cause adverse outcomes?

5.1.5.2 Evidence
There have been two Cochrane systematic review (1,2) and one independent SR (3) (Ghoneim et al.), which reported on 12 RCTs or quasi-RCTs of injectable agents. In general, the trials were only of moderate quality and small and many of them had been reported in abstract form. Wide confidence intervals meant a meta-analysis was not possible. Since the Cochrane review, two further RCTs have been reported (4,5).

Each injectable product has been the subject of many case series. Short-term efficacy in reducing the symptoms of SUI has been demonstrated for all materials used. In 2006, NICE published an extensive review of these case series (6). These case series have added very little to the evidence provided by RCTs. There has been only one placebo-controlled RCT, in which an autologous fat injection was compared with the placebo of a saline injection.

Polytetrafluoroethylene (Polytef)
There are no RCTs available. NICE 2006 (6) did not recommend this treatment because of the high incidence of adverse events.

Glutaraldehyde cross-linked bovine collagen (Contigen)
Most evidence from RCTs of the efficacy of collagen comes from six trials, in which collagen has been used as a comparator to an experimental synthetic product (see below). This implies that collagen has been regarded as the ‘gold standard’ bulking agent. In one RCT, collagen was compared to open surgery (7).

Autologous fat
One study found no difference in efficacy between autologous fat and saline injection (22% vs. 20% improvement at 3 months, respectively) (8). Due to a fatality from fat embolism, NICE 2006 (6) and the Cochrane Review (2) made a strong recommendation that this treatment should not be used.

Silicon particles (Macroplastique™)
Silicon particles have been compared to collagen in two RCTs, only one of which has been published as a full article (9). No significant difference in efficacy was found.

Carbon beads (Durasphere™)
Carbon beads have been compared to collagen in two RCTs (5,10). Although one study lacked appropriate statistical power, the other was a good-quality study (n = 235), with 12 months’ follow-up, that showed no difference in efficacy.

Calcium hydroxylapatite (CaHA) (Coaptite™)
A study with small sample size comparing collagen to hydroxylapatite found the failure rate was significantly higher at 6 months for collagen (6/18 vs. 3/22, respectively) (11).

Ethylene vinyl alcohol copolymer (EVOH) (Uryx™)
There is one RCT (n = 210), comparing ethylene copolymer to collagen, which demonstrated similar efficacy at 6 months’ follow-up (12).

Porcine dermal implant (Permacol™)
There is one very small RCT comparing porcine dermis to silicon particles. There was no significant difference in failure rates between the two procedures at 6 months’ follow-up (13).

Hydrogel cross-linked with polyacrilamide (Bulkamid™)
No RCT data are available. There is a single multicentre case series of 135 women, which reported 66% success rate with 35% participants requiring re-injection (14).
Non-animal stabilised hyaluronic acid/dextranomer (NASHA/Dx) (Zuidex™)

There is one RCT, comparing dextranomer (placed in mid-urethra) to collagen injection (at the bladder neck). At 12 months, results were inferior in women given dextranomer (15). However, this product has now been withdrawn from the market because of high complication rates.

Stem cells

Early reports of dose-ranging studies (16) suggest that stem cell injection is a safe procedure in the short term. However, its efficacy (compared to its bulking effect) has yet to be established.

Comparison with open surgery

Two RCTs studies compared collagen injection to conventional surgery for SUI (autologous sling vs. silicon particles and collagen vs. assorted procedures). The studies reported greater efficacy but higher complication rates for open surgery. In comparison, collagen injections showed inferior efficacy but equivalent levels of satisfaction and fewer serious complications (7,17).

Another trial found that a perurethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection (18). A recent small RCT found no difference in efficacy between a mid-urethral and bladder neck injection of collagen (4).

### Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periurethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.</td>
<td>2a</td>
</tr>
<tr>
<td>Repeat injections to achieve therapeutic effect are often required.</td>
<td>2a</td>
</tr>
<tr>
<td>Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.</td>
<td>2a</td>
</tr>
<tr>
<td>Adverse effect rates are lower compared to open surgery.</td>
<td>2a</td>
</tr>
<tr>
<td>There is no evidence that one type of bulking agent is better than another type.</td>
<td>1b</td>
</tr>
<tr>
<td>Transperineal route of injection may be associated with a higher risk of urinary retention compared to the transurethral route.</td>
<td>2b</td>
</tr>
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### Recommendations for surgery for uncomplicated stress urinary incontinence in women

<table>
<thead>
<tr>
<th>Recommendations for surgery for uncomplicated stress urinary incontinence in women</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer the mid-urethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.</td>
<td>A</td>
</tr>
<tr>
<td>Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if mid-urethral sling cannot be considered.</td>
<td>A</td>
</tr>
<tr>
<td>Inform older women with stress urinary incontinence about the increased risks associated with surgery, including the lower probability of success.</td>
<td>B</td>
</tr>
<tr>
<td>Inform women that any vaginal surgery may have an impact on sexual function.</td>
<td>C</td>
</tr>
<tr>
<td>Warn women who are being offered a retropubic insertion synthetic sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.</td>
<td>A</td>
</tr>
<tr>
<td>Warn women who are being offered transobturator insertion of mid-urethral sling about the higher risk of pain and dyspareunia in the longer term.</td>
<td>A</td>
</tr>
<tr>
<td>Warn women undergoing autologous facial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.</td>
<td>A</td>
</tr>
<tr>
<td>Do a cystoscopy as part of retropubic insertion of a mid-urethral sling, or if difficulty is encountered during transobturator sling insertion, or if there is a significant cystocele.</td>
<td>C</td>
</tr>
<tr>
<td>Women being offered a single-incision sling device should be warned that long-term efficacy remains uncertain.</td>
<td>C</td>
</tr>
<tr>
<td>Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.</td>
<td>A</td>
</tr>
<tr>
<td>Only offer adjustable mid-urethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.</td>
<td>C</td>
</tr>
<tr>
<td>Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.</td>
<td>A</td>
</tr>
</tbody>
</table>

5.1.5.3 Research priorities

- What is the influence of surgical skill on the outcome of surgery?
- How does minimally invasive first-line surgery compare to conservative treatment in treatment of women with SUI?
• How do single-incision slings compare to gold standard operations in treatment of women with SUI?
• What is the effect of varying tension of a midurethral sling on cure or improvement of SUI?

5.1.5.4 References
5.2 Complicated SUI in women
This section will address surgical treatment for women who have had previous surgery for SUI, which has failed, or those women who have undergone previous radiotherapy affecting the vaginal or urethral tissues. Neurological lower urinary tract dysfunction is not considered because it is reviewed by the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction (1). Women with associated genitourinary prolapse are included in this 2013 edition (see section 5.3).

5.2.1 Colposuspension or sling following failed surgery
The reported failure rates from any operation for SUI vary widely from 5-80%, depending on how failure has been defined. Even with a very tight definition this implies that, of the many thousands of women undergoing primary surgery for SUI, there will be hundreds who later require further surgery for recurrent symptoms. A primary operation may fail from the start or in other cases occur years after the original procedure. There may be persistent or recurrent SUI, or the development of de novo UUI. This means that careful urodynamic evaluation becomes an essential part of the work-up of these patients.

However, the underlying reasons for failure are poorly understood. Consequently, the decision on which operation to offer in the secondary setting is usually driven by individual opinion about these mechanisms, familiarity with certain procedures, and experience in personal series. Most surgeons believe that the results of any operation will be inferior to the same operation used as a primary procedure, and will warn their patients accordingly.

The EAU Panel has limited their literature search to the surgical management of recurrent SUI. It is presumed that the management of de novo UUI will follow the pathway recommended for the management of primary UUI and DO, starting with conservative management. The Panel has not addressed the management of voiding difficulty because this does not require further treatment for incontinence.

5.2.1.1 Question
In women who have had failed surgery for SUI, what is the effectiveness of any second-line operation, compared to any other second-line operation, in terms of cure or improvement of UI, QoL or adverse events.

5.2.1.2 Evidence
Most of the data on surgery for SUI refers to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients is usually too small to allow meaningful comparisons.

The latest International Consultation on Incontinence includes a review of this topic (2) up till 2008 and the subject has also been reviewed by Ashok (3) and Lovatsis et al. (4). A further literature review has been carried out since that time by the Panel.

Cochrane reviews of individual operative techniques have not included separate evaluation of outcomes in women undergoing second-line surgery. However, there is a current protocol to address this issue (5).

Only one RCT was found (abstract only) comparing TVT to laparoscopic colposuspension in women with recurrent SUI. This small study found similar cure rates and adverse events in the short term for both procedures (6).

Post-hoc subgroup analysis of high-quality RCTs comparing one procedure to another have confirmed

higher failure rates for both SUI and other complications of surgery, for all women undergoing second-line surgery, whichever intervention they had undergone (7-10). However a history of prior surgery for UI is not an independent predictor of failure at 2 years in women undergoing open colposuspension or autologous fascial sling (8).

One large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for abdominal perineal sling (11).

Several cohort studies have reported outcomes for TVT specifically for primary and secondary cases. Evidence on the effectiveness of second-line retropubic tapes conflicts with some series showing equivalent outcomes for primary and secondary cases (12,13), whilst other research has shown inferior outcomes for secondary surgery (14,15). Other confounding variables make meaningful conclusions difficult.

There are numerous small case series reporting satisfactory outcomes for redo procedures of many types, but this evidence is difficult to interpret in a way that allows conclusions about the best therapeutic approach.

Systematic review of older trials of open surgery for SUI suggest that the longer-term outcomes of redo open colposuspension may be poor compared to autologous fascial slings (16). Successful results have been reported from midurethral slings after various types of primary surgery, while good outcomes are reported for both repeat TVT and for ‘tightening’ of TVT, but data are limited to small case series only.

Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
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<tbody>
<tr>
<td>The risk of treatment failure from surgery for SUI is higher when women have had prior surgery for incontinence or prolapse.</td>
<td>1</td>
</tr>
<tr>
<td>Most procedures will be less effective when used as a second-line procedure than when used for primary surgery.</td>
<td>2</td>
</tr>
<tr>
<td>In women who have had more than two procedures for SUI, the results of open colposuspension are inferior to autologous fascial sling.</td>
<td>2</td>
</tr>
<tr>
<td>There is no evidence that any other operation is superior to another in the cure or improvement of SUI in women who have had previous surgery.</td>
<td>3</td>
</tr>
</tbody>
</table>

5.2.1.3 References


5.2.2 External compression devices for intrinsic sphincter deficiency
Some of the earliest techniques for treating SUI simply applied intra-corporeal compression external to the urethra. External compression devices are still widely used in the treatment of recurrent SUI after the failure of previous surgery. They are also commonly used in women with neurological LUTD, in whom there is thought to be profound intrinsic failure of the sphincter mechanism, characterised by very low leak point pressures or low urethral closure pressures. This is a common finding following failure of a previous operation for incontinence but should be confirmed by urodynamic evaluation.

There are two intracorporeal external urethral compression devices available. They are the adjustable compression therapy (ACT) device and the artificial urinary sphincter (AUS). Using US or fluoroscopic guidance, the ACT device is inserted by placement of two inflatable spherical balloons on either side of the bladder neck. Each volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. More recently, an adjustable artificial urinary sphincter (Flowsecure) has been introduced. It has the added benefit of ‘conditional occlusion’, enabling it to respond to rapid changes in intra-abdominal pressure.

5.2.2.1 Question
- In women with SUI, does insertion of an external compressive device cure SUI, improve QoL or cause adverse outcomes?
- How do external compression devices compare to other surgical treatments for SUI?

5.2.2.2 Evidence
The major advantage of AUS over other anti-incontinence procedures is the perceived ability of women to be able to void normally (1). However, voiding dysfunction is a known side effect, with a lack of data making it difficult to assess its importance. Because of significant differences in design between devices and in selection criteria between case series, results obtained with specific devices cannot be extrapolated generally to the use of adjustable devices. A recent consensus report has standardised the terminology used for reporting complications arising from implantation of materials into the pelvic floor region (2).

Artificial urinary sphincter (AUS)
The 2011 Cochrane review on AUS (3) applies only to men with post-prostatectomy incontinence. A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women (4).
There are no RCTs regarding the AUS in women. There are a few case series in women, including four series (n = 611), with study populations ranging from 45 to 215 patients and follow-up ranging from 1 month to 25 years (5-8). Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cures in 59-88% of patients. However, common side effects included mechanical failure requiring revision (up to 42% at 10 years) and explantation (5.9-15%). In a retrospective series of 215 women followed up for a mean of 6 years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy (8). Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation (6).

A newly introduced artificial sphincter using an adjustable balloon capacity through a self-sealing port, and stress responsive design, has been introduced to clinical use. A series of 100 patients reported 28% explantation at 4 years but the device has undergone redesign and more up to date evidence is awaited (9).

Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions (10, 11).

Adjustable compression device (ACT)
There are no RCTs on use of the ACT device. There are four case series (n = 349), with follow-up ranging from 5 to 84 months (12-15). An improvement in UI outcomes was reported, ranging from 47% objective cure to 100% subjective improvement. However, most patients required adjustment to achieve continence and 21% required explantation.

Evidence summary

| Implantation of an artificial sphincter can improve or cure incontinence in women with SUI caused by sphincter insufficiency. | LE 3 |
| Implantation of the ACT device may improve complicated UI. | LE 3 |
| Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the adjustable compression device. | LE 3 |
| Explantation is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy. | LE 3 |

Recommendations for surgery for complicated stress urinary incontinence in women

| The choice of surgery for recurrent stress urinary incontinence should be based on careful evaluation of the individual patient including video-urodynamics. | GR C |
| Warn women with recurrent stress urinary incontinence, that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications. | GR C |
| Consider secondary synthetic sling, colposuspension or autologous sling as first options for women with complicated stress urinary incontinence. | GR C |
| Do not undertake open colposuspension in women who have had more than two previous operations for incontinence. | GR C |
| Implantation of AUS or ACT for women with complicated stress urinary incontinence should only be offered in high-volume centres. | GR C |
| Warn women receiving AUS or ACT that, even in high-volume centres, there is a high risk of complications, mechanical failure or a need for explantation. | GR C |

AUS = artificial urinary sphincter; ACT = adjustable compression therapy.

Research priorities
What is the most effective surgical procedure in women requiring second-line surgery for SUI after failure of a previous operation?

References


5.3 Women with both SUI and pelvic organ prolapse

There is a clear association between the presence of POP and SUI. Although the subject of prolapse is not part of the remit of these Guidelines, the extent to which it impacts on the management of SUI will be addressed. The aim is to assess the surgical options available to women who require surgery for POP and who have associated UI (either symptomatic and asymptomatic), and to assess the value of prophylactic anti-incontinence surgery in women with no evidence of UI.
5.3.1 Questions

• In women with both SUI and POP, does combined surgery for POP and SUI provide better cure or improvement of UI compared to surgery for POP or SUI alone?

• In continent women with POP alone does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?

• In women with POP and occult SUI (i.e. seen only on urodynamics), does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?

5.3.1.1 Evidence

Women with POP and associated UI
A Cochrane review in 2011 included six trials of moderate quality (1).

Incontinence post-operative rates were 15% for combined surgery (where a mid-urethral sling was used as the incontinence operation) versus 44% with POP surgery alone, and this significant difference persisted beyond 12 months. There is significant heterogeneity among trials and the results are mainly driven by one study which compared a mid-urethral sling + anterior repair versus anterior repair alone. No other studies in this group used a mid-urethral sling as a comparator in the combined surgery arm. There was a significantly higher rate of adverse events reported in the combined surgery group.

A recent RCT has shown no difference in the 5-year outcomes when colposuspension was used as the incontinence procedure (persistent UI in 56.5% with combined surgery vs. 40.9% with POP surgery alone) (2), although the longer-term outcomes suggested higher UI rates in women undergoing colposuspension (3). The addition of this study to the Cochrane meta-analysis makes no difference to the conclusions. Another two small RCTs showed no difference in outcomes (4,5).

Continent women with POP
The 2011 Cochrane review included three trials of moderate quality showing that post-operative incontinence rates at < 12 months were 21.7% in the combined surgery group versus 31.7% in POP surgery alone, mainly driven by one study (6).

One trial reported better QoL outcomes following combined surgery. There was no difference in rate of adverse events reported.

Two other trials have shown significantly higher rates of post-operative UI for women undergoing prolapse surgery alone, but the incidence of adverse events such as bladder perforation, UTI, bleeding, and voiding dysfunction was higher in the combined surgery patients. The number needed to treat to prevent incontinence in one woman was 6.3 at 12 months (2,7).

Women with POP and occult UI
In this group of women, the presence of occult UI was dependent on a urodynamics diagnosis which, in turn, is dependent on the performance of the prolapse reduction stress test. The 2011 Cochrane review included five trials of moderate quality addressing this point. Overall, 83% of women are free of objective evidence of SUI at 12 months with combined surgery versus 52% with prolapse surgery alone. There was no reported difference in the incidence of adverse events. The 2011 OPUS trial (n = 337) showed that women had an eight-fold higher risk of UI if the POP surgery was not accompanied by an operation for SUI (7). The prolapse reduction stress test was positive in 29.6% women in the combined treatment arm (using TVT) and 71.9% women in the POP repair + sham incision treatment arm.

It is difficult to generalise the results of trials using very different procedures to treat UI. Studies using mid-urethral slings generally have shown more significant differences in UI outcomes with combined procedures than when other types of anti-incontinence procedure have been used. Individual patient characteristics may play the most important role in shaping treatment decisions. The evidence suggests that most women may be dry after prolapse surgery alone but the risks of repeat surgery, should it become necessary, may outweigh the potential benefits.
Evidence summary

<table>
<thead>
<tr>
<th>Women with prolapse + UI</th>
<th>LE</th>
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<tbody>
<tr>
<td>• Surgery for POP + SUI shows a higher rate of cure in the short term than POP surgery alone</td>
<td>1a</td>
</tr>
<tr>
<td>• There is conflicting evidence on the relative benefit of combined surgery long term</td>
<td>1b</td>
</tr>
<tr>
<td>• Combined surgery for POP+SUI carries a higher risk of adverse events</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continent women with POP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Are at risk of developing UI post-operatively</td>
<td>1a</td>
</tr>
<tr>
<td>• The addition of a prophylactic anti-incontinence procedure reduces the risk of post-operative UI</td>
<td>1b</td>
</tr>
<tr>
<td>• The addition of a prophylactic anti-incontinence procedure increases the risk of adverse events to the same extent</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women with prolapse and occult SUI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Surgery for POP + SUI shows a higher rate of cure in the short term than POP surgery alone</td>
<td>1a</td>
</tr>
<tr>
<td>• Combined surgery for POP + SUI carries a higher risk of adverse events</td>
<td>1b</td>
</tr>
</tbody>
</table>

Recommendations for women requiring surgery for bothersome POP who have symptomatic or unmasked stress urinary incontinence

<table>
<thead>
<tr>
<th>Offer simultaneous surgery for POP and stress urinary incontinence.</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warn women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone.</td>
<td>A</td>
</tr>
</tbody>
</table>

Recommendations for women requiring surgery for bothersome POP without symptomatic or unmasked stress urinary incontinence

<table>
<thead>
<tr>
<th>Warn women that there is a risk of developing de novo stress urinary incontinence after prolapse surgery.</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform women that the benefit of prophylactic stress urinary incontinence surgery is uncertain.</td>
<td>C</td>
</tr>
<tr>
<td>Warn women that the benefit of surgery for stress urinary incontinence may be outweighed by the increased risk of adverse events with combined surgery compared to prolapse surgery alone.</td>
<td>A</td>
</tr>
</tbody>
</table>

POP = pelvic organ prolapse.

5.3.1.2 References

5.4 Men with SUI

5.4.1 Bulking agents in men

Injection of bulking agents has been used to try and improve the coaptation of a damaged sphincter zone. More recently, more modern compounds have been used to treat female and male SUI, e.g. bovine collagen (Contigen™), cross-linked polyacrylamide hydrogel (Bulkamid™) and dextranomer/hyaluronic acid copolymer
(Deflux™), pyrolytic carbon particles (Durasphere™) and polymethylsyloxane (Macroplastique™). Initial reports showed limited efficacy in treating incontinence following radical prostatectomy incontinence (1,2).

5.4.1 Question
In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

5.4.1.2 Evidence
Most studies are case series with small sample sizes. Small cohort studies showed a lack of benefit using a number of different materials (3,4). However, polyacrylamide hydrogel resulted in limited improvement in QoL without curing the UI (3). A Cochrane review on the surgical treatment of post-prostatectomy incontinence found only one study that fulfilled the inclusion criteria (5). A prospective, randomised study compared the AUS to silicon particles (Macroplastique™) in 45 patients (1). Eighty-two per cent of patients receiving an AUS were continent compared to 46% of patients receiving silicone particles. In patients with severe incontinence, this difference was significant, but in patients with moderate and mild incontinence, the difference was less.

Evidence summary LE
<table>
<thead>
<tr>
<th>Evidence statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no evidence that bulking agents cure post-prostatectomy incontinence.</td>
<td>2a</td>
</tr>
<tr>
<td>There is weak evidence that bulking agents can offer temporary, short-term, improvement in QoL in men with post-prostatectomy incontinence.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that one bulking agent is superior to another.</td>
<td>3</td>
</tr>
</tbody>
</table>

5.4.1.3 References

5.4.2 Fixed male sling
As well as external compression devices and bulking agents, slings have been introduced to treat post-prostatectomy incontinence. Fixed slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery and cannot be re-adjusted post-operatively.

For the restoration of continence by these male slings, two concepts are now being proposed:
- Continence restoration by urethral compression (InVance®, Istop TOMS, Argus®)
- Continence restoration by repositioning the bulb of urethra (AdVance) (1).

In principle, the AUS can be used for all degrees of post-prostatectomy incontinence, while male slings are advocated for mild-to-moderate UI. However, the definitions of mild and moderate UI are not clear. The definition of cure, used in most studies, was no pad use or one security pad per 24 hours. Some authors used a stricter criterion of less than 2 g urine loss in a 24-hour pad test (2).
5.4.2.1 Question
In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

5.4.2.2 Evidence
Concerning the surgical treatment of post-prostatectomy incontinence, three recent literature reviews are available (3-5). There are a large number of uncontrolled case series concerning men implanted with several types of slings (6-13).

For the repositioning sling (AdVance), the benefit after a mean follow-up of 3 years has been published on 136 patients (14). Earlier data were available from other cohort studies, totalling at least 614 patients with a mean follow-up of between 3 months and 3 years. Subjective cure rates for the device vary between 8.6% and 73.7%, with a mean of 49.5%. Radiotherapy was a negative prognostic factor (12, 15). Post-operative voiding dysfunction occurred in 5.7-13.3%, while erosions and chronic pain were uncommon (0-0.4%) (2,6,14-20). The overall failure rate was about 20%.

The previously available “InVance” device has now been removed from the market.

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.</td>
<td>3</td>
</tr>
<tr>
<td>Men with severe incontinence, previous radiotherapy or urethral stricture surgery have poor outcomes from fixed male slings.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that one type of male sling is better than another.</td>
<td>3</td>
</tr>
</tbody>
</table>

5.4.2.3 References


5.4.3 Adjustable slings in males
Adjustability in male sling surgery attempts to adjust the tension of the sling post-operatively. Three main systems have been used in men: the Remex system, the Argus system and the ATOMS system.

5.4.3.1 Question
In men with post-prostatectomy incontinence or SUI, does insertion of an adjustable suburethral sling cure or improve SUI, improve QoL, or cause adverse outcomes?
5.4.3.2 Evidence
There are no prospective RCTs comparing adjustable male slings to any other procedure. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success. Some have been published only as conference abstracts.

Remeex® system
For the Remeex® system, only two abstracts, with conflicting findings, have been published. One study followed 19 patients for nearly 7 years and reported 70% success (1), with no explants, infections or erosions. The second study followed 14 patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% (2).

Argus® system
Data on the Argus® system have been reported for 404 men, but only four series have reported on more than 50 patients (3-5), with the longest follow-up being 2.4 years. Success rates varied between 17% and 91.6%, with a mean of 57.6% predominantly reporting a subjective cure. The number of implants requiring re-adjustment was reported as between 22.9% and 41.5% (4,6,7). Infection of the device occurred in 5.4-8% (3,5,7). Erosions were reported in 5-10% (8,9). Urethral perforations occurred in 2.7-16% (3,5). Pain at the implant site was usually only temporary, but chronic pain has been reported (3,7-9). These complications resulted in explantation rates of 10-15% (4,6).

The ATOMS system consists of a mesh implant with an integrated adjustable cushion, which uses a titanium port left in the subcutaneous tissue of the lower abdomen for adjustment of cushion volume. Some initial reports show objective cure rates of 60.5% and improvement rates of 23.7% but with the need for up to nine post-operative adjustments (10, 11).

### Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited evidence that adjustable male slings can cure or improve SUI in men.</td>
<td>3</td>
</tr>
<tr>
<td>There is limited evidence that early explantation rates are high.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that adjustability of the male sling offers additional benefit over other types of sling.</td>
<td>3</td>
</tr>
</tbody>
</table>

5.4.3.3 References


5.4.4 Compressive devices in males

External compression devices can be divided into two types: circumferential and non-circumferential compression of the urethral lumen (1). The artificial urinary sphincter (AUS) has been used for more than 30 years and is the standard treatment for moderate-to-severe male SUI. Most data available on the efficacy and adverse effects of AUS implantation is from older retrospective cohort studies with RCTs not performed due to the lack of a comparator. Several modifications of the standard single-cuff transperineal technique have been described, including transcorporeal implantation, double-cuff implants and trans-scrotal approaches (2). Men considering insertion of an AUS should understand that they must be able to operate a scrotal pump, requiring adequate dexterity and cognitive function. If the ability of an individual to operate the pump is uncertain, it may not be appropriate to implant an AUS. There are several recognised complications of AUS implantation, e.g. mechanical dysfunction, urethral constriction by fibrous tissue, erosion and infection.

The non-circumferential compression devices consist of two balloons placed close to the anastomotic urethra. The balloons can be filled and their volume can be adjusted post-operatively through an intrascrotal port.

5.4.4.1 Question

In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL, or cause adverse outcomes?

5.4.4.2 Evidence

Artificial urinary sphincter

Although the AUS is considered to be the standard treatment for men with SUI, there are two systematic reviews (2,3) presenting limited evidence, of generally poor quality, except for one RCT comparing with bulking agents (4). More recent case series confirm the previous data (5,6). A continence rate of about 80% can be expected, while this may be lower in men who have undergone pelvic radiotherapy (1).

Trigo Rocha et al. published a prospective cohort study on 40 patients with a mean follow-up of 53 months (7). Pad use was reduced significantly and continence was achieved in 90%, with a significant improvement in QoL. The revision rate was 20%. From all urodynamic parameters, only low bladder compliance had a negative impact on the outcome, although another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation (8).

The penoscrotal approach was introduced to limit the number of incisions and to allow simultaneous implantation of penile and sphincter prostheses. It is uncertain whether this approach alters the outcome (9-11). The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking (12, 13).

The dual-cuff placement was introduced to treat patients who remained incontinent with a single 4-cm cuff in place. However, it has not improved control of UI, while the availability of a 3.5-cm cuff may have eliminated
the need for a dual cuff (14-16). Patients who experienced complete continence after AUS implantation had a higher erosion risk (17). One small series reported results of AUS implantation after failure of previous Advance sling, showing no difference in efficacy between secondary and primary implantation (18).

**Non-circumferential compression device (ProAct®)**

There have been trials to treat post-prostatectomy SUI by insertion of a device consisting of balloons with adjustable volume external to the proximal bulbar urethra. A prospective cohort study (n = 128) described the functional outcome as 'good' in 68%, while 18% of the devices had to be explanted (19). A subgroup of radiotherapy patients only had 46% success and a higher percentage of urethral erosions.

A quasi-randomised trial comparing a non-circumferential compression device (ProAct®) with bone-anchored male slings found both types of device resulted in similar improvement of SUI (68% vs. 65%, respectively) (20). Other prospective series have shown similar continence outcomes, but several re-adjustments of the balloon volume were required to achieve cure. Adverse events were frequent, leading to an explantation rate of 11-58% (2,21-25). Although most studies have shown a positive impact on QoL, a questionnaire study showed that 50% of patients were still bothered significantly by persistent incontinence (26).

A newly introduced artificial sphincter using an adjustable balloon capacity through a self-sealing port, and stress responsive design has been introduced to clinical use. A series of 100 patients reported 28% explantation at 4 years but the device has undergone redesign and more up to date evidence is awaited (27).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited evidence that primary AUS implantation is effective for cure of SUI in men.</td>
<td>2b</td>
</tr>
<tr>
<td>Long-term failure rate for AUS is high although device replacement can be performed.</td>
<td>3</td>
</tr>
<tr>
<td>Previous pelvic radiotherapy does not appear to affect the outcome of AUS implantation.</td>
<td>3</td>
</tr>
<tr>
<td>Men who develop cognitive impairment or lose manual dexterity will have difficulty operating an AUS.</td>
<td>3</td>
</tr>
<tr>
<td>Tandem-cuff placement is not superior to single-cuff placement.</td>
<td>3</td>
</tr>
<tr>
<td>The penoscrotal approach and perineal approach appear to give equivalent outcomes.</td>
<td>3</td>
</tr>
<tr>
<td>Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI.</td>
<td>3</td>
</tr>
<tr>
<td>The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations for surgery in men with stress urinary incontinence</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only offer bulking agents to men with mild post-prostatectomy incontinence who desire temporary relief of incontinence symptoms.</td>
<td>C</td>
</tr>
<tr>
<td>Do not offer bulking agents to men with severe post-prostatectomy incontinence.</td>
<td>C</td>
</tr>
<tr>
<td>Offer fixed slings to men with mild-to-moderate post-prostatectomy incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Warn men that severe incontinence, prior pelvic radiotherapy or urethral stricture surgery, may worsen the outcome of fixed male sling surgery.</td>
<td>C</td>
</tr>
<tr>
<td>Offer AUS to men with moderate-to-severe post-prostatectomy incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Implantation of AUS or ACT for men should only be offered in high volume centres.</td>
<td>C</td>
</tr>
<tr>
<td>Warn men receiving AUS or ACT that, even in high volume centres, there is a high risk of complications, mechanical failure or a need for explantation.</td>
<td>C</td>
</tr>
<tr>
<td>Do not offer non-circumferential compression device (ProACT®) to men who have had pelvic radiotherapy.</td>
<td>C</td>
</tr>
</tbody>
</table>

AUS = artificial urinary sphincter; ACT = artificial compression device.

### 5.4.4.3 Research priorities

What are the comparative indication, efficacy and risk of different operations for post-prostatectomy incontinence?

### 5.4.4.4 References


http://www.uroweb.org/events/abstracts-online/?AID=23216


5.5  Surgical interventions for refractory DO  
5.5.1  Intravesical injection of botulinumtoxinA  
Botulinum toxin (BTX) injections into the bladder wall are being increasingly used to treat persistent or refractory UUI in adult women, as well as in men despite the lack of high-quality data on BTX in males. Almost all reported studies have used BTX A (1,2). Injection techniques have not been standardised and the various studies differ with reference to the number of injections, the sites of injection and the injection volumes (1,2). Surgeons must realise that there are different products of botulinum toxin, onabotulinumtoxinA (botox in Europe) abobotulinumtoxinA (Dysport in Europe) and incobotulinum toxin (Xeomin) and that the doses are not interchangeable between the different products. The effects of repeat injection have not been well studied in patients with UUI. The most important adverse event is an increase in PVR that may require clean intermittent catheterisation (CIC), which is itself associated with an increased risk of UTIs (1,2).

5.5.1.1  Question  
In adults with refractory UUI, does botulinum toxin injection in the bladder wall lead to a reduction in the number of incontinence episodes and/or to a higher percentage of continent patients compared to placebo?

5.5.1.2  Evidence  
Three systematic reviews on the use of BTX have been published (1-3). Only the last review used cure rate as an outcome measure. It included data from a new dose-finding study (4) and supplementary data obtained from the authors (5), including dry rates at 6 and 12 weeks (results summarized in Table 6). The rate of de novo CIC was 9.1% for 100 U and 18.2% for 200 U. Higher cure rates but also higher PVR requiring CIC were found with higher doses.
Table 6: (summarising the likelihood of achieving continence for varying doses of botulinum toxin)

<table>
<thead>
<tr>
<th>BTX (onabotulinumtoxinA), dosage (U)</th>
<th>Odds ratio for becoming dry (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>2.28 (0.95-5.49; p = 0.07)</td>
</tr>
<tr>
<td>100</td>
<td>4.39 (1.91-10.12; p = 0.0005)</td>
</tr>
<tr>
<td>150</td>
<td>4.96 [2.14-11.53; p = 0.0002]</td>
</tr>
<tr>
<td>200</td>
<td>4.34 [2.49-7.59; p &lt; 0.0001]</td>
</tr>
<tr>
<td>300</td>
<td>7.05 (2.68-18.51, p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

Although 300 U was shown to be the most efficacious dose, it is not a recommended dose because of the high rates of PVR requiring CIC. A dose of 100-200 U seems to have comparable efficacy in the meta-analysis. As part of this meta-analysis, two small RCTs comparing BTX doses between 100 and 200 units (6,7) showed no difference in efficacy for different doses. A further large RCT has been presented in abstract form at both American Urological Association and International Continence Society meetings, confirming the efficacy of onabotulinumtoxinA 100 U against placebo (8).

The QoL after onabotulinumtoxin administration has been shown to be sustained for 36 weeks (5) and in another study the gains in QoL achieved by increasing the dose, were marginal (9).

Successful UUI treatment with onabotulinumtoxinA does not appear to be related to the existence of DO. In a subanalysis of the Dmochowsky dose-finding study, no differences were found regardless of the occurrence of DO at baseline (5). Likewise, onabotulinumtoxinA improved UUI in a cohort of 5 male and 27 female patients with OAB and without DO (10).

Other systematic reviews (1,2) showed variation in the number of injections given and dilutions of BTX used, though 20 mL volume given at 20 sites was the most common. The choice of injection site did not appear to impact on efficacy or adverse events. However, two recent small RCTs show conflicting results on whether trigonal injection alters the efficacy of BTX injection; one study having found no difference between including trigonal injection and avoidance of the trigone (11), whilst another study showed superior symptomatic improvement if the trigone was included in the injection protocol (2), though UUI was no specifically evaluated in the latter study.

Cohort studies have shown the effectiveness of botulinum toxin injections in the elderly and frail elderly (12), though comparison of cohort groups suggests that there is a lower success rate in the frail elderly and also a higher rate of increased PVR (> 150 mL) in this group (11).

A recent RCT compared onabotulinumtoxinA injection to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed a similar reduction in urge urinary incontinence episodes over the course of 6 months (13). Patients receiving onabotulinumtoxinA were more likely to have complete resolution of UUI (27% vs. 13%, p = 0.003), but also had higher rates of urinary retention during the initial 2 months (5% vs 0%) and of UTIs (33% vs. 13%). Patients taking antimuscarinics were more likely to have dry mouth.

Dowson et al. (14) reported in a cohort of 100 patients a rapid decline of the patients willing to receive repeated onabotulinumtoxinA 200 U injections. In fact, 25 patients abandoned the treatment after the first injection and more 12 after the second injection. Fear of de novo CIC, poor response and treatment invasiveness were given as the major reasons for discontinuation.

Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single treatment session of intravesical onabotulinumtoxinA (100-300 U) is more effective than placebo at curing UUI and improving UUI and QoL for up to 12 months.</td>
<td>1a</td>
</tr>
<tr>
<td>Doses of onabotulinumtoxinA above 100 U are associated with an increased risk of de novo CIC.</td>
<td>1a</td>
</tr>
<tr>
<td>Doses of onabotulinumtoxinA above 100 U do not add additional improvement in QoL.</td>
<td>1b</td>
</tr>
<tr>
<td>There is no evidence that repeated injections of botulinumtoxinA have reduced efficacy.</td>
<td>3</td>
</tr>
<tr>
<td>There is a high risk of increased PVR when injecting elderly frail patients.</td>
<td>3</td>
</tr>
<tr>
<td>There is a high risk of UTI in those who require CIC.</td>
<td>1b</td>
</tr>
<tr>
<td>There is no evidence that one technique of injecting botulinumtoxinA is more efficacious or harmful than another.</td>
<td>1b</td>
</tr>
</tbody>
</table>
OnabotulinumtoxinA 100 U is superior to solifenacin in curing severe forms of UUI.  
Repeated injections of onabotulinumtoxinA may be associated with a high discontinuation rate.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer botulinum toxin A intravesical injections to patients with urge urinary incontinence refractory to antimuscarinic therapy.</td>
<td>A</td>
</tr>
<tr>
<td>Always check the botulinum toxin brand before injection, as units among the available brands are not interchangeable.</td>
<td>A</td>
</tr>
<tr>
<td>Offer onabotulinumtoxinA 100 U as initial dose to minimise the risk of urinary retention and urinary tract infection.</td>
<td>A</td>
</tr>
<tr>
<td>Warn patients of the limited duration of response, the possible prolonged need to self-catheterise (ensure that they are willing and able to do so) and the associated risk of urinary tract infection.</td>
<td>A</td>
</tr>
<tr>
<td>Patients should also be informed of the licensing status of botulinumtoxinA, and that long-term adverse effects, although improbable, remain uncertain.</td>
<td>A</td>
</tr>
</tbody>
</table>

5.5.1.4. Research priorities
- What is the most effective method of injecting botulinum toxin in terms of the site of injection, number of injections, and optimum dilution of the toxin?
- What is the long-term effect of repeated intravesical injection of botulinum toxin?

5.5.1.3 References


5.5.2 Sacral nerve stimulation (neuromodulation)

Under fluoroscopic control, an electrode is placed percutaneously in the sacral foramen alongside a sacral nerve, usually S3, in the first stage of a two-stage implantation (FS2S). Once it has been shown that the patient can respond, the patient proceeds to the second stage of implantation, in which the electrode is connected by cables under the skin to an implanted, programmable, pulse generator. The generator provides stimulation within established stimulation parameters. In earlier techniques for stimulating the sacral nerve, a temporary test (wire) electrode was placed near the nerve, and then percutaneous nerve evaluation (PNE) and test stimulation, provided by an external pulse generator, was performed. Generally, the PNE lasted for 5-7 days.

More recently, the permanent electrode has been used for a longer test phase, as part of a two-stage procedure. Once the PNE or FS2S has been shown to be successful, the patient proceeds to full implantation with the pulse generator. Patients, in whom selected symptoms of UUI are reduced by more than 50% during the test phase, are candidates for the permanent implant. Schmidt et al. first described the technique of PNE of the S3 sacral nerve (1). The two-stage implant was introduced by Janknegt et al. (2). Spinelli et al. introduced the minimally invasive percutaneous implantation of a tined lead (3).

5.5.2.1 Question

In adults suffering from refractory UUI, what is the clinical effectiveness of sacral nerve neuromodulation compared to alternative treatments?

5.5.2.2 Evidence

A Cochrane review of the literature until March 2008 (4) identified three RCTs that investigated sacral nerve stimulation in patients with refractory UUI. One of these RCTs was only published as an abstract and is not considered here (5,6). The quality of the other two RCTs was poor. No details of method of randomisation or concealment of randomisation were given. Assessors were not blind to the treatment allocation; it was impossible to blind the patients since all had to respond to a PNE before randomisation. In addition, the numbers randomised did not match the numbers in the results in these two studies.

One multicentre RCT involved implantation of half of the participants (5), while the remaining patients formed the control group (delayed implantation) by staying on medical treatment for 6 months. The control group was subsequently offered implantation. Fifty percent of the immediately implanted group had > 90% improvement in UUI at 6 months compared to 1.6% of the control group (5). The other RCT (6) achieved similar results, although these patients had already been included in the first report (5). However, Weil et al. (6) showed that the effect on generic QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions.

The results of 17 case series of patients with UUI, who were treated early in the experience with sacral nerve stimulation were reviewed (7). After a follow-up duration of between 1 and 3 years, approximately 50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50-90% improvement, and another 25% demonstrated < 50% improvement. Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33% (7).

In a subanalysis of the RCT, the outcomes of UUI patients, with or without pre-implant DO, were compared. Similar success rates were found in patients with and without urodynamic DO (8).

There are two case series describing the longer-term outcome of sacral nerve neuromodulation, with a mean or median follow-up of at least 5 years, in patients with refractory UUI (9,10). These studies have reported continued success (> 50% improvement on original symptoms) by 50-63% of patients available for follow-up. Only one study reported cure rates averaging 15% (10).
Technical modifications have been made, including a change in the anatomical site of the pulse generator, introduction of the tined lead and different test-phase protocols prior to definitive implantation. The lead may also be implanted using a minimally invasive percutaneous procedure (3). The effect of these changes on the outcome of implantation is uncertain.

### Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of UUI, but no sham controls have been used.</td>
<td>1b</td>
</tr>
<tr>
<td>In those patients who have been implanted, more than 50% improvement is maintained in at least 50% of patients at 5 years’ follow-up, and 15% remain cured.</td>
<td>3</td>
</tr>
<tr>
<td>One-stage implantation results in more patients receiving the final implant than occurs with prior temporary test stimulation.</td>
<td>4</td>
</tr>
</tbody>
</table>

### Recommendations

If available, offer to patients, who have urge urinary incontinence refractory to conservative therapy, the opportunity to be treated with sacral nerve neuromodulation before bladder augmentation or urinary diversion is considered. **A**

#### 5.5.2.3 Research priority

A RCT comparing a strategy of botulinum toxin injection, repeated as required, against a strategy of test and permanent sacral nerve neuromodulation, with accompanying health economic analysis, is required.

#### 5.5.2.4 References

5.5.3  **Cystoplasty/urinary diversion**

### 5.5.3.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The aim is to disrupt involuntary detrusor contraction, increase compliance and increase bladder capacity. The segment of bowel most often used is distal ileum, but any bowel segment can be used if it has the appropriate mesenteric length to reach the pelvic cavity without tension. One study did not find any difference between bivalving the bladder in the sagittal plane and bivalving it in the coronal plane (1,2).

There are no RCTs comparing bladder augmentation to other treatments for patients with UUI. Most often, bladder augmentation is used to correct neurogenic DO or small-capacity, low-compliant, bladders caused by fibrosis, tuberculosis, radiation or chronic infection.

A number of case series have been reported (2-9), but none within the last 10 years. All these series included a large proportion of patients with neurological bladder dysfunction. The largest case series of bladder augmentation in UUI included 51 women with UUI (3). At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. It is difficult to extract data on non-neurogenic patients from these case series, but in general the results for patients with idiopathic DO (58%) seemed to be less satisfactory than for patients with neurogenic overactivity (90%).

Adverse effects were common and have been summarised in a review over 5-17 years of more than 267 cases, 61 of whom had non-neurogenic UUI (10). In addition, many patients may require clean intermittent self-catheterisation to obtain adequate bladder emptying (Table 7).

#### Table 7: Complications of bladder augmentation

<table>
<thead>
<tr>
<th>Short-term complications</th>
<th>Affected patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel obstruction</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>1.5</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.75</td>
</tr>
<tr>
<td>Fistula</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-term complications</th>
<th>Affected patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean intermittent self-catheterisation</td>
<td>38</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>70% asymptomatic; 20% symptomatic</td>
</tr>
<tr>
<td>Urinary tract stones</td>
<td>13</td>
</tr>
<tr>
<td>Metabolic disturbance</td>
<td>16</td>
</tr>
<tr>
<td>Deterioration in renal function</td>
<td>2</td>
</tr>
<tr>
<td>Bladder perforation</td>
<td>0.75</td>
</tr>
</tbody>
</table>

### 5.5.3.2 Detrusor myectomy (bladder auto-augmentation)

Detrusor myectomy aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a bladder mucosal ‘bulge’ or pseudodiverticulum. It was initially described as an alternative to bladder augmentation in children (11). An additional, non-randomised study (12), which compared bladder augmentation with detrusor myectomy in adult patients with neurogenic and non-neurogenic bladder dysfunction, demonstrated a much lower incidence of short-term complications. However, the poor long-term results caused by fibrosis of the pseudodiverticulum led to the abandonment of this technique in patients with neurogenic dysfunction. A small study of five patients with UUI (13) showed good outcome in all patients at the initial post-operative visit, but clinical and urodynamic failure in four of the five patients at 3 months.

### 5.5.3.3 Urinary diversion

Urinary diversion remains a reconstructive option for patients, who decline repeated surgery for UI. It is rarely needed in the treatment of non-neurogenic UUI. There are no studies that have specifically examined this technique in the treatment of non-neurogenic UI, although the subject has been reviewed by the Cochrane group (1,14).
Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic DO.</td>
<td>3</td>
</tr>
<tr>
<td>Augmentation cystoplasty and urinary diversion are associated with high risks of short-term and longterm severe complications.</td>
<td>3</td>
</tr>
<tr>
<td>The need to perform clean intermittent self-catheterisation following augmentation cystoplasty is very common.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty with urinary diversion.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence on the long-term effectiveness of detrusor myectomy in adults with idiopathic DO.</td>
<td>3</td>
</tr>
</tbody>
</table>

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only offer augmentation cystoplasty to patients with detrusor overactivity incontinence who have failed conservative therapy, in whom the possibility of botulinum toxin and sacral nerve stimulation has been discussed.</td>
<td>C</td>
</tr>
<tr>
<td>Warn patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.</td>
<td>C</td>
</tr>
<tr>
<td>Do not offer detrusor myectomy as a treatment for urinary incontinence.</td>
<td>C</td>
</tr>
<tr>
<td>Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of urinary incontinence and who will accept a stoma.</td>
<td>C</td>
</tr>
<tr>
<td>Warn patients undergoing augmentation cystoplasty or urinary diversion of the high risk of short-term and long-term complications, and the possible small risk of malignancy.</td>
<td>C</td>
</tr>
<tr>
<td>Life-long follow-up is recommended for patients who have undergone augmentation cystoplasty or urinary diversion.</td>
<td>C</td>
</tr>
</tbody>
</table>

5.5.3.4 References


APPENDIX A: MIXED URINARY INCONTINENCE

A.1 Introduction
About one-third of women with UI have mixed urinary incontinence (MUI), rather than pure stress UI (SUI) or urge UI (UUI). In addition, a mixed combination of symptoms becomes more common with increasing age. However, although many studies include patients with MUI, it is rare for these studies to provide a separate analysis of MUI. It is therefore difficult to find evidence specifically related to MUI.

This issue was addressed by the EAU Panel after the initial work on the preceding chapters had been completed. It was realised that a crucial part of developing the clinical algorithms was to provide advice on how to manage this large group of patients. A decision was therefore made to include a rapid review of this topic, but the iterative process underpinning the Panel’s advice on this issue was necessarily shorter and less robust than for the preceding sections, and will be addressed more systematically for future editions.

A limited literature search was carried out from June 2008 for the terms, ‘mixed incontinence’ and ‘mixed urinary incontinence’ in PubMed. A separate search was also done for these terms within all known systematic reviews published since 2008 that had already been used for the rest of these Guidelines.

A.2 Question
In adults with MUI, is the outcome of a certain treatment different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

A.3 Evidence
No specific systematic reviews were found that addressed the above question. Systematic reviews on conservative therapies, drug therapy and surgery were also reviewed for any analyses of specific incontinence categories, but none were found.

However, a Cochrane report on pelvic floor muscle training (PFMT) (1) concluded that training was less likely to result in a cure in patients with MUI than in patients with pure SUI, though it is not clear from the report how this conclusion was reached.

A.3.1 RCTs in MUI population, which compare one treatment to another
An RCT in MUI patients compared intravaginal electrical stimulation to PFMT. No difference was seen in outcome, but this was a small underpowered study (2).

A.3.1.1 Duloxetine
In one RCT, involving 588 women, subjects were stratified into either stress-predominant, urge-predominant or balanced MUI groups and randomised to receive duloxetine or placebo. Duloxetine was effective in reducing episodes of incontinence and improving QoL compared to placebo in all subgroups (3).

A.3.1.2 Transvaginal obturator tape
In an RCT including 96 women with MUI, objective improvement was better for patients treated with transvaginal obturator tape + the Ingelman Sundberg operation versus patients treated with obturator tape alone (4).

A.3.1.3 Tolterodine
In an RCT of 854 women with MUI, tolterodine ER was effective compared to placebo in reducing frequency, urgency and UUI, but not SUI. These results show that the effect of tolterodine was not altered by the presence of SUI (5).

A.3.2 RCTs, including a subanalysis of MUI patients within treatment arms and allowing comparison to patients with pure SUI or pure UUI
Many RCTs include both patients with pure UI (stress or urge) and patients with MUI, in which pure UI predominates. However, very few RCTs report separate outcomes for MUI and pure UI groups.

A small and underpowered RCT (n = 71) compared delivery of PFMT, with or without an instructive audiotape. It showed equal efficacy for different types of UI (6).

An RCT in 121 women with SUI, UUI or MUI compared transvaginal electrical stimulation with sham stimulation and was found to be equally effective in UUI as in MUI (7).
A.3.2.1 Drugs
Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of subpopulations (8). In another study, secondary analysis showed that tolterodine compared to placebo (n = 1380) was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI (9). Similar findings apply to solifenacin (10, 11).

A.3.2.2 Surgery
Post-hoc analysis of the SISTER trial showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of pre-operative urgency. This applied to both stress-specific and non-stress incontinence outcomes (12).

A similar post-hoc review of an RCT comparing transobturator and retropubic midurethral slings showed that the greater the severity of pre-operative urgency the more likely that treatment would fail, as assessed objectively, even if surgery had been similar (13).

However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO [14]).

A.3.3 Large cohort studies, including a separate analysis of patients with MUI
Following a RCT of PFMT, a review of 88 women available for follow-up at 5 years found that outcomes were less satisfactory in women with MUI than in women with pure SUI (15).

A.3.3.1 Surgery for SUI
Some authors have reported the disappearance of urgency in up to 40% of women after successful SUI surgery for MUI, suggesting that urgency is an accompanying feature of SUI (14, 16-18).

In a case series of 192 women undergoing midurethral sling insertion, overall satisfaction rates were lower for women with mixed symptoms and overactive detrusor function according to pre-operative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) (19). One study compared two parallel cohorts of patients undergoing surgery for SUI, with and without DO, and found inferior outcomes in women with MUI (20).

However, in a study of the bulking agent, Bulkmad, similar outcomes were reported in women with pure SUI and MUI (21).

One cohort of 450 women, undergoing midurethral sling surgery, had significantly worse outcomes for increased amounts of urgency. In urgency-predominant MUI, the success rate fell to 52% compared to 80% in stress-predominant MUI (22). In a second study in 1113 women treated with transvaginal obturator tape, SUI was cured equally in stress-predominant MUI or urgency-predominant MUI. However, women with stress-predominant MUI were found to have significantly better overall outcomes than women with urgency-predominant MUI (23).

A.4 Evidence statements

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic floor muscle training is less effective for mixed UI than for SUI alone.</td>
<td>2</td>
</tr>
<tr>
<td>Electrical stimulation is equally effective for mixed UI and SUI.</td>
<td>1b</td>
</tr>
<tr>
<td>Antimuscarinic drugs are equally effective in improving symptoms of urgency and UUI in patients with MUI as in patients with UUI alone.</td>
<td>1a</td>
</tr>
<tr>
<td>Duloxetine is equally effective in improving SUI in patients with MUI as in patients with SUI alone.</td>
<td>1a</td>
</tr>
<tr>
<td>Women with MUI are less likely to be cured of their incontinence by SUI surgery than women with SUI alone.</td>
<td>1c</td>
</tr>
<tr>
<td>The response of pre-existing urgency symptoms to SUI surgery is unpredictable and symptoms may improve or worsen.</td>
<td>3</td>
</tr>
</tbody>
</table>
A.5  Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat the most bothersome symptom first in patients with mixed urinary incontinence.</td>
<td>C</td>
</tr>
<tr>
<td>Warn patients with mixed urinary incontinence that the chance of success of pelvic floor muscle training is less satisfactory than for stress urinary incontinence alone.</td>
<td>B</td>
</tr>
<tr>
<td>Offer antimuscarinic drugs to patients with urgency-predominant mixed urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>Warn patients with mixed urinary incontinence that surgery is less likely to be successful than surgery in patients with stress urinary incontinence alone.</td>
<td>A</td>
</tr>
</tbody>
</table>

A.6  Research priority

Research trials should define accurately what is meant by ‘mixed urinary incontinence’.

There is a need for well-designed trials comparing treatments in populations with MUI, and in which the type of MUI has been accurately defined.

A.7  References


http://www.ncbi.nlm.nih.gov/pubmed/324089


APPENDIX B: OLDER PEOPLE WITH URINARY INCONTINENCE

B.1 Introduction
For the purposes of the Guidelines, older people can be defined by age thresholds, which are typically greater than 65 years or greater than 75 years, or in terms of level of physical or cognitive impairment, i.e. ‘frailty’. However, it should be noted that such impairment requiring people to live in supervised environments, such as care homes, can also be experienced by younger people. Older people with UI deserve special consideration for a number of reasons. Physiological changes with natural ageing mean that all types of UI become more common with increasing age. Urinary incontinence commonly co-exists with other comorbid conditions, reduced mobility, coordination or balance or impaired cognition and may require specific interventions, such as timed, prompted or assisted toileting.

Comorbidities also increase the risk of adverse drug effects, such as cognitive impairment with antimuscarinic medication. Ageing of the pelvic tissues may compromise success of surgery for SUI. At an individual level, expectations of assessment and treatment may need to be modified to tailor offered management to specific circumstances, needs, and preferences, while taking into account any loss of capacity for consent on the part of the patient.

B.2 Conservative treatment of elderly people with UI

B.2.1 Correcting underlying disease
In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects on UI of medication, comorbidity or ageing. Urinary incontinence, especially in the elderly, can be worsened or caused by underlying diseases, especially conditions that cause polyuria, nocturia, increased abdominal pressure or CNS disturbances. These conditions include:
• cardiac failure (1);
• chronic renal failure;
• diabetes (1,2);
• chronic obstructive pulmonary disease (3);
• neurological disorders;
• stroke;
• dementia;
• multiple sclerosis;
• general cognitive impairment;
• sleep disturbances, e.g. sleep apnoea.

It is possible that correction of the underlying disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients often suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient’s UI.

Only one study was found that addressed the question of whether correcting underlying disease could improve symptoms of UI. The study found no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life versus conventional treatment (4). This was despite the known benefit of close control of blood glucose levels on other known consequences of type 1 diabetes mellitus, including renal and visual impairment. A higher prevalence of UI was associated with an increase in age and body mass index in this study.

B.2.2 Adjustment of medication
In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects on UI of medication, comorbidity or ageing.

Although changing drug regimens for underlying disease may be considered a possible early intervention for UI, there is very little evidence of benefit (1). There is also a theoretical risk that stopping or altering medication may result in more harm than benefit.

Several case series have suggested a link between drugs with a CNS site of action and UI (4). A secondary analysis of a large observational database of elderly Italians found a higher risk of UI among those taking benzodiazepines.
B.2.3 **Constipation**

One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc, reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both constipation and UI (8). Another study found bowel function improved after successful treatment of voiding problems with sacral nerve stimulation (16). A different study recommended the simultaneous treatment of constipation and urinary disorders in children and adolescents with LUTS.

B.2.4 **Caffeine**

A further interventional study in the elderly showed borderline significance for the benefit of reducing caffeine intake on UI (5).

B.2.5 **Physical activity**

Three RCTs in the elderly confirmed that exercise, as a component of a multidimensional regime, including pelvic floor muscle training (PFMT) and weight loss, was effective in improving UI in women. It is not clear which component of such a regimen is most important (6-8).

B.2.6 **Behavioural therapy**

Bladder training (BT) combined with PFMT is better than standard care for controlling UI in elderly women living in institutions (9). However, BT alone is inferior to a high-intensity programme of PFMT to improve stress urinary incontinence (SUI) in elderly women (10). Bladder training is better than intravaginal pessaries to control SUI, although the improvement may only be short term.

A high-quality systematic review by Flanagan et al. examined the effectiveness of prompted voiding (the giving of positive reinforcement for requesting toileting assistance either spontaneously or following verbal prompts from a caregiver), as an intervention for elderly people with UI living in assisted care setting such as nursing homes (11). The review included nine RCTs, which all showed a positive effect on continence outcomes of prompted voiding in comparison to standard care using intervals of 1, 2 or 3 hours. This review (11) and a further Cochrane review (12) also identified five RCTs that consistently showed that a behaviour modification programme known as ‘Functional Incidental Training (FIT)’, which included prompted voiding, improved continence in addition to activities of daily living (ADL). The review by Flanagan et al. (11) included two RCTs that showed no added clinical benefit of oxybutinin or oestrogen when combined with prompted voiding. This review found one RCT of timed voiding (defined as fixed, pre-determined time intervals between toileting, applicable for those with or without cognitive impairment; an assisted toileting programme was used for those unable to undertake independent toileting) that showed inconsistent improvement in continence over standard care among cognitively impaired adults. Overall, the findings were consistent with previous systematic reviews (13).

B.2.7 **PFMT in the elderly**

An RCT assessing PFMT versus bladder training in 83 women > 65 yrs old showed that PFMT was significantly better (PFMT median leakage on stress test 0.0 g, 95% CI 0.2-0.9; BT median 0.3 g, 95% CI 0.2-1.7). Although this difference was significant, the practical value of this difference is debatable, as is the method of using stress tests to quantify leakage (10).

In a study of Japanese women aged ≥ 70 years with UI, PFMT with general fitness training was effective for cure and improvement of UI after a 3-month period of supervised exercise (6).

A programme of supervised education and skill building around PFMT and BT for women aged ≥ 65 years was effective in decreasing the impact of UI, but there was no change in overall quality of life compared with no intervention (14). Electrical stimulation of the pelvic floor using an intravaginal device was no more effective in a group of women aged ≥ 65 years with UI compared to patient-led home-based PFMT with verbal instruction (15).

One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc, reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both constipation and UI (8). Another study found bowel function improved after successful treatment of voiding problems with sacral nerve stimulation (16). A different study recommended the simultaneous treatment of constipation and urinary disorders in children and adolescents with LUTS.
B.2.8 Evidence summary for conservative treatment of elderly people with UI

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly nursing home patients with established UI do not benefit from treatment of asymptomatic bacteriuria.</td>
<td>2</td>
</tr>
<tr>
<td>Improved diabetic control neither resolves nor improves UI.</td>
<td>3</td>
</tr>
<tr>
<td>Diuretics in elderly patients does not cause or worsen UI.</td>
<td>3</td>
</tr>
<tr>
<td>Multimodal behavioural therapy improves both constipation and UI in the elderly.</td>
<td>1b</td>
</tr>
<tr>
<td>Moderate exercise is associated with lower rates of UI in middle-aged or older women.</td>
<td>2b</td>
</tr>
<tr>
<td>Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.</td>
<td>1a</td>
</tr>
<tr>
<td>The inclusion of prompted voiding in behavioural modification programmes improves continence in elderly, care-dependent people.</td>
<td>1b</td>
</tr>
<tr>
<td>Timed voiding may reduce leakage episodes in elderly cognitively impaired people.</td>
<td>2</td>
</tr>
<tr>
<td>Pelvic floor muscle training appears effective for improvement of UI in elderly women.</td>
<td>1b</td>
</tr>
</tbody>
</table>

B.2.9 Recommendations

<table>
<thead>
<tr>
<th>Recommendations for conservative treatment of elderly people with incontinence</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.</td>
<td>B</td>
</tr>
<tr>
<td>Support other healthcare professionals in use of rehabilitation programmes, including prompted voiding for the care of elderly care-dependent people with urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>For adults with urinary incontinence, treat co-existing constipation.</td>
<td>C</td>
</tr>
<tr>
<td>Offer pelvic floor muscle training to elderly women with urinary incontinence.</td>
<td>B</td>
</tr>
</tbody>
</table>

B.3 Antimuscarinic agents, the elderly and cognition

Although the prevalence of UI increases with age, this is not reflected by research targeted to elderly people with UI. Drug trials usually exclude patients with several comorbidities and those taking multiple medications. However, the mechanisms underlying UI in the elderly are more likely to be multifactorial than in younger patients. The elderly are also likely to be taking medications that may affect the efficacy or adverse effects of a new drug.

There have been two systematic reviews of antimuscarinic agents in elderly patients (13, 17). One review was confined to evidence on nursing home residents with UUI (13). A community-based cohort study on the burden of antimuscarinic drugs in an elderly population (n = 372) found a high incidence of cognitive dysfunction (18). The Oregon systematic review of treatments for OAB reported specifically on outcomes in elderly patients (19). A further systematic review with a search cut-off date of December 2011 focused in part on the efficacy and safety of antimuscarinic drugs in the elderly (20). One recent review included nine studies in which the cognitive impact of antimuscarinics was tested but evidence was found to be inconclusive (21).

There have been very few trials specifically investigating the cognitive changes that might occur with the use of antimuscarinic agents. Most trials have been done in healthy volunteers of different age groups and only for a short period (varying from a single dose to 12 weeks). Other publications describe post-hoc analyses of other trials or reviewed only a number of selected publications. In general, these trials have measured CNS side effects in a non-specific way that does not allow the impact on cognition to be considered in a particular patient population (22, 23). Meta-analyses have been limited by study heterogeneity, dosing inconsistency and reporting bias. There is a need for more detailed, standardised measurement of age-stratified CNS outcomes in clinical trials to provide better information to patients and clinicians about the CNS risks associated with antimuscarinic agents.

Studies on antimuscarinic effects have been performed in elderly persons (24) and in people with dementia with UUI (25). There have been no specific studies in vulnerable patient populations, who are likely to have cognitive dysfunction and might suffer deterioration of their cognitive function due to using antimuscarinic medication. However post-hoc analysis of healthy elderly sub-groups from RCTs of antimuscarinic agents provide some lower-level evidence of relative harms.

B.3.1 Oxybutynin

Two studies in the elderly demonstrated additional benefit for UI from oxybutynin IR combined with scheduled
voiding versus scheduled voiding alone. Another study found no differences in efficacy or harms between oxybutynin ER and IR in elderly patients (26). Subanalysis of an elderly subgroup from a RCT population assessing oxybutinin 5 mg ER showed no significant improvement compared to placebo in UUI over a 4-week period (27).

There is some evidence that oxybutynin IR may cause or worsen cognitive dysfunction in adults (24, 28, 29). A crossover RCT in elderly volunteers given oxybutynin IR reported increased cognitive dysfunction with oxybutynin, but a short-term RCT of oxybutynin ER in elderly women with cognitive dysfunction observed no increase in delirium (30).

A large observational study (n = 3536) suggested that more rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction (31).

### B.3.2 Solifenacin

One pooled analysis from several RCTs (32) suggested that solifenacin was effective and did not increase cognitive impairment in the elderly. Another RCT found no age-related differences in the pharmacokinetics of solifenacin between elderly, middle-aged or younger patients. One post-marketing surveillance study reported more frequent adverse events in subjects over 80 years old. Another study on healthy elderly volunteers showed no cognitive effect (29). In a subanalysis of a large trial, solifenacin 5-10 mg appeared effective for symptom and quality of life improvement among people aged older than 75 years who had not responded to tolterodine (33).

### B.3.3 Tolterodine

Pooled data from RCTs showed no change in efficacy or side effects related to age, but reported a higher discontinuation rate for both tolterodine and placebo in elderly patients (28). Two RCTs of tolterodine specifically designed in the elderly found that tolterodine showed a similar efficacy and side effect profile, as in younger patients. Post-hoc analysis from other RCTs has shown little effect on cognition. One trial showed lower rates of depression amongst elderly participants treated with tolterodine ER compared to oxybutynin IR (34).

### B.3.4 Darifenacin

Two RCTs carried out specifically in the elderly population (one RCT in patients with UUI and the other RCT in volunteers) concluded that darifenacin was effective and the risk of cognitive change measured as memory scanning tests were no different to placebo (35, 36). Another comparison between darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in patients receiving oxybutynin ER (24).

### B.3.5 Trospium chloride and fesoterodine

No published evidence was found regarding the comparative efficacy and side effect profiles of trospium or fesoterodine in the elderly compared with younger patients. However, there is some evidence that trospium does not impair cognitive function (25, 37, 38) and that it is effective compared to placebo in this group (39).

Two separate pooled analyses of the same two RCTs of fesoterodine in the elderly confirmed the efficacy of the 8 mg but not the 4 mg dose in the over-75s. Adherence to treatment was lower in the over-75-year-old group, but the effect on mental status was not reported (40, 41).

When starting anticholinergic medication in patients at risk of worsening cognitive function, it has been suggested that mental function is assessed objectively and monitored to detect any significant changes during treatment (42).

### B.3.6 Evidence summary

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
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<tbody>
<tr>
<td>Oxybutynin IR may worsen cognitive function.</td>
<td>1b</td>
</tr>
<tr>
<td>Oxybutynin IR is less effective in people with impaired orientation, cerebral cortical underperfusion and reduced bladder sensation.</td>
<td>2</td>
</tr>
<tr>
<td>The effectiveness and risk of adverse events of solifenacin, tolterodine and darifenacin do not differ with patient age.</td>
<td>3</td>
</tr>
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</table>
B.3.7  Recommendations

<table>
<thead>
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<th>Recommendations for antimuscarinic drugs</th>
<th>GR</th>
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</thead>
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<tr>
<td>Offer IR or ER formulations of antimuscarinic drugs as initial drug therapy for adults with urge urinary incontinence.</td>
<td>A</td>
</tr>
<tr>
<td>If IR formulations of antimuscarinic drugs are unsuccessful for adults with urge urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.</td>
<td>A</td>
</tr>
<tr>
<td>Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.</td>
<td>B</td>
</tr>
<tr>
<td>Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urge urinary incontinence (&lt; 30 days).</td>
<td>A</td>
</tr>
<tr>
<td>When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of cognitive side effects, especially in those receiving cholinesterase inhibitors.</td>
<td>C</td>
</tr>
<tr>
<td>Avoid using oxybutynin IR in patients who are at risk of cognitive dysfunction.</td>
<td>A</td>
</tr>
<tr>
<td>Consider use of trospium chloride in patients known to have cognitive dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>Use solifenacin, tolterodine and darifenacin with caution in patients with cognitive dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>Do an objective assessment of mental function before treating patients whose cognitive function may be at risk.</td>
<td>C</td>
</tr>
<tr>
<td>Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction.</td>
<td>C</td>
</tr>
</tbody>
</table>

IR = immediate release; ER = extended release.

B.4  Surgery for UI in the elderly

There are no RCTs comparing surgical treatment in older versus younger women although subgroup analyses of some RCTs have included a comparison of older with younger cohorts.

An RCT of 537 women comparing retropubic to transobturator tape, showed that cure rates decreased and failure increased with each decade over the age of 50 (43). An RCT assessing risk factors for failure of tension-free vaginal tape (TVT) versus transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at 1 year (44). In a subanalysis of the SISTER trial cohort of 655 women at 2 years of follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urge UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to normal post-operative voiding (45).

Another RCT compared immediate TVT versus delayed TVT in older women, confirming significant efficacy for the operated women, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) (46).

A cohort study of 256 women undergoing inside-out TVT-O reported similar efficacy in older versus younger women but there was a higher risk of de novo urgency in older patients (47).

A case series of 157 elderly (> 70 years) women with OAB given botox for the first time divided them into frail elderly (52), elderly without impaired activities of daily living (47) and those aged 58-70 years old (58). They found a higher rate of post-voiding residual (> 150 mL) in the frail elderly (59.6%) compared to 42.6% and 34.5% in the other groups, respectively (48).

Cohort studies have shown the effectiveness of botulinum toxin injections in the elderly and frail elderly (49), although a comparison of cohort groups suggests that there is a lower success rate in the frail elderly and also a higher rate of increased PVR (> 150 mL) in this group.

B.4.1  Evidence summary for surgery for UI in the elderly

<table>
<thead>
<tr>
<th>Evidence statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older women benefit from surgical treatment for incontinence.</td>
<td>1</td>
</tr>
<tr>
<td>The risk of failure from surgical repair of SUI, or of suffering adverse events, appears to increase with age.</td>
<td>2</td>
</tr>
<tr>
<td>There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.</td>
<td>4</td>
</tr>
</tbody>
</table>
B.4.2 Recommendations for surgery for UI in the elderly

**Recommendation**
Inform older women with stress urinary incontinence about the increased risks associated with surgery, including the lower probability of success.

**GR**
B

### B.5 References


### 6. Abbreviations Used in the Text

This list is not comprehensive for the most common abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>adjustable compression therapy (device)</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>AUS</td>
<td>artificial urinary sphincter</td>
</tr>
<tr>
<td>BT</td>
<td>bladder training</td>
</tr>
<tr>
<td>BTX</td>
<td>botulinum toxin</td>
</tr>
<tr>
<td>CIC</td>
<td>clean intermittent catheterisation</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>DO</td>
<td>detrusor overactivity</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>ER</td>
<td>extended release</td>
</tr>
<tr>
<td>FS2S</td>
<td>first stage of two-stage (implantation of sacral neuromodulator)</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>I-QoL</td>
<td>Incontinence Quality of Life</td>
</tr>
<tr>
<td>IR</td>
<td>immediate release</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>MPR</td>
<td>medication possession rate (drug adherence)</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MUI</td>
<td>mixed urinary incontinence</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence (UK)</td>
</tr>
<tr>
<td>OAB</td>
<td>overactive bladder</td>
</tr>
<tr>
<td>PFMT</td>
<td>pelvic floor muscle training</td>
</tr>
<tr>
<td>PICO</td>
<td>Population, Intervention, Comparison, Outcome</td>
</tr>
<tr>
<td>POP</td>
<td>pelvic organ prolapse</td>
</tr>
<tr>
<td>PNE</td>
<td>percutaneous nerve evaluation</td>
</tr>
<tr>
<td>PPI</td>
<td>post-prostatectomy urinary incontinence</td>
</tr>
<tr>
<td>PROMS</td>
<td>patient-reported outcome measures</td>
</tr>
<tr>
<td>PTNS</td>
<td>posterior tibial nerve stimulation</td>
</tr>
<tr>
<td>PVR</td>
<td>post-voiding residual</td>
</tr>
<tr>
<td>Qmax</td>
<td>maximum urinary flow rate</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guideline Network</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>TDS</td>
<td>transdermal delivery system</td>
</tr>
<tr>
<td>TVT</td>
<td>tension-free vaginal tape</td>
</tr>
<tr>
<td>TBT-O</td>
<td>transobturator tension-free vaginal tape</td>
</tr>
<tr>
<td>TVTS</td>
<td>tension-free vaginal tape secure</td>
</tr>
<tr>
<td>UI</td>
<td>urinary incontinence</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UUI</td>
<td>urge urinary incontinence</td>
</tr>
</tbody>
</table>

### Conflict of Interest

All members of the Urinary Incontinence Guidelines panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Initial assessment
- History
- Physical examination
- Questionnaire optional
- Voiding dairy
- Urinalysis
- Post void residual if voiding difficulty
- Pad test if quantification of leakage is desired

Reasons for specialist referral
- Haematuria
- Pain
- Recurrent UTI
- Grade 3 or symptomatic prolapse
- Previous pelvic radiotherapy
- Previous surgery for UI
- Pelvic mass
- Suspicion of fistula

Discuss management

Stress Urinary Incontinence
- Advise on bowels, drugs, co-morbidity, fluid intake
- Advise on weight loss
- Consider intervention related to cognitive impairment (scheduled voiding)
- Offer pads or other containment device if needed
- Consider reducing caffeine intake
- Consider topical oestrogen for post-menopausal women
- Offer Desmopressin for short term symptom relief
- Offer timed or prompted voiding in elderly /care dependent people

Mixed Urinary Incontinence

Urge Urinary Incontinence

Supervised, intensive PFMT +/- Biofeedback GA
+-/ Bladder training GA

Offer Duloxetine for temporary improvement GA

Bladder training GA

Anti-muscarinics GA
or Mirabegron GB

Consider PTNS GB

Failed conservative or drug therapy - proceed to surgery
Surgical treatment in women

Failed conservative or drug therapy

Stress Urinary Incontinence

Mixed Urinary Incontinence

Urgo Urinary Incontinence

Offer urodynamics if findings may change the choice of surgery
Do video-urodynamics if considering second line surgery

GB
GC

Offer MUS
Consider peri-urethral injections for temporary relief of symptoms

GA

Stress predominant

Offer fascial sling or colposuspension if MUS unavailable
GA

Failure

Re-evaluate patient and consider second-line surgery - re-enter algorithm at appropriate stage
GA

Urgency predominant

Offer Botulinum toxin A or the opportunity for SNS
GA

Discuss bladder augmentation or urinary diversion
GA
Man presenting with Urinary Incontinence

Initial assessment
- History
- Physical examination
- Questionnaire optional
- Voiding dairy
- Urinalysis
- Post void residual if voiding difficulty
- Pad test if quantification of leakage is desired

Reasons for specialist referral
- Haematuria
- Pain
- Recurrent UTI
- Previous pelvic radiotherapy
- Abnormal DRE
- Findings suspicious of voiding dysfunction

Discuss management

Stress Urinary Incontinence
- Advise on bowels, drugs, co-morbidity, fluid intake
- Advise on weight loss
- Consider intervention related to cognitive impairment (scheduled voiding)
- Offer pads or other containment device if needed
- Consider reducing caffeine intake
- Offer Desmopressin for short term symptom relief
- Offer timed or prompted voiding in elderly/care dependent people

Mixed Urinary Incontinence
- Provide information on pelvic floor exercise

Urge Urinary Incontinence
- Bladder training

Offer Duloxetine for temporary improvement

Anti-muscarinics
- GA
- or Mirabegron

Failed conservative or drug therapy - proceed to surgery
Surgical treatment in men
Failed conservative or drug therapy

Stress Urinary Incontinence

Mixed Urinary Incontinence

Urge Urinary Incontinence

Perform urodynamics, cystoscopy and consider imaging of lower urinary tract
a; to exclude bladder outlet obstruction or
b; if the result would alter the choice of surgery

Consider peri-urethral injection for temporary relief, and minimally invasive compression devices

Consider fixed slings for men with PRPI

Offer AUS to men with persistent moderate to severe PPI

Offer Botulinum toxin A or the opportunity for treatment with SNS

Discuss bladder augmentation or urinary diversion

Stress predominant

Urgency predominant

GB

GA

GC
Guidelines on Neurogenic Lower Urinary Tract Dysfunction

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<td>4.2.2.1.1</td>
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<td>Peripheral temporary electrostimulation</td>
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<td>4.2.2.1.3</td>
<td>Intravesical electrostimulation</td>
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</table>
1. BACKGROUND

1.1 Aims and objectives
The purpose of these clinical guidelines is to provide useful information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up observation of the condition of neurogenic lower urinary tract dysfunction (NLUTD). These guidelines reflect the current opinion of the experts in this specific pathology and thus represent a state-of-the-art reference for all clinicians, as of the date of its presentation to the European Association of Urology (EAU).

The EAU Guidelines panel consists of an international multidisciplinary group of experts, including urologists specialised in the care of spinal cord injured (SCI) patients, as well as a specialist in the field of urodynamic technologies.

The terminology used and the diagnostic procedures advised throughout these guidelines follow the recommendations for investigations on the lower urinary tract (LUT) as published by the International Continence Society (ICS) (1-3).

1.2 Methodology

1.2.1 Data identification
Literature searches were carried out for all sections of the Neurogenic Lower Urinary Tract Dysfunction guidelines. Focus of all searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomised controlled trials) in accordance with EAU methodology. In case sufficient data was identified to answer the clinical question, the search was not expanded to include lower level literature. The search was limited to English language publications, animal studies were excluded. Additionally, the guidelines panel have included scientific material from foreign language publications and textbooks.

1.2.2 Evidence sources
Searches were carried out in Medline and Embase on the Dialog-Datastar platform. The searches used the controlled terminology of the respective databases. Both MeSH and EMTREE were analysed for relevant terms. In many cases the use of free text ensured the sensitivity of the searches.

Randomised controlled trial (RCT) strategies used were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform and then translated into Datastar syntax.

1.2.3 Level of evidence and grade of recommendation
References used in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (4). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence (LE)*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

* Modified from Sackett, et al. (4).

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there
is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (5-7).

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett, et al. (4).*

1.2.4 Publication history

The current guidelines present a limited update of the 2008 publication. The EAU published the first guidelines on Neurogenic LUTS 2003 with an update in 2008. A review paper was published in the scientific journal of the association in 2009 (8).

A quick reference document presenting the main findings of the Neurogenic LUTS guidelines is available. All texts can be viewed and downloaded for personal use at the EAU website:

http://www.uroweb.org/guidelines/online-guidelines/.

There is a need for ongoing re-evaluation of the information presented in the current guidelines by an expert panel. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

Summary of updated information

An updated literature search was done covering the chapters on Epidemiology, Diagnosis and Assessment, Medical Treatment, Sexuality/Fertility and Quality of Life. New additions are the Introduction in this chapter 1, Bladder Rehabilitation and the chapters on Infections, Sexual Dysfunction and Fertility. Chapter 2 “Epidemiology” has been updated and chapter 3 “Diagnosis” completely renewed.

Readers are advised to consult the other EAU guidelines which may address different aspects of the topics discussed in this document.

1.3 Introduction

The function of the lower urinary tract (LUT) is mainly storage and voiding of urine, which is regulated by a neural control system in the brain and spinal cord that coordinates the activity of the urinary bladder and bladder outlet. Therefore, any disturbance of the nervous systems that control the LUT, including the peripheral nerves in the pelvis, can result in neurogenic lower urinary tract dysfunction (NLUTD). Depending on the extent and location of the disturbance, a variety of different NLUTDs might occur, which can be symptomatic or asymptomatic. Furthermore, NLUTD can cause a variety of long-term complications; the most dangerous being damage of renal function. As symptoms and long-term complications do not correlate (9), it is important to identify patients with NLUTD, and establish if they have a low or high risk of subsequent complications.

According to current knowledge, elevated storage pressure in the bladder, either alone or combined with vesicoureteric reflux (VUR), is the most important risk factor for renal damage (10). Sustained elevated storage pressure in the bladder is mainly due to a combination of increased detrusor activity during the storage phase (detrusor overactivity [DO] or low compliance), combined with detrusor-sphincter-dyssynergia (DSD). The combination of these two findings is mainly caused by suprasacral infrapontine spinal lesions. Furthermore, elevated detrusor leak point pressure has been demonstrated to be a risk factor for renal deterioration in patients with meningomyelocele (11). Therefore, renal failure has been the leading cause of death in patients with spinal cord injury for a long time (12). Even today, 26% of patients with
meningomyelocele who do not undergo urological treatment develop renal damage. Detrusor leak point pressure ≥ 40 cm H2O and low bladder compliance are the main risk factors for renal damage (13).

In recent years, adequate diagnosis and treatment of NLUTD in patients with spinal cord lesions have improved the situation of these patients. Nowadays, respiratory diseases are the most frequent (21%) cause of death in patients with SCI (14).

In all other patients with NLUTD, the risk of renal damage is significantly lower. However, in Multiple Sclerosis (MS), urodynamics and clinical symptoms do not correlate, which means that asymptomatic patients can present with abnormal urodynamic findings (15). LUT symptoms do not always lead to urological evaluation in patients with MS, even if the symptoms are troublesome (16). Therefore, urological assessment is important in MS patients (17); although respiratory diseases are currently the leading cause of death for patients with MS (18).

In Parkinson disease (PD), NLUTD has not been mentioned as a significant cause of death. Moreover, patients with PD commonly suffer from overactive bladder without DSD (19), which does not seem to be as threatening to the upper urinary tract as DO with DSD. In patients with PD, urodynamic diagnosis of DO correlates well with diagnosis made by questionnaires (20). For these reasons, regular urodynamic follow-up might be less important in PD patients compared with patients suffering from MS or SCI. The same is true for type 2 diabetes, which frequently leads to NLUTD (21), but cardiovascular diseases are the main cause of death in these patients (22).

In summary, treatment and intensity of follow-up examinations are based on the type of NLUTD and the underlying cause.

1.4 References

2. RISK FACTORS AND EPIDEMIOLOGY

2.1 Introduction
Neurogenic lower urinary tract dysfunction may be caused by various diseases and events affecting the nervous systems controlling the LUT. The resulting LUTD depends grossly on the location and the extent of the neurological lesion (see also Section 2.3).

There are no figures on the overall prevalence of NLUTD in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of those for the development of NLUTD. It is important to realise that most of these data show a very wide range of prevalence figures because of the low level of evidence in most published data and smaller sample sizes.

2.1.1 Brain tumours
Brain tumours can cause LUTD in 24% of patients (1). More recently, mostly case reports to small series have been published (2-3). In a series of patients with brain tumours, voiding difficulty was reported in 46/152 (30%) of patients with tumours in the posterior fossa, while urinary incontinence occurred in only three (1.9%) patients (4). Urinary retention was found in 12/17 (71%) children with pontine glioma (5).

2.1.2 Dementia
It is not easy to distinguish dementia-associated LUTD from LUTD caused by age-related changes of the bladder and other concomitant diseases. Therefore, the true incidence of incontinence caused by dementia is unknown. However, it has been shown that incontinence is much more frequent in geriatric patients with
dementia than in patients without dementia (6,7).

Alzheimer, Lewy body dementia, Binswanger, Nasu-Hakola and Pick diseases frequently cause NLUTD (6-13). The occurrence of incontinence is reported to be between 23% and 48% (14,15) in patients with Alzheimer’s disease. In Lewy body dementia, 92% of NLUTD is attributed to DO and 53% to incontinence (16). The onset of incontinence usually correlates with disease progression (17). A male-to-female ratio of dementia-related incontinence was found to be 1:15.

2.1.3 Mental retardation
In mental retardation, depending on the grade of the disorder, 12-65% of LUTD has been described (18,19).

2.1.4 Cerebral palsy
Lower urinary tract dysfunction has been described in about 30-40% (20,21).

2.1.5 Normal pressure hydrocephalus
There have only been case reports of LUTD (22-24).

2.1.6 Basal ganglia pathology (Parkinson disease, Huntington’s disease, Shy-Drager syndrome, etc.)
Parkinson disease is accompanied by NLUTD in 37.9-70% (25-27).

In the rare Shy-Drager syndrome, almost all patients have NLUTD (27), with incontinence found in 73% (28).

Hattori, et al. (29) reported that 60% of Parkinson patients had urinary symptoms. However, Gray et al. (30) reported that functional disturbances of the LUT in PD were not disease-specific and were correlated only with age. Control-based studies have given the prevalence of LUT symptoms as 27-63.9% using validated questionnaires (31-33), or 53% in men and 63.9% in women using a validated questionnaire, which included a urinary incontinence category (33), with all these values being significantly higher than in healthy controls. Ransmayr reported a prevalence of urge episodes and urge incontinence in 53% Lewy body patients, whereas this was observed in 27% of the PD study population, of which 46% were also diagnosed with DO (34). In most patients, the onset of the bladder dysfunction occurred after the motor disorder had appeared.

2.1.7 Cerebrovascular pathology
Cerebrovascular (CVA) pathology causes hemiplegia with remnant incontinence NLUTD in 20-50% of patients (35,36), with decreasing prevalence in the post-insult period (37). In 1996, 53% of patients with CVA pathology had significant urinary complaints at 3 months (38). Without proper treatment, at 6 months after the CVA, 20-30% of patients still suffered from urinary incontinence (39). The commonest cystometric finding was DO (40-45).

In 39 patients who had brainstem strokes, urinary symptoms were present in almost 50%, nocturia and voiding difficulty in 28%, urinary retention in 21%, and urinary incontinence in 8%. Several case histories have been published presenting difficulties with micturition in the presence of various brainstem pathologies (46-48).

2.1.8 Demyelinisation
Multiple sclerosis causes NLUTD in 50-90% of the patients (49-51). The reported incidence of voiding dysfunction in multiple sclerosis is 33-52% in patients sampled consecutively, regardless of urinary symptoms. This incidence is related to the disability status of the patient (52). There is almost a 100% chance of having LUTD once these patients experience difficulties with walking. NLUTD is the presenting symptom in 2-12% of patients, with this finding being as high as 34% in some studies (53). LUTD appears mostly during the 10 years following the diagnosis (54).

2.1.9 Spinal cord lesions
Spinal cord lesions can be traumatic, vascular, medical or congenital. An incidence of 30-40 new cases per million population is the accepted average for the USA. Most of these patients will develop NLUTD (55). The prevalence of spina bifida and other congenital nerve tube defects in the UK is 8-9 per 10,000 aged 10-69 years, with the greatest prevalence in the age group 25-29 years (56), and in the USA 1 per 1,000 births (57). The incidence of urothrovalesque dysfunction in myelomingingocele is not completely known, but most studies suggest it is very high at 90-97% (58). About 50% of these children will have DSD (59,60).

In a large review specific data were presented for intradural metastasis from renal carcinoma with 22% of patients presenting with NLUTD (61).

Central cord syndrome is an incomplete SCI. A case series (n = 50) presented NLUTD in 42% of patients at admission, 12% had residual disturbance during follow up, but most of the 12% related to patients > 70 years old (60% of that age bracket) (62).
In a hereditary spastic paraplegia series, 38 (77.6%) out of 49 patients presented with NLUTD (63).

Caudal Regression Syndrome (CRS): In a case series 61% of patients diagnosed with CRS presented with NLUTD (n = 69). 20% of these CRS patients presented with one kidney (64). Special attention is to be paid to the combination of traumatic SCI and brain injuries: the incidence of traumatic SCI with clinical concomitant brain injury has increased over the past 50 years. These findings have consequences for the diagnosis and treatment of NLUTD (65). In 25% of children with high anorectal malformations, innate NLUTD is present (66).

2.1.10 Disc disease
This is reported to cause NLUTD in 28-87% of the patients (< 20%) (67,68). The incidence of cauda equine syndrome due to central lumbar disc prolapse is relatively rare and is about 1-5% of all prolapsed lumbar discs (68-75). There have been case reports of NLUTD without cauda equine syndrome (76) and small series with 90% cure of incontinence (77).

2.1.11 Spinal stenosis and spine surgery
About 50% of patients seeking help for intractable leg pain due to spinal stenosis report symptoms of LUTD, such as a sense of incomplete bladder emptying, urinary hesitancy, incontinence, nocturia or urinary tract infections (UTIs) (78). These symptoms may be overlooked or attributed to primary urological disorders, with 61-62% affected by LUTD (79,80). The prevalence of neurological bladder is more significantly associated with the anteroposterior diameter of the dural sac than with its cross-sectional area. Spinal surgery is related to LUTD in 38-60% of patients (81,82). In a series with sacrectomy for sacral chordoma’s NLUTD was found in 74% (83).

2.1.12 Peripheral neuropathy
Diabetes: This common metabolic disorder has a prevalence of about 2.5% in the American population, but the disease may be subclinical for many years. No specific criteria exist for secondary neuropathy in this condition, but it is generally accepted that 50% of patients will develop somatic neuropathy, with 75-100% of these patients developing NLUTD (84,85). Diabetic patients suffer from various polyneuropathies, with ‘diabetic cystopathy’ reported in 43-87% of insulin-dependent diabetics without gender or age differences. It is also described in about 25% of type 2 diabetic patients on oral hypoglycaemic treatment (86).

The prevalence of NLUTD in type 2 diabetes gets higher with increasing severity of cardiac autonomic neuropathy (87).

Alcohol abuse will eventually cause peripheral neuropathy. This has a reported prevalence that varies widely from 5-15% (88) to 64% (89). NLUTD is probably more likely to be present in patients with liver cirrhosis. The parasympathetic nervous system is attacked more than the sympathetic nervous system (89).

Less prevalent peripheral neuropathies include the following:

- Porphyria: bladder dilatation occurs in up to 12% of patients (90).
- Sarcoïdosis: NLUTD is rare (91).
- Lumbosacral zone and genital herpes: incidence of LUT dysfunction is as high as 28% when only lumbosacral dermatome-involved patients are considered. The overall incidence is 4% (92,93). NLUTD is transient in most patients.
- Guillain Barré syndrome: the prevalence of micturition disorders varies from 25% to more than 80% (94,95), but is regressive in most cases (96). The true incidence is uncertain because, during the acute phase, patients are usually managed by indwelling catheter.

2.1.13 Other conditions (systematic lupus erythaematosus)
Nervous system involvement occurs in about half of patients with systemic lupus erythaematosus (SLE). Symptoms of LUTD can occur, but data on prevalence are rare and give an incidence of 1% (97,98).

In familial amyloidotic polyneuropathy (FAP) approx. 50% of patients present with NLUTD (99).
2.1.14 **Human immunodeficiency virus**
Voiding problems have been described in 12% of HIV-infected patients, mostly in advanced stages of the disease (100,101).

2.1.15 **Regional spinal anaesthesia**
This may cause NLUTD but no prevalence figures have been found (102,103). NLUTD have been described after image-guided transfomaminal lumbar spine epidural steroid injection (104), and intrathecal methotrexate injection (105).

2.1.16 **Iatrogenic**
Abdominoperineal resection of the rectum has been described as causing NLUTD in up to 50% of patients (106,107). One study reported that NLUTD remains a long-term problem in only 10% (108); however, the study was not clear whether this was because the neurological lesion was cured or bladder rehabilitation was successful. Surgical prevention with nerve preservation was shown to be important (109,110).

NLUTD has been reported following simple hysterectomy (111) and in 8-57% of patients following radical hysterectomy or pelvic irradiation for cervical cancer (112-115). Surgical prevention can be used (116). Neurological dysfunction of the pelvic floor has been demonstrated following radical prostatectomy (117).

### 2.2 Standardisation of terminology

#### 2.2.1 Introduction
Several national or international guidelines have already been published for the care of patients with NLUTD (118-121). The ICS NLUTD standardisation report (119) deals specifically with the standardisation of terminology and urodynamic investigation in patients with NLUTD. Other relevant definitions are found in the general ICS standardisation report (122).

Section 2.2.2 lists the definitions from these references, partly adapted, and other definitions considered useful for clinical practice in NLUTD (Tables 3 and 4). For specific definitions relating to urodynamic investigation, the reader is referred to the appropriate ICS report (119).

#### 2.2.2 Definitions

**Table 3: Definitions useful in clinical practice**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acontractility, detrusor</td>
<td>See below under voiding phase (table 4)</td>
</tr>
<tr>
<td>Acontractility, urethral sphincter</td>
<td>See below under storage phase (table 4)</td>
</tr>
<tr>
<td>Autonomic dysreflexia</td>
<td>Increase of sympathetic reflex due to noxious stimuli with symptoms or signs of headache, hypertension, flushing face and perspiration</td>
</tr>
<tr>
<td>Capacity</td>
<td>See below under storage phase</td>
</tr>
<tr>
<td>Catheterisation, indwelling</td>
<td>Emptying of the bladder by a catheter that is introduced (semi-)permanently</td>
</tr>
<tr>
<td>Catheterisation, intermittent (IC)</td>
<td>Emptying of the bladder by a catheter that is removed after the procedure, mostly at regular intervals</td>
</tr>
<tr>
<td>• Aseptic IC</td>
<td>The catheters remain sterile, the genitals are disinfected, and disinfecting lubricant is used</td>
</tr>
<tr>
<td>• Clean IC</td>
<td>Disposable or cleansed re-usable catheters, genitals washed</td>
</tr>
<tr>
<td>• Sterile IC</td>
<td>Complete sterile setting, including sterile gloves, forceps, gown and mask</td>
</tr>
<tr>
<td>• Intermittent self-catheterisation (ISC)</td>
<td>IC performed by the patient</td>
</tr>
<tr>
<td>Compliance, detrusor</td>
<td>See below under storage phase</td>
</tr>
<tr>
<td>Condition</td>
<td>Evidence of relevant pathological processes</td>
</tr>
<tr>
<td>Diary, urinary</td>
<td>Record of times of micturitions and voided volumes, incontinence episodes, pad usage, and other relevant information</td>
</tr>
</tbody>
</table>
**Frequency volume chart (FVC)**
Times of micturitions and voided volumes only

**Micturition time chart (MTC)**
Times of micturitions only

**Filling rate, physiological**
Below the predicted maximum: body weight (kg) / 4 in mL/s (122,123)

**Hesitancy**
Difficulty in initiating micturition; delay in the onset of micturition after the individual is ready to pass urine

**Intermittency**
Urine flow stops and starts on one or more occasions during voiding

**Leak point pressure (LPP)**
See below under storage phase

**Lower motor neuron lesion (LMNL)**
Lesion at or below the S1-S2 spinal cord level

**Neurogenic lower urinary tract dysfunction (NLUTD)**
Lower urinary tract dysfunction secondary to confirmed pathology of the nervous supply

**Observation, specific**
Observation made during specific diagnostic procedure

**Overactivity, bladder**
See below under symptom syndrome (table 4)

**Overactivity, detrusor**
See below under storage phase

**Rehabilitation, LUT**
Non-surgical non-pharmacological treatment for LUT dysfunction

**Sign**
To verify symptoms and classify them

**Sphincter, urethral, non-relaxing**
See below under voiding phase

**Symptom**
Subjective indicator of a disease or change in condition, as perceived by the patient, carer, or partner that may lead the patient to seek help from healthcare professionals

**Upper motor neuron lesion (UMNL)**
Lesion above the S1-S2 spinal cord level

**Voiding, balanced:**
In patients with NLUTD (< 80 mL or < 20% of bladder volume)
Voiding with physiological detrusor pressure and low residual

**Voiding, triggered**
Voiding initiated by manoeuvres to elicit reflex detrusor contraction by exteroceptive stimuli

**Volume, overactivity**
See below under storage phase

---

**Table 4: Further definitions useful in clinical practice**

<table>
<thead>
<tr>
<th><strong>Storage phase</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum anaesthetic bladder capacity</strong></td>
<td>Maximum bladder filling volume under deep general or spinal anaesthesia</td>
</tr>
<tr>
<td><strong>Increased daytime frequency</strong></td>
<td>Self-explanatory; the normal frequency can be estimated at about 8 times per day (124)</td>
</tr>
<tr>
<td><strong>Nocturia</strong></td>
<td>Waking at night one or more times to void</td>
</tr>
<tr>
<td><strong>Urgency</strong></td>
<td>The symptom of a sudden compelling desire to pass urine that is difficult to defer</td>
</tr>
<tr>
<td><strong>Urinary incontinence</strong></td>
<td>Any involuntary leakage of urine</td>
</tr>
<tr>
<td>• <strong>Stress urinary incontinence</strong></td>
<td>On effort or exertion, or on sneezing or coughing</td>
</tr>
<tr>
<td>• <strong>Urge urinary incontinence</strong></td>
<td>Accompanied by or immediately preceded by urgency</td>
</tr>
<tr>
<td>• <strong>Mixed urinary incontinence</strong></td>
<td>Associated with urgency but also exertion, effort, sneezing, or coughing</td>
</tr>
<tr>
<td>• <strong>Continuous urinary incontinence</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bladder sensation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>Symptom and history</strong></td>
<td>Awareness of bladder filling and increasing sensation up to a strong desire to void</td>
</tr>
</tbody>
</table>
- **Urodynamics**
  - First sensation of bladder filling, first desire to void, and strong desire to void at realistic bladder volumes

**Increased**

- **Symptom and history**
  - An early and persistent desire to void

- **Urodynamics**
  - Any of the three urodynamic parameters mentioned under 'normal' persistently at low bladder volume

**Reduced**

- **Symptom and history**
  - Awareness of bladder filling but no definite desire to void

- **Urodynamics**
  - Diminished sensation throughout bladder filling

**Absent**

- **Symptom and history**
  - Perception of bladder filling as abdominal fullness, vegetative symptoms, or spasticity

**Definitions valid after urodynamic confirmation only**

### Cystometric capacity
- **Bladder volume at the end of the filling cystometry**

### Maximum cystometric capacity
- **Bladder volume at strong desire to void**

### High-capacity bladder
- **Bladder volume at cystometric capacity far over the mean voided volume, estimated from the bladder diary, with no significant increase in detrusor pressure under non-anaesthetised condition**

### Normal detrusor function
- **Little or no pressure increase during filling: no involuntary phasic contractions despite provocation**

### Detrusor overactivity
- **Involuntary detrusor contractions during filling; spontaneous or provoked**

### Phasic DO
- **Characteristic phasic contraction**

### Terminal DO
- **A single contraction at cystometric capacity**

### High pressure DO
- **Maximal detrusor pressure > 40 cm H₂O (119,125)**

### Overactivity volume
- **Bladder volume at first occurrence of DO**

### Detrusor overactivity incontinence
- **Self-explanatory**

### Leak point pressure

#### Detrusor leak point pressure (DLPP)
- **Lowest value of detrusor pressure at which leakage is observed in the absence of abdominal strain or detrusor contraction**

#### Abdominal leak point pressure
- **Lowest value of intentionally increased intravesical pressure that provokes leakage in the absence of a detrusor contraction**

### Detrusor compliance
- **Relationship between change in bladder volume (ΔV) and change in detrusor pressure (Δpdet):**
  \[ C = \frac{\Delta V}{\Delta pdet} \text{ (mL/cmH}_2\text{O)} \]

#### Low detrusor compliance
- **C = \Delta V / \Delta pdet < 20 mL/cm H₂O (106)**

### Break volume
- **Bladder volume after which a sudden significant decrease in detrusor compliance is observed**

### Urethral sphincter acontractility
- **No evidence of sphincter contraction during filling, particularly at higher bladder volumes, or during abdominal pressure increase**

### Voiding phase

#### Slow stream
- **Reduced urine flow rate**

#### Intermittent stream (intermittency)
- **Stopping and starting of urine flow during micturition**

#### Hesitancy
- **Difficulty in initiating micturition**

#### Straining
- **Muscular effort to initiate, maintain, or improve urinary stream**
Terminal dribble
Prolonged final part of micturition when the flow has slowed to a trickle/dribble

Definitions valid after urodynamic confirmation only

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal detrusor function</td>
<td>Voluntarily initiated detrusor contraction that causes complete bladder emptying within a normal time span</td>
</tr>
<tr>
<td>Detrusor underactivity</td>
<td>Contraction of reduced strength/duration</td>
</tr>
<tr>
<td>Acontractile detrusor</td>
<td>Absent contraction</td>
</tr>
<tr>
<td>Non-relaxing urethral sphincter</td>
<td>Self-explanatory</td>
</tr>
<tr>
<td>Detrusor sphincter dyssynergia (DSD)</td>
<td>Detrusor contraction concurrent with an involuntary contraction of the urethra and/or periurethral striated musculature</td>
</tr>
</tbody>
</table>

Post-micturition phase
Feeling of incomplete emptying (symptom only)
Post-micturition dribble: involuntary leakage of urine shortly after finishing the micturition
Pain, discomfort or pressure sensation in the LUT and genitalia that may be related to bladder filling or voiding, may be felt after micturition, or be continuous

Symptom syndrome: combination of symptoms
- Overactive bladder syndrome: urgency with or without urge incontinence, usually with frequency and nocturia
- Synonyms: urge syndrome, urgency-frequency syndrome
- This syndrome is suggestive for LUTD

2.3 References
   http://www.ncbi.nlm.nih.gov/pubmed/8695676


3. DIAGNOSIS

3.1 Introduction
A thorough medical history and physical examination is mandatory, before any additional diagnostic
investigations are planned. The clinical assessment of patients with NLUTD includes a detailed history, a patient voiding diary and systematic physical examination. The initial evaluation is essential to determine the therapeutic scheme for long-term treatment and follow-up.

3.2 Classification
The NLUTD classification provides a standardised terminology. Several classification systems have been proposed, but a simple classification focusing on therapeutic consequences has been developed by Madersbacher (1) (LE: 4). This classification describes several NLUTD symptoms on the basis of the contraction state of the bladder and external urethral sphincter during voiding and filling phase (Figure 1).

Figure 1: Madersbacher classification system with typical neurogenic lesions [1]

3.3 Timing of diagnosis and treatment
Early diagnosis and treatment are essential in both congenital and acquired NLUTD. Irreversible changes within the LUT may occur, even with normal neurological reflexes (2,3) (LE: 3). Additionally, NLUTD can be the presenting feature of neurological pathology (4,5) (LE: 3). Early intervention, e.g. intermittent catheterisation (IC), can prevent irreversible deterioration of the lower and upper urinary tract (6) (LE: 3).

3.4 Patient history
History taking is the cornerstone of evaluation and should include past and present symptoms and disorders. The patient’s past history should be taken in detail, particularly in cases of non-traumatic neurological bladder dysfunction with a slow insidious onset. Occasionally, this is traceable to childhood or adolescence (7) (LE: 4). Urinary history consists of symptoms related to both storage and evacuation functions of the LUT.

Bowel history is important since patients with NLUTD may suffer from a related neurogenic condition of the lower gastrointestinal tract. This may reflect the neurological condition of the urinary bladder (7) (LE: 4). Sexual function may also be impaired because of the neurogenic condition.

Table 5 gives an overview of the items that should be assessed. These items are important to guide the decision process of diagnostic investigations and treatment options.

Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria and fever) that warrant further investigation. However, it is usually difficult for patients with SCI to report accurately symptoms related to urinary tract infections (8-10) (LE: 3).
Table 5: History examination in neurogenic lower urinary tract dysfunction*

<table>
<thead>
<tr>
<th>Past history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood - adolescence - adult</td>
</tr>
<tr>
<td>Hereditary or familial risk factors</td>
</tr>
<tr>
<td>Menarche (age); may suggest metabolic disorder</td>
</tr>
<tr>
<td>Obstetric history</td>
</tr>
<tr>
<td>History of diabetes; in some cases correction will resolve the neurological problem</td>
</tr>
<tr>
<td>Diseases, e.g. syphilis, Parkinsonism, multiple sclerosis, encephalitis</td>
</tr>
<tr>
<td>Accidents and operations, especially those involving the spine and central nervous system</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Present history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present medication</td>
</tr>
<tr>
<td>Lifestyle (smoking, alcohol and drugs); may influence bowel and urinary function</td>
</tr>
<tr>
<td>Quality of life</td>
</tr>
<tr>
<td>Life expectancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific urinary history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset urological history</td>
</tr>
<tr>
<td>Relief after voiding; to detect the extent of a neurological lesion in the absence of obstructive uropathy</td>
</tr>
<tr>
<td>Bladder sensation</td>
</tr>
<tr>
<td>Initiation of micturition (normal, precipitate, reflex, strain, Credé)</td>
</tr>
<tr>
<td>Interruption of micturition (normal, paradoxical, passive)</td>
</tr>
<tr>
<td>Enuresis</td>
</tr>
<tr>
<td>Mode and type of voiding (catheterisation)</td>
</tr>
<tr>
<td>Urinary diary; (semi)objective information about number of voids, day- and night-time voiding frequency, volumes voided, incontinence, urge episodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bowel history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency and faecal incontinence</td>
</tr>
<tr>
<td>Desire to defecate</td>
</tr>
<tr>
<td>Defecation pattern</td>
</tr>
<tr>
<td>Rectal sensation</td>
</tr>
<tr>
<td>Initiation of defecation (digital rectal stimulation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sexual history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital or sexual dysfunction symptoms</td>
</tr>
<tr>
<td>Sensation in genital area</td>
</tr>
<tr>
<td>Specific male: erection, (lack of) orgasm, ejaculation</td>
</tr>
<tr>
<td>Specific female: dyspareunia, (lack of) orgasm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired or congenital neurological condition</td>
</tr>
<tr>
<td>Mental status and comprehension</td>
</tr>
<tr>
<td>Neurological symptoms (somatic and sensory), with onset, evolution and any treatment</td>
</tr>
<tr>
<td>Spasticity or autonomic dysreflexia (lesion above level Th 6)</td>
</tr>
<tr>
<td>Mobility and hand function</td>
</tr>
</tbody>
</table>


Voiding diaries offer information on the number of voids, volumes voided, incontinence, and urge episodes. A 24-hour voiding diary was shown to be reliable in women with urinary incontinence (12,13) (LE: 3). However, no such information is available in patients with neurological incontinence. A voiding diary is also useful in patients performing intermittent catheterisation (11) (LE: 4).
3.5 Physical examination
In addition to a detailed patient history and a general examination, attention should be paid to possible physical and mental handicaps with respect to the planned investigation.

Neurological status should be described as completely as possible (Table 5). Patients with very high neurological lesions may suffer from a significant drop in blood pressure when moved in a sitting or standing position. All sensations and reflexes in the urogenital area must be tested. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2). Availability of this clinical information is essential for the reliable interpretation of subsequent diagnostic investigations.

![Figure 2: The neurological status of a patient with neurogenic lower urinary tract dysfunction (NLUTD) must be described as completely as possible: (a) dermatomes of spinal cord levels L2-S4; (b) urogenital and other reflexes in the lower spinal cord.]

Table 6: Neuro-urological items to be specified*

<table>
<thead>
<tr>
<th>Sensations S2-S5 (both sides)</th>
<th>Presence (increased/normal/reduced/absent)</th>
<th>Type (sharp/blunt)</th>
<th>Afflicted segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflexes (increased/normal/reduced/absent)</td>
<td>Bulbocavernous reflex</td>
<td>Perianal reflex</td>
<td>Knee and ankle reflexes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal sphincter tone</td>
<td>Presence (increased/normal/reduced/absent)</td>
<td>Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)</td>
<td></td>
</tr>
<tr>
<td>Prostate palpation</td>
<td>Descensus (prolapse) of pelvic organs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Caution
Autonomic dysreflexia (AD) is a sudden and exaggerated autonomic response to stimuli in patients with spinal cord injuries or dysfunction above level Th 5-Th 6. Hypertension is a relatively common manifestation of AD and can have life-threatening results if not properly managed (14-16) (LE: 3; GR: C).
3.5.1 Recommendations for history taking and physical examination*

<table>
<thead>
<tr>
<th>History taking</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>An extensive general history is mandatory, concentrating on past and present symptoms and conditions for urinary, bowel, sexual, and neurological functions, and on general conditions that might impair any of these.</td>
<td>A</td>
</tr>
<tr>
<td>Special attention should be paid to the possible existence of alarm signs, such as pain, infection, haematuria, fever, etc, that warrant further specific diagnosis.</td>
<td>A</td>
</tr>
<tr>
<td>A specific history should be taken for each of the four mentioned</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual patient handicaps should be acknowledged in planning further investigations.</td>
<td>A</td>
</tr>
<tr>
<td>The neurological status should be described as completely as possible. Sensations and reflexes in the urogenital area must all be tested.</td>
<td>A</td>
</tr>
<tr>
<td>The anal sphincter and pelvic floor functions must be tested extensively.</td>
<td>A</td>
</tr>
<tr>
<td>Urinalysis, blood chemistry, voiding diary, residual and free flowmetry, incontinence quantification and urinary tract imaging should be performed.</td>
<td>A</td>
</tr>
</tbody>
</table>

* All grade A recommendations based on panel consensus.

3.6 Urodynamics

3.6.1 Introduction

Urodynamic investigation is the only method that can objectively assess the (dys-)function of the LUT. It is essential to describe the LUT status in patients with NLUTD. In these patients, particularly when DO might be present, the invasive urodynamic investigation is even more provocative than in other patients. Any technical source of artefacts must be critically considered. The quality of the urodynamic recording and its interpretation must be ensured (17).

In patients at risk for autonomic dysreflexia, it is advisable to measure blood pressure during the urodynamic study.

In many patients with NLUTD, it may be helpful to assess the maximum anaesthetic bladder capacity. The rectal ampulla should be empty of stool before the start of the investigation. Drugs that influence the LUT function should be stopped at least 48 hours before the investigation (if feasible) or otherwise be considered when interpreting the data obtained.

All urodynamic findings must be reported in detail and performed according to the ICS technical recommendations and standards (17-19).

3.6.2 Urodynamic tests

A bladder diary is a semi-objective qualification of the LUT. It is a highly advisable diagnostic tool. For reliable interpretation, it should be recorded over at least 2-3 days (18,20). Possible pathological findings: high voiding frequency, very low or very high voided volumes, nocturnal voidings, urgency, incontinence.

Free uroflowmetry and assessment of residual urine gives a first impression of the voiding function. It is mandatory before planning any invasive urodynamics. For reliable information, it should be repeated at least 2-3 times (18,21,22). Possible pathological findings: low flow rate, low voided volume, intermittent flow, hesitancy, residual urine.

Care must be taken when assessing the results in patients who are not able to void in a normal position. Both the flow pattern and the flow rate may be modified by inappropriate positions and by any constructions to divert the flow.

Filling cystometry: The only method to quantify the filling function has limited significance as a solitary procedure. It is much more powerful if combined with bladder pressure measurement during micturition and even more in video-urodynamics. This investigation is necessary to document the status of the LUT function during the filling phase. The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline, as fast filling and room-temperature saline are provocative (18).

Possible pathological findings include DO, low detrusor compliance, abnormal bladder and other sensations, incontinence, incompetent or relaxing urethra.

Detrusor leak point pressure (DLPP): This specific investigation may estimate the risk for the upper urinary tract or for secondary bladder damage (18,23). The DLPP is a screening test only, because it gives no impression of
the duration of the high pressure during the filling phase, which can be expected to have even more impact on the upper urinary tract (24). A high DLPP thus warrants further testing by video-urodynamics.

**Pressure flow study:** This measurement reflects the co-ordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more powerful in combination with filling cystometry and with video urodynamics. It is necessary to document the function of the LUT function during the voiding phase. Possible pathological findings: Detrusor underactivity/acontractility, DSD, non-relaxing urethra, residual urine.

Most types of obstruction caused by NLUTD are due to DSD (25,26), non-relaxing urethra, or non-relaxing bladder neck (18,27,28). Pressure-flow analysis mostly assesses the amount of mechanical obstruction caused by the urethra’s inherent mechanical and anatomical properties and has limited value in patients with NLUTD.

**Electromyography (EMG):** Registration of the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter, or the striated pelvic floor muscles. The correct interpretation may be difficult due to artefacts introduced by other equipment used. In the urodynamic setting an EMG is useful as a gross indication of the patient’s ability to control the pelvic floor. Possible pathological findings: Inadequate recruitment on specific stimuli (bladder filling, hyperreflexive contractions, onset of voiding, coughing, Valsalva, etc.). More detailed analysis (motor unit potentials, single-fibre EMG) is only possible as part of a neurophysiological investigation.

**Urethral pressure measurement:** This investigation has only a very limited place in NLUTD. There exists no basic consensus on parameters indicating pathological findings (29).

**Video-urodynamics:** This combination of filling cystometry and pressure flow study with imaging is the gold standard for urodynamic investigation in NLUTD (18,30,31). Possible pathological findings: All as described under cystometry and pressure flow study, plus morphological pathology of the LUT and the upper urinary tract.

**Ambulatory urodynamics:** Functional investigation of the urinary tract utilising predominantly natural filling of the urinary tract and reproducing normal subject activity (32).

This type of study should be considered when office urodynamics do not reproduce the patient’s symptoms and complaints. Possible pathological findings include those found under filling cystometry and pressure flow study, provided the flow is measured also. It should be kept in mind that during this study the actual bladder volume is unknown.

**Provocative tests during urodynamics:** The LUT function can be provoked by coughing, triggered voiding, or anal stretch.

Fast-filling cystometry with cooled saline (the ‘ice water test’) is considered a discriminative test between upper motor neuron lesion (UMN) and lower motor neuron lesion (LMN) (33-38). Patients with UMN will develop a detrusor contraction if the detrusor muscle is intact, while patients with lower lesions will not. The test gives false-positive results in young children (35) and does not seem to be fully discriminative in other patients (36,37).

It was thought that a positive bethanechol test (39) (detrusor contraction > 25 cm H₂O) provided proof of a detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor; however, in practice, the test has given equivocal results. Recently, a variation of this method was reported using intravesical electromotive administration of the bethanechol (40); this test turned out to be both selective and predictive for successful oral bethanechol treatment.

### 3.6.3 Specific uro-neurophysiological tests

These tests are advised as part of the neurological work-up of the patient. They comprise:

- EMG (in a neurophysiological setting) of pelvic floor muscles, urethral sphincter and/or anal sphincter;
- nerve conduction studies of pudendal nerve;
- reflex latency measurements of bulbocavernosus and anal reflex arcs;
- evoked responses from clitoris or glans penis;
- sensory testing on bladder and urethra.

Other elective tests may be asked for specific conditions that became obvious during patient work-up and urodynamic investigations. Possible pathological findings are dependent on the type of the test.
3.6.4 Recommendations for urodynamics and uro-neurophysiology

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urodynamic investigation is necessary to document the (dys-)function of the LUT.</td>
<td>A</td>
</tr>
<tr>
<td>The recording of a bladder diary is advisable.</td>
<td></td>
</tr>
<tr>
<td>Non-invasive testing is mandatory before invasive urodynamics is planned.</td>
<td>B</td>
</tr>
<tr>
<td>Video-urodynamics is the gold standard for invasive urodynamics in patients with NLUTD. If this is not available, then a filling cystometry continuing into a pressure flow study should be performed.</td>
<td>A</td>
</tr>
<tr>
<td>A physiological filling rate and body-warm saline must be used.</td>
<td>A</td>
</tr>
<tr>
<td>Specific uro-neurophysiological tests are elective procedures.</td>
<td>C</td>
</tr>
</tbody>
</table>

3.7 Typical manifestations of neurogenic lower urinary tract dysfunction

Typical findings in NLUTD are listed below:

**Filling phase**
- hyposensitivity or hypersensitivity;
- vegetative sensations;
- low compliance;
- high capacity bladder;
- detrusor overactivity, spontaneous or provoked;
- sphincter acontractility.

**Voiding phase**
- detrusor acontractility;
- DSD;
- non-relaxing urethra;
- non-relaxing bladder neck.

These signs warrant further neurological evaluation, as LUTD may be the presenting symptom of NLUTD (41-45).

3.8 References


4. TREATMENT

4.1 Introduction

The primary aims for treatment of NLUTD and their priorities are (1-4):

1. Protection of the upper urinary tract.
2. Improvement of urinary continence.
3. Restoration of (parts of) the LUT function.
4. Improvement of the patient’s QoL.

Further considerations are the patient’s disability, cost-effectiveness, technical complexity, and possible complications (4).

Preservation of the upper tract function is of paramount importance (1-7). Renal failure was the main factor for mortality in the SCI patient surviving the trauma (5-7). This has led to the golden rule in treatment of NLUTD: ensure that the detrusor pressure remains within safe limits during both the filling phase and the voiding phase (1-4). This approach has indeed significantly reduced the mortality from urological causes in this patient group (8).

The therapy of urinary incontinence is important for social rehabilitation of the patient and thus contributes substantially to the QoL. It is also pivotal in preventing UTI (6,7). If complete continence cannot be achieved, methods to attain a socially acceptable control of incontinence can be used.

The patient’s QoL is an essential part of any treatment decision.

In patients with high detrusor pressure during the filling phase (DO, low detrusor compliance) or during the voiding phase (DSD, other causes of bladder outlet obstruction), treatment is aimed primarily at ‘conversion of an active, aggressive high-pressure bladder into a passive low-pressure reservoir’ despite the resulting residual urine (1).

4.2 Non-invasive conservative treatment

4.2.1 Assisted bladder emptying

Incomplete bladder emptying is a serious risk factor for UTI, developing a high intravesical pressure during the filling phase, and incontinence. Methods to improve the voiding process are practised in patients with NLUTD.

Third party bladder expression (Credé): Regrettfully, this method is still applied, foremost in infants and young children with myelomeningocele and sometimes in tetraplegics. Because of the high pressures that may be created during this procedure, it is potentially hazardous for the urinary tract (9).

Voiding by abdominal straining (Valsalva): The considerations mentioned under Credé above also apply to the Valsalva manoeuvre (1,9-11). For both methods of emptying, long-term complications are hardly avoidable (9,10) and the already weak pelvic floor function may be further impaired, thus exacerbating the existing incontinence (11).

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with UMNL can elicit reflex contraction of the detrusor (1,11). Morbidity occurs more often during the first decades of treatment (12-16). Strict urodynamic control is therefore required (1,11).

Behavioural modification techniques: These are used to improve continence and include prompted voiding, timed voiding (bladder training), and lifestyle modification (17-20).

Pelvic floor muscle exercises: These aim to improve continence. They may be helpful in selected patients with NLUTD (21-23).

Biofeedback: This method can be used for supporting the voiding pattern modification (24,25).

4.2.2 Lower urinary tract rehabilitation

4.2.2.1 Bladder rehabilitation including electrical stimulation

4.2.2.1.1 Introduction

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with NLUTD. Regaining voluntary control over LUTD has been described in individuals with non-neurogenic bladder dysfunction, using behavioural treatment in patients with urge incontinence and biofeedback training for stress urinary incontinence. However, evidence for bladder rehabilitation using electrical stimulation in neurogenic patients is lacking and mainly based on pilot studies with small patient numbers.
A strong contraction of the urethral sphincter and/or pelvic floor, but also anal dilatation, manipulation of the genital region, and physical activity reflexly inhibit the micturition (11,26). Whereas the first mechanism is affected by activation of efferent fibres, the latter ones are produced by activation of afferents (14). Electrical stimulation of the pudendal nerve afferents produces a strong inhibition of the micturition reflex and of the detrusor contraction (27). This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level (11,28,29). It might also imply that patients with incomplete lesions will benefit (11,29,30), but patients with complete lesions will not (31).

4.2.2.1.2 Peripheral temporary electrostimulation
Posterior tibial nerve stimulation and external temporary electrical stimulation (e.g. penile/clitoral or intracavital) suppress neurogenic DO during acute stimulation (32). Both techniques have also demonstrated sustained prolonged effects (3 months and 1 year, respectively) in patients with neurogenic bladder dysfunction due to MS (33.34).

In MS patients, combining active neuromuscular electrical stimulation with pelvic floor muscle training and electromyography biofeedback achieved a substantial reduction of LUTD (35). Furthermore, this treatment combination was significantly superior (p = 0.0028) to electrostimulation alone.

Biofeedback: This method can be used for supporting the voiding pattern modification (24,25).

4.2.2.1.3 Intravesical electrostimulation
Intravesical electrostimulation can increase bladder capacity, improve bladder compliance as well as the sensation of bladder filling in patients with incomplete SCI or meningomyelocele (36). In patients with neurogenic detrusor hypocontractility, intravesical electrostimulation may also improve voiding and reduce residual urine volume (37).

4.2.2.1.4 Chronic peripheral pudendal stimulation
The results of a pilot study showed that chronic peripheral pudendal stimulation (chronic, defined as a period of 2 weeks) in patients with incomplete SCI produced significant neuromodulatory effects in the brain which led to changes in urodynamic parameters (38).

4.2.2.1.5 Repetitive transcranial magnetic stimulation
Although repetitive transcranial magnetic stimulation improved voiding symptoms in patients with PD or MS, the duration of the effect, stimulation parameters and the appropriate patient selection are still under investigation (39,40).

4.2.2.1.6 Summary
To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation. However, there is a lack of well-designed studies for all techniques. The different techniques of external temporary electrostimulation, possibly combined with biofeedback training, may be useful, especially in patients with MS or incomplete spinal cord injury. Further studies are necessary to evaluate the usefulness of these techniques.

4.2.3 Drug treatment
A single, optimal, medical therapy for NLUTD is not yet available. Currently, a combination of therapies is the best way to maximise outcomes (41-50) (LE: 1a).

4.2.3.1 Antimuscarinic drugs
Antimuscarinic drugs are the first-line choice for treating NLUTD. They are the most useful medications available for NLUTD and provide an established approach to managing neurogenic detrusor overactivity (NDO) (41-47,51-53) (LE: 1a). Previously, these drugs were known as ‘anticholinergic’, but they are now described as muscarinic receptor antagonists because of their action in binding to muscarinic receptors. Antimuscarinic drugs are used to stabilise the detrusor muscle, which reduces its overactivity and makes it moderately refractory to parasympathetic stimulation. This results in improved bladder compliance and reduced symptoms of overactive bladder (47,51), which in turn helps to prevent renal and bladder damage and potentially improve long-term outcomes (54) (LE: 1a).

Neurogenic patients may need a higher dose of antimuscarinic agents than patients with idiopathic DO (47,48,55-57) (LE: 1b). However, adverse events due to the higher dosage may lead to early discontinuation of therapy (19,21,56,58,59) (LE: 1b).
4.2.3.1 Choice of antimuscarinic agent

Oxybutynin chloride (47) (LE: 1a) (48-51,57-59), trospium chloride (47,55,56,60), tolterodine tartrate (61-63) and propiverine (47,58,64,65) (LE: 1a) are established, effective, medical treatments. These antimuscarinic agents are known to be well tolerated and safe, even during long-term treatment. They have diverse tolerance profiles, so that a different antimuscarinic agent may be prescribed if a patient experiences adverse effects or if the therapeutic effect is not sufficient (66).

Darifenacin has recently been evaluated in neurogenic overactive bladder secondary to MS (67,68), with results similar to other muscarinic drugs. Solifenacin has also been introduced, even though to date there has been no published clinical evidence of the use of solifenacin in NDO. Data is awaited from an ongoing trial.

4.2.3.1.1 Side-effects

Antimuscarinic agents have some minor side-effects, e.g. dry mouth. It has been suggested that different ways of administration may help to reduce side-effects. In a selected group of patients, transdermal oxybutynin was found to be well tolerated and effective (69,70), while intravesical oxybutynin led to abolishment of the bladder-cooling reflex (71). However, further research is needed into the use of alternative methods of administration, particularly long-term results (LE: 2a).

4.2.3.2 Other agents

4.2.3.2.1 Phosphodiesterase inhibitors (PDE5Is)

These have demonstrated significant effects upon DO in pilot studies and in the future may become an alternative or adjunct to antimuscarinic treatment (72).

4.2.3.3 Adjunct desmopressin

Additional treatment with desmopressin might improve the efficacy of treatment (73-75) (LE: 3).

4.2.3.4 Drugs with different mechanisms of action

4.2.3.4.1 Detrusor underactivity

Cholinergic drugs, such as bethanechol chloride and distigmine bromide, have been considered to enhance detrusor contractility and promote bladder emptying, but are not routinely used in clinical practice. The available studies do not support the use of parasympathomimetic agents, especially when frequent and/or serious possible side-effects are considered (76) (LE: 1a).

Combination therapy with an antimuscarinic drug and alpha-blocker appears to be more useful than monotherapy with either agent (77). In conclusion, there is no drug with evidence of efficacy for underactive detrusor (11,78-81) (LE: 2a).

4.2.3.4.2 Decreasing bladder outlet resistance

Alpha-blockers (non-selective and selective) have been partially successful for decreasing bladder outlet resistance, residual urine and autonomic dysreflexia (11,82-86) (LE: 2a).

4.2.3.4.3 Increasing bladder outlet resistance

Several drugs have shown efficacy in selected cases of mild stress urinary incontinence, but there have been very few publications in patients with NLUTD (11,87).

4.2.3.4.4 Conclusions and recommendations on drug treatments

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term efficacy and safety of antimuscarinic therapy for NDO is well documented.</td>
<td>1a</td>
</tr>
<tr>
<td>A combination of antimuscarinic agents is now used more frequently and is often considered to maximise outcomes for NDO.</td>
<td>1a</td>
</tr>
<tr>
<td>Alternative ways of administration of antimuscarinic agents, such as transdermally and intravesically, should now be considered.</td>
<td>2a</td>
</tr>
<tr>
<td>There is no drug with evidence of efficacy for underactive detrusor.</td>
<td>2a</td>
</tr>
<tr>
<td>Alpha-blockers have been partly successful in decreasing bladder outlet resistance and autonomic dysreflexia prophylaxis in spinal cord injury.</td>
<td>2a</td>
</tr>
<tr>
<td>There is a lack of prospective, randomised, controlled studies in the medical management of NLUTD.</td>
<td></td>
</tr>
</tbody>
</table>
Antimuscarinic therapy for NDO is effective and safe to use, also long term. A
Outcomes for NDO can be maximised by considering a combination of antimuscarinic agents. A
Alternative ways of administration of antimuscarinic agents, such as transdermally and intravesically, should be considered with the aim of reducing side-effects. B
Alpha-blockers may help to decrease bladder outlet resistance and may be a preventive measure in spinal cord injury to prevent autonomic dysreflexia. B

NDO = neurogenic detrusor overactivity.

4.2.4 External appliances
As an ultimate remedy, social continence may be achieved by collecting urine during incontinence (1,11). Condom catheters with urine collection devices are a practical method for men. Otherwise, incontinence pads may offer a reliable solution. In both cases, the infection risk must be closely observed (11). Because of the risk of developing high intravesical pressure, the penile clamp is absolutely contraindicated.

4.2.5 Statements & guidelines on non-invasive conservative treatment

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first aim of any therapy is the protection of the upper urinary tract.</td>
<td>1</td>
</tr>
<tr>
<td>A condom catheter or pads may reduce urinary incontinence to a socially acceptable situation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mainstay of treatment for overactive detrusor is anticholinergic drug therapy.</td>
<td>A</td>
</tr>
<tr>
<td>Lower urinary tract rehabilitation may be effective in selected cases (patients that do not suffer from a complete spinal cord lesion).</td>
<td></td>
</tr>
<tr>
<td>Any method of assisted bladder emptying should be used with the greatest caution.</td>
<td>A</td>
</tr>
</tbody>
</table>

4.3 Minimal invasive treatment

4.3.1 Catheterisation
Intermittent self- or third-party catheterisation (88,89) is the gold standard for the management of NLUTD (1,11). It is effective in patients with:
• Detrusor underactivity or acontractility (1).
• With DO, provided the overactivity can be controlled (1,11,90-95).
Sterile IC, as originally proposed by Guttmann and Frankel (67), significantly reduces the risk of UTI and/or bacteriuria (1,11,96,97), compared with clean IC introduced by Lapides, et al. (89). However, it cannot be considered a routine procedure (11,97). Aseptic IC is an alternative (1,98), which provides a significant benefit in reducing the potential for external contamination of an intermittent urinary catheter (99). Insufficient patient education and the inherent greater risk of UTI in patients with NLUTD are contributing factors (11,100-104).
The average frequency of catheterisations per day is 4-6 times and the catheter size should be 12-14 Fr. Less frequent catheterisation results in higher catheterisation volumes and a higher risk of UTI (1,100-103). More frequent catheterisation increases the risk of cross-infections and other complications (1,100-103). Bladder volume at catheterisation should be lower than 400 mL.
The prevalence of complications can be limited by adequate patient education, use of nontraumatising techniques and adequate precautions to prevent infections (11,104).
Indwelling transurethral catheterisation and, to a lesser extent, suprapubic cystostomy are significant and early risk factors for UTI and other complications (11,16,105-114). Silicone catheters are preferred because they are less susceptible to encrustation and because of the high incidence of latex allergy in the NLUTD population.
4.3.2 Recommendations for catheterisation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent catheterisation is the standard treatment for patients who are</td>
<td></td>
</tr>
<tr>
<td>unable to empty their bladder.</td>
<td></td>
</tr>
<tr>
<td>Patients should be well instructed in the technique and risks of IC.</td>
<td></td>
</tr>
<tr>
<td>Aseptic IC is the method of choice.</td>
<td></td>
</tr>
<tr>
<td>The catheter size should be 12-14 Fr.</td>
<td></td>
</tr>
<tr>
<td>The frequency of IC is 4-6 times per day.</td>
<td></td>
</tr>
<tr>
<td>The bladder volume should remain below 400 mL.</td>
<td></td>
</tr>
<tr>
<td>Indwelling transurethral and suprapubic catheterisation should be used only</td>
<td></td>
</tr>
<tr>
<td>exceptionally, under close control, and the catheter should be changed</td>
<td></td>
</tr>
<tr>
<td>frequently. Silicone catheters are preferred and should be changed every</td>
<td></td>
</tr>
<tr>
<td>2-4 weeks, while (coated) latex catheters need to be changed every 1-2</td>
<td></td>
</tr>
<tr>
<td>weeks.</td>
<td>A</td>
</tr>
</tbody>
</table>

IC = intermittent catheterisation.

4.3.3 Intravesical drug treatment

To reduce DO, anticholinergics can also be applied intravesically (115-121). This approach may reduce adverse effects because the anticholinergic drug is metabolised differently (119) and a greater amount is sequestered in the bladder, even more than with electromotive administration (120,121).

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres and thereby decrease DO for a period of a few months until the sensation of these fibres has been restored (122-127).

The dosage is 1-2 mMol capsaicin in 100 mL 30% alcohol, or 10-100 nMol resiniferatoxin in 100 mL 10% alcohol for 30 minutes. Resiniferatoxin has about a 1,000-fold potency compared to capsaicin, with less pain during the instillation, and is effective in patients refractory to capsaicin. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A injections in the detrusor (127).

4.3.4 Intravesical electrostimulation

Intravesical electrostimulation (128) enhances the sensation for bladder filling and urge to void and may restore the volitional control of the detrusor (11,129,130). Daily stimulation sessions of 90 minutes with 10 mApulses of 2 ms duration at a frequency of 20 Hz (130,131) are used for at least 1 week (131). It appears that patients with peripheral lesions are the best candidates, that the detrusor muscle must be intact, and that at least some afferent connection between the detrusor and the brain must still be present (11,130,131). Also, the positioning of the stimulating electrodes and bladder filling are important parameters (132). With these precautions, the results in the literature are still not unequivocal: both positive (129,131,133,134) and negative (LE: 3) (135,136) results have been reported.

4.3.5 Botulinum toxin injections in the bladder

Botulinum toxin causes a long-lasting but reversible chemical denervation that lasts for about 9 months (137-143). The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. Botulinum toxin A has been proven effective in a randomised placebo-controlled trial in NLUTD (144).

Repeated injections seem to be possible without loss of efficacy (143,145,146). Generalised muscular weakness is an occasional adverse effect (141,143,146). Histological studies have not found ultrastructural changes after injection (147).

4.3.6 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the upper urinary tract. This can be achieved by surgical interventions (bladder neck or sphincter incision or urethral stent) or by chemical denervation of the sphincter. Incontinence may result and can be managed by external devices (see Section 4.2.5).

Botulinum toxin sphincter injection can be used to treat detrusor sphincter dyssynergia effectively by injection in a dosage that depends on the preparation used. The dyssynergia is abolished for a few months, necessitating repeat injections. The efficacy of this treatment is high and there are few adverse effects (148-150).

Balloon dilatation: although favourable immediate results were reported (151), no further reports since 1994 have been found. Consequently, this method is no longer recommended.
Sphincterotomy: by staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra (1,11,144). The laser technique appears to be advantageous (1,152). Sphincterotomy also needs to be repeated at regular intervals in a substantial proportion of patients (153), but is efficient and without severe adverse effects (1,9,151-154). Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered (1,155).

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) (1,9,152,155). When the detrusor is hypertrophied and causes thickening of the bladder neck, this procedure makes no sense (1).

Stents: Implantation of urethral stents causes the continence to be dependent on the adequate closure of the bladder neck only (1,4). Although the results are comparable with sphincterotomy and the stenting procedure has a shorter surgery time and reduced hospital stay (156,157), the costs (1) and possible complications or re-interventions (156,158,159) are limiting factors in its use.

Increasing bladder outlet resistance: This can improve the continence condition. Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with NLUTD (4,16,160-164).

Urethral inserts: Urethral plugs or valves for management of (female) stress incontinence have not been applied in patients with NLUTD. The experience with active pumping urethral prosthesis for treatment of the underactive or acontractile detrusor was disappointing (165).

### 4.3.7 Recommendations for minimal invasive treatment*

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity.</td>
<td>A</td>
</tr>
<tr>
<td>Sphincterotomy is the standard treatment for detrusor sphincter dyssynergia.</td>
<td>A</td>
</tr>
<tr>
<td>Bladder neck incision is effective in a fibrotic bladder neck.</td>
<td>B</td>
</tr>
</tbody>
</table>

*Guidelines for catheterisation are listed separately under Section 4.3.2.

### 4.4 Surgical treatment

#### 4.4.1 Urethral and bladder neck procedures

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure during the filling, which may become even higher during the voiding phase. Procedures to treat sphincteric incontinence are suitable only when the detrusor activity is, or can be, controlled, when no significant reflux is present. Moreover, these procedures require the urethra and bladder neck to be in good condition and mostly result in intermittent catheterisation being performed after the procedure (4).

Urethral sling: Various materials have been used for this procedure with enduring positive results (4,166-179). The procedure is established in women; for men, the artificial sphincter is obviously the first choice (4).

Artificial urinary sphincter: This device has stood the test of time in patients with NLUTD (4). It was introduced by Light and Scott (180) for this patient group and the need for revisions (181) has decreased significantly with new generations of devices (172,182-185).

Functional sphincter augmentation: By transposing the gracilis muscle to the bladder neck (186) or to the proximal urethra (187), the possibility exists for creating a functional autologous sphincter by electrical stimulation (186,187). This would open the possibility of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter (188) procedure for bladder neck reconstruction in children with bladder exstrophy and the Kropp urethral lengthening (189) improved by Salle (190) are established methods to restore continence provided that intermittent catheterisation is practiced and/or bladder augmentation is performed (172,181,189-200).

#### 4.4.2 Detrusor myectomy (auto-augmentation)

The idea of enlarging a shrunken bladder by removing lateral detrusor tissue to free the entrapped ureter in a non-functional fibrotic detrusor was put forward by Couvelaire (201). Since its clinical introduction by
Cartwright and Snow (202) in children and by Stöhrer (203) in adults, this procedure for reducing DO or improving low detrusor compliance has gained popularity because of its acceptable long-term results, its low surgical burden, its low rate of long-term adverse effects, its positive effect on the patient’s QoL, and because it does not preclude further interventions (1,4,202-221).

The procedure is performed extraperitoneally under general anaesthesia and consists of the dissection of about 20% of the detrusor tissue around the umbilicus, leaving the mucosa intact (1,202,203). A diverticulum will develop, but this may take 1-2 years in adults (1,191,192). A laparoscopic procedure (205,209,213,222), covering of the mucosa at the detrusor defect (transperitoneal) (24,212,214,218), supporting the bladder (202,218), or simple incision of the detrusor muscle (detrusor myotomy) (220,221) are proposed variations of the procedure but offer no essential advantages.

4.4.3 Denervation, deafferentation, neurostimulation, neuromodulation

Various procedures estimated to destroy the peripheral detrusor innervation have been abandoned because of poor long-term results and severe complications (4). These procedures include bladder distension, cytolysis, transvaginal denervation (Ingelman-Sundberg procedure) and subtrigonal phenol injections.

Sacral rhizotomy, also known as sacral deafferentation (SDAF), has achieved some success in reducing DO (16,223-227), but it is used nowadays mostly as an adjuvant to sacral anterior root stimulation (228-239). Alternatives for rhizotomy are sought in this treatment combination (240-242).

Sacral anterior root stimulation (SARS) is aimed at producing a detrusor contraction. The technique was developed by Brindley (243) and is applicable only in complete lesions above the implant location because of its stimulation amplitude over the pain threshold. The urethral sphincter efferents are also stimulated, but as the striated muscle relaxes faster than the smooth muscle of the detrusor, a so-called ‘post-stimulus voiding’ will occur. This approach has been successful in highly selected patients (228-239). By changing the stimulation parameters, this method can also induce defecation or erection.

The sacral nerve stimulation or sacral neuromodulation is based on the research by Schmidt and Tanagho (244). This technique stimulates the afferents and thereby probably restores the correct balance between excitatory and inhibitory impulses from and to the pelvic organs at a sacral and supra-sacral level, thus reducing the DO (28,245). It is used either as a temporary procedure using foramen electrodes with an external stimulator, with the expectation that the changes will persevere after treatment, or as a chronic procedure with an implanted stimulator. In the latter case, a test procedure, the percutaneous nerve evaluation (PNE), with an external stimulator is performed before the implant to judge the patient’s response. This procedure also has considerable success in selected patients (210,246-250).

On the basis of the successful application of these systems, future developments towards a device that may be more integrated in the body are under research (251).

4.4.4 Bladder covering by striated muscle

When the bladder is covered by a (part of) striated muscle that can be stimulated electrically, or ideally could be contracted volitionally, an acontractile bladder could be restored to perform a voiding function. The rectus abdominis (252) and the latissimus dorsi (253) have been used successfully in patients with NLUTD.

4.4.5 Bladder augmentation or substitution

Replacing or expanding the bladder by intestine or other passive expandable coverage will reduce detrusor compliance and at least reduce the pressure effect of DO. The inherent complications associated with these procedures include recurrent infection, stone building, perforation or diverticula, possible malignant changes, and for intestine metabolic abnormality, mucus production and impaired bowel function (4,254-256). Since the age of the NLUTD patient population, when the surgery is performed, is generally much lower than that of patients with bladder malignancy, who are elected for this surgery, it is important that any possible, very long-term, complications in particular are appraised. Thus, the procedures should be used with caution in NLUTD patients, but may become necessary if all less-invasive treatment methods have failed.

Bladder augmentation, by procedures such as clam cystoplasty, is a valid option to decrease detrusor pressure and increase bladder capacity, whenever more conservative approaches have failed. A number of different techniques have been published. The results of the various procedures are very good and comparable (208,210-212,215-217,255-258). Bladder substitution to create a low pressure reservoir may be indicated in patients with severely thick and fibrotic bladder wall. Scaffolds, probably of tissue-engineered material for bladder augmentation or substitution or alternative techniques, are promising future options (216,259-264).

4.4.6 Urinary diversion

When no other therapy has been successful, urinary diversion must be considered for the protection of the upper tract and for the patient’s QoL (4,265).
**Continent diversion:** This should be the first choice for diversion. In patients for whom indwelling catheterisation or suprapubic catheterisation is the only feasible treatment option, change to a continent stoma may be a better prospect (4). Some patients with limited dexterity prefer a stoma to using the urethra for catheterisation (4). The continent stoma is created following various techniques. All of them, however, do show frequent complications, including leakage or stenosis (4,266). The short-term continence rates are over 80% and good protection of the upper urinary tract is achieved (4,13,264-278). For cosmetic reasons, the umbilicus is often used for the stoma site, but this may have a higher risk of stenosis (269,271,276).

**Incontinent diversion:** If catheterisation is impossible, incontinent diversion with urine collecting devices are indicated. Fortunately, nowadays, this indication is seldom because many appropriate alternatives can be offered (4). Ultimately, it could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in devastated LUTs, when the upper urinary tract is severely compromised, and in patients who refuse other therapy (4). An ileal segment is used for the deviation in most cases (4,279-283). The rather poor long-term results and the expected complications warrant a permanent follow-up (4).

**Undiversion:** Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of the detrusor pressure and the incontinence (4). Also, in young patients, body image may play a role (273). The patient must be carefully counselled and must comply meticulously with the instructions (4). Successful undiversion can then be performed (284).

### 4.5 Recommendations for surgical treatment

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor Overactive</td>
<td>Detrusor myectomy is an acceptable option for the treatment of overactive bladder when more conservative approaches have failed. It is limited invasive and has minimal morbidity.</td>
</tr>
<tr>
<td></td>
<td>Sacral rhizotomy with SARS in complete lesions and sacral neuromodulation in incomplete lesions are effective treatments in selected patients.</td>
</tr>
<tr>
<td></td>
<td>Bladder augmentation is an acceptable option for decreasing detrusor pressure whenever less invasive procedures have failed. For the treatment of a severely thick or fibrotic bladder wall, a bladder substitution might be considered.</td>
</tr>
<tr>
<td>Underactive</td>
<td>SARS with rhizotomy and sacral neuromodulation are effective in selected patients.</td>
</tr>
<tr>
<td></td>
<td>Restoration of a functional bladder by covering with striated muscle is still experimental.</td>
</tr>
<tr>
<td>Urethra Overactive (DSD)</td>
<td>Prefer to guidelines for minimal invasive treatment (see Section 4.3.6).</td>
</tr>
<tr>
<td>Underactive</td>
<td>The placement of a urethral sling is an established procedure.</td>
</tr>
<tr>
<td></td>
<td>The artificial urinary sphincter is very effective.</td>
</tr>
<tr>
<td></td>
<td>Transposition of the gracilis muscle is still experimental.</td>
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</table>

*DSD = detrusor sphincter dyssynergia; SARS = sacral anterior root stimulation.*

### 4.6 References


http://www.springerlink.com/content/k16411w744170641/


http://icsoffice.org/Publications/ICI_2/chapters/Chap10E.pdf


http://www.springerlink.com/content/9cevbv7hayf09xta/


5. URINARY TRACT INFECTION IN NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

5.1 Introduction
A detailed discussion of the clinical presentation, diagnosis, microbiological considerations and treatment strategies of complicated UTI can be found in the EAU Guidelines on Urological Infections (1). As stated in these guidelines, bacteriuria in patients with SCI should not be treated, even in cases of intermittent catheterisation. Generally, most knowledge concerning UTI in neurogenic patients comes from studies of patients with SCI and is therefore not directly transferable to other populations, such as MS, stroke, or PD.

5.2 Recurrent urinary tract infection in neurogenic patients
Recurrent UTI in patients with NLUTD may indicate a suboptimal management of the underlying functional problem, e.g. high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function and the removal of bladder stones or other direct supporting factors are mandatory. Additionally, UTI prevention strategies can be applied (1).

5.3 Prevention
It is generally agreed that the best prevention of UTI in neurogenic patients is a well-balanced management of the LUTD, including low-pressure urine storage, maintaining a periodical, low resistance and ensuring complete voiding. If clean, intermittent catheterisation (CIC) is used for emptying, aseptic technique and sterile lubricated (2) or hydrophilic catheters (3,4) should be used. Regular voiding and a minimal daily fluid intake of 30 mL/kg body weight are considered to be supportive factors in UTI prevention.

Various approaches have been tried to minimise UTIs in neurogenic bladder. Randomised controlled trials have shown that cranberry extracts have no benefit (5-7). Research has also shown that both methenamine hippurate (8) and bladder irrigation are ineffective (9). Although urine acidification therapy using drugs, such as L-methionine, is widely used in neurogenic patients in an attempt to prevent UTIs, there is little scientific evidence to support its use. Low-dose, long-term, antibiotic prophylaxis may be an option for patients with recurrent UTI (10), but has the disadvantage of possibly increasing bacterial resistance (11). Vaccination therapy for UTI prevention has not been tested in neurogenic patients.

5.3.1 Recommendations for the treatment of urinary tract infection

<table>
<thead>
<tr>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Bacteriuria in patients with spinal cord injury should not be treated, even in</td>
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<td>cases of intermittent catheterisation.</td>
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<tr>
<td>As in the general population, the use of long term antibiotics in recurrent</td>
<td></td>
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<tr>
<td>UTIs may cause bacterial resistance and caution is advised.</td>
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<tr>
<td>Protection of the urinary tract is the main focus.</td>
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</tbody>
</table>

UTI = urinary tract infection.

5.4 References
6. TREATMENT OF VESICO-URETERAL REFUX

6.1 Treatment options

The treatment options for vesico-ureteral reflux in patients with NLUTD do not differ essentially from those in other reflux patients. They become necessary when the high intravesical pressure during the filling phase or during the voiding phase have been treated successfully, but where the reflux did not resolve (1-4). Subtrigonal injections with bulking agents or ureteral re-implantation are the standard procedures.

Subtrigonal injections of bulking agents: This minimal invasive procedure has a relatively good effect with complete success in about 65% of patients (5-12). It can also be easily repeated if not effective and thereby the success rate can be increased to about 75% after the second or third session.

Ureteral re-implantation: This technique has an immediate and long-lasting result in over 90% of the patients (11-13). In deciding which procedure will be offered to the patient, the relative risks of more invasive surgery and of less successful therapy should be considered.


6.2 References

7. SEXUAL (DYS)FUNCTION AND FERTILITY

7.1 Spinal cord injury and sexuality - introduction
Neurological diseases and injuries have a distinct impact on sexual health, but guidelines for their management are still lacking (1). Periodical check-ups using validated questionnaires will help to assess and therefore improve sexual rehabilitation and response (2) (LE: 3).

7.2 Male sexuality: erectile dysfunction
7.2.1 Medical treatment - Phosphodiesterase type 5 inhibitors
Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in men with SCI and ED. They are safe and effective for long-term use. The most common side-effects in men with SCI are headache and flushing, while men with tetraplegia or high-level paraplegia may have postural hypotension for several
hours after using a PDE5I.

Phosphodiesterase type 5 inhibitors are currently the first-line treatment option for ED in patients with SCI because of their high efficacy and safety rates (3-5) (LE: 1b). However, little is known about the effect on erectile function in neurological patients. Tadalafil and sildenafil citrate are effective and safe long-term treatments for patients with MS and PD, respectively (8-11) (LE: 1b).

The great majority of neurogenic patients require long-term therapy for ED. However, some patients have a low compliance rate or they stop therapy because of side-effects (3). In addition, some patients with severe neurological damage may be resistant to PDE5Is (12).

7.2.2 Mechanical devices
Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular (6,7).

7.2.3 Intracavernosal injections
Patients not responding to oral drugs may be offered intracavernosal injections. Intracavernosal penile injectable medications (ICI) are very effective for the treatment of ED in men with SCI, but their use requires careful dose titration and some precautions. The reported complications of intracavernous drugs include priapism and corpora cavernosa fibrosis.

An intracavernosal injection of vasoactive medication is the first therapeutic option to consider in patients taking nitrate medications, for whom there are concerns about drug interactions with PDE5Is, or in patients for whom PDE5Is are ineffective.

Topical agents for penile smooth muscle relaxation (prostaglandin) or intraurethral preparation of prostaglandin E1 (MUSE) were found to be less effective in SCI patients suffering from ED (13).

7.2.4 Penile prostheses
Penile prostheses may be effective for treatment of ED in men with SCI and should be offered when all conservative treatments have failed. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type (14-16).

7.2.5 Recommendations sexual dysfunction

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Oral PDE5Is are the first-line treatment for erectile dysfunction in men with</td>
<td>A</td>
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<tr>
<td>spinal cord injury.</td>
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<tr>
<td>Intracavernosal injections of vasoactive drugs (alone or in combination) are</td>
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<tr>
<td>the second-line treatment when oral medications have failed.</td>
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<tr>
<td>Mechanical devices such as vacuum devices and rings may be effective but are</td>
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<tr>
<td>not as popular.</td>
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<tr>
<td>Surgical prostheses should be reserved for selected patients who have not</td>
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<td>responded to conservative therapies.</td>
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7.3 Male fertility
Reproductive dysfunction in men with SCI is a common condition and is due to a combination of ED, ejaculatory failure, and abnormal semen parameters, even if the definitive causal mechanism is unknown (17) (LE: 3). Assisted reproductive technologies may be needed.

Pregnancy rates are lower than in the general population. But since the advent of intracytoplasmic sperm injection (ICSI) men with SCI now have a good chance of becoming biological fathers (18-20).

In men with retrograde ejaculation, the use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation (21). More comparative trials are needed to evaluate the impact of intracavernosal injections on ejaculation and orgasmic function, their early use for increasing the recovery rate of a spontaneous erection, and their effectiveness and tolerability in the long-term (3). Prostatic massage is a safe and easy method to use for obtaining semen in men with lesions above T10 (22).

The two most commonly used methods of sperm retrieval are vibrostimulation (VS) and transrectal electroejaculation (EEJ) (23-25). Semen retrieval is more likely with VS in men with lesions above T10 (26-28).

Midodrine may be combined with VS in men not responding to VS alone. However, EEJ is the second choice for sperm retrieval when repeated tries at VS have failed (29).

Surgical procedures, such as epididymal (MESA) or testicular (TESE) sperm retrieval, may be used if VS and EEJ are not successful (30,31).
7.3.1  Sperm quality and motility

The following has been reported about sperm quality and motility:

- Vibratory stimulation produces samples with better sperm motility than electrostimulation (24,32).
- Antegrade samples have better sperm motility than retrograde samples.
- EEJ with interrupted current produces better sperm motility than does continuous current (33).
- Bladder management with clean intermittent catheterisation may improve semen quality compared to indwelling catheterisation, reflex voiding or bladder expression (34).
- Sperm quality in patients with SCI is enhanced by processing in able-bodied seminal plasma (35).

There are no relevant publications about fertility in other neurological pathologies.

7.4  Female sexuality

Studies have shown that most women (65-80%) continue to be sexually active after SCI, but to a much lesser extent than before injury. In addition, about 25% of women with an SCI report a decreased satisfaction with their sexual life (37-39).

Studies show that the greatest physical barrier to sexual activity is urinary leakage. Problems with positioning and spasticity affect mainly tetraplegics. Peer support may help to optimise the sexual adjustment of women with SCI in achieving a more positive self-image, self-esteem and feelings of being attractive to themselves and others (40-43).

The use of specific drugs for sexual dysfunctions is indicated to treat inadequate lubrication. Sildenafil may partially reverse subjective sexual arousal difficulties, while manual and vibratory clitoral stimulation may increase genital responsiveness (44,45).

Neurophysiological studies have shown that women with the ability to perceive T11-L2 pinprick sensations may have psychogenic genital vasocongestion, while reflex lubrication and orgasm is more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5). These findings are true, even when it has not been shown in an individual woman that a specific level and degree of lesion is the cause of a particular sexual dysfunction. In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions (46-48).

Studies have reported dissatisfaction with the quality and quantity of sexuality related rehabilitation services for women with SCI and that affected women were less likely to receive sexual information than men (48-50).

7.5  Female fertility

The reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately 6 months post-SCI (51). About 70% of sexually active women use some form of contraception after injury, but fewer women use the birth control pill compared to before their injury (52).

Although pregnancy is usually normal, women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Complications of labour and delivery include bladder problems, spasticity, pressure sores, and anaemia autonomic dysreflexia (53,54). Obstetric outcomes include higher rates of caesarean sections and an increased incidence of low birth-weight babies (55).

Epidural anaesthesia is chosen and effective for most patients with autonomic dysreflexia during labour and delivery (56,57).

There is very little published data on women’s experience of the menopause following an SCI (58).

There are no relevant publications about sexuality and fertility in other neurological pathologies.

7.6  References


8. QUALITY OF LIFE

8.1 Introduction
Quality of life (QoL) is a very important aspect of the overall management of NLUTD patients (1). The type of bladder management may influence the health-related QoL (HRQoL) in patients with SCI (2). The effectiveness of urological treatment and the urodynamic functionality of the neurogenic bladder have become increasingly determinant of patient QoL (3). QoL is a reflection of the individual’s ability to cope with the new life situation (4). Despite the limitations associated with neurological pathology, adequate treatment is possible in most patients and should not interfere with social independence. QoL can be influenced by several factors including family support, adjustment and coping ability, productivity, self-esteem, financial stability, education, and the
physical and social environment (5) (LE: 3). Age, sex, ethnicity, and the patient’s acceptance of the condition should also be taken into consideration when assessing QoL (6) (LE: 3).

8.2 Quality of life assessment
There are no specific QoL questionnaires for neurogenic bladder dysfunction or NLUTD. The only validated tools are a generic Visual Analogue Scale (VAS) for symptom bother, and Qualiveen® which is a specific tool for QoL in spinal cord lesion and multiple sclerosis patients. Qualiveen appears to be a discriminative evaluation instrument (3,7-9) and a short form is now available (10).

More commonly, QoL is assessed secondarily by generic HRQoL questionnaires such as the Incontinence Quality of Life Instrument (I-QOL), King's Health Questionnaire (KHQ), Short Form 36 Health Survey Questionnaire (SF-36), Euro Quality of Life-5 Domains (EQ-5D), Short Form 6D Health Survey Questionnaire (SF-6D), or the Health Utilities Index (HUI).

Furthermore, the quality-adjusted life year (QALY) metric quantifies patient outcomes, by weighting years of life spent in a specified health state by a factor representing the value that society or patients place on that health state (11) (LE: 3).

8.3 Therapy influence on quality of life
Appropriate therapies should manage symptoms, improve urodynamic parameters, functional abilities and QoL, and avoid secondary complications (8,12). Changes in NLUTD appear to be a major determinant of patient QoL (13,14) (LE: 2a).

8.4 Conclusions and recommendations

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>One of the main aims of therapy is to improve quality of life.</td>
<td>1</td>
</tr>
<tr>
<td>There is a lack of disease-specific outcome measures assessing HRQoL in patients with NLUTD.</td>
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</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Quality of life should be assessed when evaluating lower urinary tract symptoms in neurogenic patients and when treating neurogenic bowel dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>The available validated tools are Qualiveen, a specific long- and short-form tool for spinal cord lesion and multiple sclerosis patients and VAS for symptom bother. In addition, generic (SF-36) or specific tools for incontinence (I-QOL) questionnaires can be used.</td>
<td>B</td>
</tr>
</tbody>
</table>

8.5 References
9. FOLLOW-UP

9.1 Introduction

Neurogenic lower urinary tract dysfunction is an unstable condition and can vary considerably, even within a relatively short period. Meticulous follow-up and regular checks are necessary (1-20). Depending on the type of the underlying neurological pathology and on the current stability of the NLUTD, the interval between the detailed investigations should not exceed 1-2 years. In patients with multiple sclerosis and in acute SCI, this interval is of course much smaller. Urine dip sticks should be available for the patient and urinalysis should be performed at least every second month. The upper urinary tract, the bladder shape, and residual urine should be checked every 6 months. Physical examination and blood and urine laboratory should take place every year. Any sign indicating a risk factor warrants specialised investigation.

9.2 Guidelines for follow-up

| Possible UTI checked by the patient (dip stick). |
| Urinalysis every second month. |
| Upper urinary tract, bladder morphology, and residual urine every 6 months (ultrasound). |
| Physical examination, blood chemistry, and urine laboratory every year. |
| Detailed specialist investigation every 1-2 years and on demand when risk factors emerge. The investigation is specified according to the patient’s actual risk profile, but should in any case include a video-urodynamic investigation and should be performed in a leading neuro-urological centre. |
| All of the above should be more frequent if the neurological pathology or the NLUTD status demand this. |

UTI = urinary tract infection; NLUTD = neurogenic lower urinary tract dysfunction.
9.3 References


10. CONCLUSIONS

Neurogenic lower urinary tract dysfunction is a multi-faceted pathology. It requires an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient’s expectations about his future social and physical situation with respect to the NLUTD.

The urologist or paediatric urologist can select from a wealth of therapeutical options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, a close surveillance is necessary for the patient’s entire life.

With these guidelines, we offer you expert advice on how to define the patient’s NLUTD condition as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as less invasive as possible.
### 11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVA</td>
<td>cerebrovascular</td>
</tr>
<tr>
<td>DLPP</td>
<td>detrusor leak point pressure</td>
</tr>
<tr>
<td>DO</td>
<td>detrusor overactivity</td>
</tr>
<tr>
<td>DSD</td>
<td>detrusor sphincter dyssynergia</td>
</tr>
<tr>
<td>EEJ</td>
<td>electroejaculation</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography, electromyogram</td>
</tr>
<tr>
<td>FVC</td>
<td>frequency volume chart</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>IC</td>
<td>intermittent catheterisation</td>
</tr>
<tr>
<td>ISC</td>
<td>intermittent self-catheterisation</td>
</tr>
<tr>
<td>ICS</td>
<td>international Continence Society</td>
</tr>
<tr>
<td>LPP</td>
<td>leak point pressure</td>
</tr>
<tr>
<td>LMNL</td>
<td>lower motor neuron lesion</td>
</tr>
<tr>
<td>LUT</td>
<td>lower urinary tract</td>
</tr>
<tr>
<td>LUTD</td>
<td>lower urinary tract dysfunction</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>MTC</td>
<td>micturition time chart</td>
</tr>
<tr>
<td>NDO</td>
<td>neurogenic detrusor overactivity</td>
</tr>
<tr>
<td>NLUTD</td>
<td>neurogenic lower urinary tract dysfunction</td>
</tr>
<tr>
<td>PNE</td>
<td>percutaneous nerve evaluation test</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>SARS</td>
<td>sacral anterior root stimulation</td>
</tr>
<tr>
<td>SCI</td>
<td>spinal cord injury</td>
</tr>
<tr>
<td>SDAF</td>
<td>sacral deafferentation</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>UMNL</td>
<td>upper motor neuron lesion</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
</tr>
<tr>
<td>VS</td>
<td>vibrostimulation</td>
</tr>
</tbody>
</table>

**Conflict of interest**

All members of the Neurogenic Lower Urinary Tract Dysfunction Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. METHODOLOGY

1.1 Introduction
The European Association of Urology (EAU) Urolithiasis Guidelines Panel have prepared these guidelines to help urologists assess evidence-based management of stones/calculi and incorporate recommendations into clinical practice.

The document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision.

1.2 Data identification
For this 2012 (limited) update of the Urolithiasis guidelines, a scoping search, covering all content, was performed. Time frame of the search was August 10th, 2011 to October 16th, 2012. This search was limited to level 1 evidence (systematic reviews [SRs] and meta-analyses of randomised controlled trials [RCTs]) and English language publications in peer-reviewed journals. Animal studies were excluded.

The search identified 128 unique records of which 12 references were selected for inclusion in this document, replacing, in some instances, lower level studies, or to underpin new information. Selection of the papers was done through a consensus meeting of the Panel held in December 2012.

A more detailed summary of changes can be found below.

Annual scoping searches will be repeated as a standard procedure.

1.3 Evidence sources
Searches were carried out in the Cochrane Library Database of Systematic Reviews, Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform. The searches used the controlled terminology and the use of free text ensured search sensitivity.

Randomised controlled trial strategies were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform and then translated into Datastar syntax.

There is a need for ongoing re-evaluation of the current guidelines by an expert panel. It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients - also taking personal values and preferences/individual circumstances of patients into account.

1.4 Level of evidence and grade of recommendation
References in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence (LE)*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

* Modified from Sackett et al. (1).

When recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not translate into a grade A recommendation when there are methodological limitations or disparity in published results.
Absence of high-level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptions where corroborating studies cannot be performed, perhaps for ethical or other reasons, and unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence must be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can it address local/national preferences systematically. The expert panels include this information whenever it is available.

Table 2: Grade of recommendation (GR)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without RCTs.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (1).

1.5 Publication history

The current 2013 print presents an update of the 2012 publication of the EAU Urolithiasis Guidelines, but for Chapter 11 (Metabolic evaluation and recurrence prevention), which has been replaced in its entirety. A more detailed listing is provided in section 1.5.1 “Summary of changes”. It has been attempted to limit the discussion and background information, focussing on the presentation of findings resulting in treatment recommendations. The expert panel aim to further progress this strategy in subsequent updates. All flowcharts have been reevaluated, resulting in the adaptation of existing flowcharts and the inclusion of new flowcharts, most notably in the new Chapter 11.

The first EAU Guidelines on Urolithiasis were published in 2000. Subsequent updates were presented in 2001 (partial), 2005 (comprehensive), 2008 (comprehensive), 2009, 2010, 2011 (limited) and 2012 (comprehensive update).

A quick reference document presenting the main findings of the urolithiasis guidelines is also available alongside several scientific publications in European Urology and the Journal of Urology (5-7). All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

Chapter 11 - Metabolic evaluation and recurrence prevention, was peer-reviewed prior to publication.

1.5.1 Summary of changes

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Short description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.2</td>
<td>Evaluation of patients for whom further treatment of renal stones is planned.</td>
<td>Additional recommendation for imaging has been included.</td>
</tr>
<tr>
<td>4.1.1</td>
<td>Pain relief.</td>
<td>A statement was added.</td>
</tr>
<tr>
<td>4.1.3</td>
<td>Recommendations for analgesia during renal colic.</td>
<td>A recommendation was added.</td>
</tr>
<tr>
<td>5.3.1</td>
<td>Choice of medical agents.</td>
<td>The statement has been altered. Nifedipine as a recommended medical treatment has been removed from the recommendations. Additionally, a caution for the use of medical expulsive therapy (MET) in children is provided.</td>
</tr>
<tr>
<td>5.6.</td>
<td>Endourology techniques.</td>
<td>This section has been significantly condensed, and technical information was removed.</td>
</tr>
<tr>
<td>5.6.2.1</td>
<td>Stone extraction.</td>
<td>The recommendations have been amended.</td>
</tr>
<tr>
<td>5.6.2.1</td>
<td>Stone extraction.</td>
<td>A new recommendation was added on the use of an alpha-blocker to reduce stent-related symptoms.</td>
</tr>
<tr>
<td>Section</td>
<td>Topic</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>6.4</td>
<td>Selection of procedure for active removal of kidney stones</td>
<td>The treatment algorithms for kidney stones and stones in the lower pole have been replaced. For stones &gt; 20 mm laparoscopy is no longer recommended. Treatment options include SWL and RIRS.</td>
</tr>
<tr>
<td>7.2</td>
<td>Residual stones. Therapy</td>
<td>A statement has been added regarding combination therapy.</td>
</tr>
<tr>
<td>8.2</td>
<td>Diagnostic imaging for stones in pregnancy</td>
<td>A statement regarding the limitations of ultrasound as an imaging modality has been included, as well as a statement on ureteroscopy. The recommendation regarding the use of other imaging modalities was removed.</td>
</tr>
<tr>
<td>9.1</td>
<td>Management of stone problems in children. Aetiology</td>
<td>A recommendation for stone analysis was added.</td>
</tr>
<tr>
<td>9.1.1</td>
<td>Nuclear imaging</td>
<td>The recommendations have been expanded.</td>
</tr>
<tr>
<td>10.1.2</td>
<td>Stones in urinary diversion and other voiding problems</td>
<td>Management. A new statement and a recommendation have been added.</td>
</tr>
<tr>
<td>10.2.2</td>
<td>Management of stones in patients with neurogenic bladder</td>
<td>A caution for latex allergy is included.</td>
</tr>
<tr>
<td>10.3.1</td>
<td>Management of stones in transplanted kidney. Aetiology and clinical presentation</td>
<td>A recommendation has been added for imaging assessment.</td>
</tr>
<tr>
<td>11</td>
<td>Metabolic evaluation</td>
<td>This chapter has been completely replaced. Both the structure as well as the content is entirely new. Diagnostic assessment and considerations have been captured in an algorithm, while treatment options are generally presented in tables.</td>
</tr>
</tbody>
</table>

**Potential conflict of interest statement**

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: [http://www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/online-guidelines/).

**References**


2. CLASSIFICATION OF STONES

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence (1-4).

2.1 Stone size
Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in largest diameter.

2.2 Stone location
Stones can be classified according to anatomical position: upper, middle or lower calyx; renal pelvis; upper, middle or distal ureter; and urinary bladder. Treatment of bladder stones is not discussed here.

2.3 X-ray characteristics
Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3), which varies according to mineral composition (3). Non-contrast-enhanced computer tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 6.3.4) (2,3).

Table 3: X-ray characteristics

<table>
<thead>
<tr>
<th>Radiopaque</th>
<th>Poor radiopacity</th>
<th>Radiolucent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate dihydrate</td>
<td>Magnesium ammonium phosphate</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>Apatite</td>
<td>Ammonium urate</td>
</tr>
<tr>
<td>Calcium phosphates</td>
<td>Cystine</td>
<td>Xanthine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,8-dihydroxyadenine</td>
</tr>
<tr>
<td>Drug-stones (Section 11.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.4 Aetiology of stone formation
Stones can be classified into those caused by: infection, or non-infectious causes (infection and non-infection stones); genetic defects; or adverse drug effects (drug stones) (Table 4).

Table 4: Stones classified by aetiology*

<table>
<thead>
<tr>
<th>Non-infection stones</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calcium oxalate</td>
<td></td>
</tr>
<tr>
<td>• Calcium phosphate (including brushite and carbonate apatite)</td>
<td></td>
</tr>
<tr>
<td>• Uric acid</td>
<td></td>
</tr>
<tr>
<td>Infection stones</td>
<td></td>
</tr>
<tr>
<td>• Magnesium ammonium phosphate</td>
<td></td>
</tr>
<tr>
<td>• Carbonate apatite</td>
<td></td>
</tr>
<tr>
<td>• Ammonium urate</td>
<td></td>
</tr>
<tr>
<td>Genetic causes</td>
<td></td>
</tr>
<tr>
<td>• Cystine</td>
<td></td>
</tr>
<tr>
<td>• Xanthine</td>
<td></td>
</tr>
<tr>
<td>• 2,8-dihydroxyadenine</td>
<td></td>
</tr>
<tr>
<td>Drug stones</td>
<td></td>
</tr>
</tbody>
</table>

*Section 11.4.2

2.5 Stone composition
Metabolic aspects are important in stone formation, and metabolic evaluation is required to rule out any disorders. Analysis in relation to metabolic disorders is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 5 lists the clinically most relevant substances and their mineral components.
Table 5: Stone composition

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Mineral name</th>
<th>Chemical formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>Whewellite</td>
<td>CaC₂O₄.H₂O</td>
</tr>
<tr>
<td>Calcium oxalate dihydrate</td>
<td>Wheddelite</td>
<td>CaC₂O₄.2H₂O</td>
</tr>
<tr>
<td>Basic calcium phosphate</td>
<td>Apatite</td>
<td>Ca₁₀(PO₄)₆.(OH)₂</td>
</tr>
<tr>
<td>Calcium hydroxyl phosphate</td>
<td>Hydroxylapatite</td>
<td>Ca₁₀(PO₄)₆(OH)</td>
</tr>
<tr>
<td>b-tricalcium phosphate</td>
<td>Whitlockite</td>
<td>Ca₆(PO₄)₂</td>
</tr>
<tr>
<td>Carbonate apatite phosphate</td>
<td>Dahlite</td>
<td>Ca₉(PO₄)₃.3(OH)</td>
</tr>
<tr>
<td>Calcium hydrogen phosphate</td>
<td>Brushite</td>
<td>CaHPO₄.2H₂O</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Aragonite</td>
<td>CaCO₃</td>
</tr>
<tr>
<td>Octacalcium phosphate</td>
<td>Octacalcium phosphate</td>
<td>Ca₉H₄(PO₄)₆ . 5H₂O</td>
</tr>
<tr>
<td>Uric acid dihydrate</td>
<td>Uricite</td>
<td>C₃H₄N₄O₄ . 2H₂O</td>
</tr>
<tr>
<td>Ammonium urate</td>
<td></td>
<td>NH₄₂(C₂H₃N₂O₂)</td>
</tr>
<tr>
<td>Sodium acid urate monohydrate</td>
<td></td>
<td>Na₂C₂H₃N₂O₂. H₂O</td>
</tr>
<tr>
<td>Magnesium ammonium phosphate</td>
<td>Struvite</td>
<td>MgNH₄PO₄.6H₂O</td>
</tr>
<tr>
<td>Magnesium acid phosphate tris</td>
<td>Newberyite</td>
<td>MgHPO₄.3H₂O</td>
</tr>
<tr>
<td>Magnesium ammonium phosphate</td>
<td></td>
<td>MgNH₄(PO₄) . 1H₂O</td>
</tr>
<tr>
<td>monohydrate</td>
<td></td>
<td>Dittmarite</td>
</tr>
<tr>
<td>Cystine</td>
<td></td>
<td>[SCH₂CH(NH₂)COOH]₂</td>
</tr>
<tr>
<td>Gypsum</td>
<td>Calcium sulphate dihydrate</td>
<td>CaSO₄.2 H₂O</td>
</tr>
<tr>
<td></td>
<td>Zinc phosphate tetrahydrate</td>
<td>Zn₃(PO₄)₂.4H₂O</td>
</tr>
<tr>
<td>Xanthine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,8-dihydroxyadenine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium urate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimagnesium phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matrix</td>
<td>Drug stones</td>
<td>• Active compounds crystallising in urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Substances impairing urine composition (Ch. 11.11)</td>
</tr>
<tr>
<td>Foreign body calculi</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.6 Risk groups for stone formation
The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, and is imperative for pharmacological treatment.

About 50% of recurrent stone formers have just one lifetime recurrence (4,5). Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low or high risk of recurrence (Table 6) (6,7).
Table 6: High-risk stone formers (6-12)

<table>
<thead>
<tr>
<th><strong>General factors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset of urolithiasis (especially children and teenagers)</td>
</tr>
<tr>
<td>Familial stone formation</td>
</tr>
<tr>
<td>Brushite-containing stones (CaHPO₄·₂H₂O)</td>
</tr>
<tr>
<td>Uric acid and urate-containing stones</td>
</tr>
<tr>
<td>Infection stones</td>
</tr>
<tr>
<td>Solitary kidney (the kidney itself does not particularly increase risk of stone formation, but prevention of stone recurrence is of more importance)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Diseases associated with stone formation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
</tr>
<tr>
<td>(i.e., jejuno-ileal bypass, intestinal resection, Crohn’s disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion)</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Genetically determined stone formation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystinuria (type A, B and AB)</td>
</tr>
<tr>
<td>Primary hyperoxaluria (PH)</td>
</tr>
<tr>
<td>Renal tubular acidosis (RTA) type I</td>
</tr>
<tr>
<td>2,8-dihydroxyadenine</td>
</tr>
<tr>
<td>Xanthinuria</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drugs associated with stone formation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary sponge kidney (tubular ectasia)</td>
</tr>
<tr>
<td>Ureteropelvic junction (UPJ) obstruction</td>
</tr>
<tr>
<td>Calyceal diverticulum, calyceal cyst</td>
</tr>
<tr>
<td>Ureteral stricture</td>
</tr>
<tr>
<td>Vesico-uretero-renal reflux</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
</tr>
<tr>
<td>Ureteroceles</td>
</tr>
</tbody>
</table>

2.7 References


3. DIAGNOSIS

3.1 Diagnostic imaging
Patients with urinary stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic. Standard evaluation includes detailed medical history and physical examination. Clinical diagnosis should be supported by appropriate imaging.

If available, ultrasonography (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures should not be delayed by imaging assessments. US is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calices, pelvis, and pyeloureteric and vesicoureteric junctions, as well as in patients with upper urinary tract dilatation. For stones > 5 mm, US has a sensitivity of 96% and specificity of nearly 100% (1). For all stone locations, sensitivity and specificity of US reduces to 78% and 31%, respectively (1).

The sensitivity and specificity of KUB radiography is 44-77% and 80-87%, respectively (2). KUB radiography should not be performed if NCCT is considered (3), however, it is helpful in differentiating between radiolucent and radiopaque stones and for comparison during follow-up.

<table>
<thead>
<tr>
<th>Reference</th>
<th>NCCT</th>
<th>IVU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Miller (5)</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>Niall (7)</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Sourtzis (4)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Yilmaz (6)</td>
<td>94%</td>
<td>97%</td>
</tr>
<tr>
<td>Wang (8)</td>
<td>99%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Recommendation LE GR

<table>
<thead>
<tr>
<th>With fever or solitary kidney, and when diagnosis is doubtful, immediate imaging is indicated.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

3.1.1 Evaluation of patients with acute flank pain
NCCT has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU), which was the gold standard for many years. NCCT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified.

Compared to IVU, NCCT shows higher sensitivity and specificity for identifying urinary stones (Table 7) (4-9).

Table 7: Comparison of NCCT and IVU

<table>
<thead>
<tr>
<th>Reference</th>
<th>NCCT</th>
<th>IVU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Miller (5)</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>Niall (7)</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Sourtzis (4)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Yilmaz (6)</td>
<td>94%</td>
<td>97%</td>
</tr>
<tr>
<td>Wang (8)</td>
<td>99%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Recommendation
NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU (10).

<table>
<thead>
<tr>
<th>Method</th>
<th>Radiation exposure (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUB radiography</td>
<td>0.5-1</td>
</tr>
<tr>
<td>IVU</td>
<td>1.3-3.5</td>
</tr>
<tr>
<td>Regular-dose NCCT</td>
<td>4.5-5</td>
</tr>
<tr>
<td>Low-dose NCCT</td>
<td>0.97-1.9</td>
</tr>
<tr>
<td>Enhanced CT</td>
<td>25-35</td>
</tr>
</tbody>
</table>

Table 8: Radiation exposure of imaging modalities (19-22)

Recommendation
If NCCT is indicated in patients with BMI < 30, use a low-dose technique.

3.1.2 Evaluation of patients for whom further treatment of renal stones is planned

Recommendation
A contrast study is recommended if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.

Enhanced CT is preferable because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. IVU may also be used.

* Upgraded based on panel consensus.

3.1.3 References


3.2 Diagnostics - metabolism-related

Each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood besides imaging. At that point, no distinction is made between high- and low-risk patients.
Table 9: Recommendations: basic laboratory analysis - emergency urolithiasis patients (1-4)

<table>
<thead>
<tr>
<th>Urine</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sediment/dipstick test of spot urine sample</td>
<td>A*</td>
</tr>
<tr>
<td>• red cells</td>
<td>A</td>
</tr>
<tr>
<td>• white cells</td>
<td></td>
</tr>
<tr>
<td>• nitrite</td>
<td></td>
</tr>
<tr>
<td>• approximate urine pH</td>
<td></td>
</tr>
<tr>
<td>Urine culture or microscopy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum blood sample</td>
<td>A*</td>
</tr>
<tr>
<td>• creatinine</td>
<td></td>
</tr>
<tr>
<td>• uric acid</td>
<td></td>
</tr>
<tr>
<td>• ionised calcium</td>
<td></td>
</tr>
<tr>
<td>• sodium</td>
<td></td>
</tr>
<tr>
<td>• potassium</td>
<td></td>
</tr>
<tr>
<td>Blood cell count</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>A*</td>
</tr>
<tr>
<td>If intervention is likely or planned:</td>
<td></td>
</tr>
<tr>
<td>Coagulation test (PTT and INR)</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

CPR = C-reactive protein; INR = international normalised ratio; PTT = partial thromboplastin time.

3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients. However, if no intervention is planned, examination of sodium, potassium, CRP, and blood coagulation time can be omitted.

Only patients at high risk for stone recurrence should undergo a more specific analytical programme (4). Stone-specific metabolic evaluation is described in Chapter 11.

The easiest means to achieve correct diagnosis is by analysis of a passed stone using a valid method as listed below (see 3.2.2). Once mineral composition is known, the potential metabolic disorders can be identified.

3.2.2 Analysis of stone composition

Stone analysis should be performed in all first-time stone formers.

In clinical practice, repeat stone analysis is needed in case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period (6).

Patients should be instructed to filter their urine to retrieve a concrement for analysis. Stone passage and restoration of normal renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) (5,7-10). Equivalent results can be obtained by polarisation microscopy, but only in centres with expertise.

Chemical analysis (wet chemistry) is generally deemed to be obsolete (5).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always perform stone analysis in first-time formers using a valid procedure (XRD or IRS).</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>Repeat stone analysis in patients:</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>• presenting with recurrent stones despite drug therapy;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• with early recurrence after complete stone clearance;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• with late recurrence after a long stone-free period because stone composition may change (3).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. TREATMENT OF PATIENTS WITH RENAL COLIC

4.1 Renal colic

4.1.1 Pain relief

Pain relief is the first therapeutic step in patients with an acute stone episode (1,2).

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in patients with acute stone colic (3-6), and have better analgesic efficacy than opioids. Patients receiving NSAIDs are less likely to require further analgesia in the short term.

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed (7,8) (Section 4.1.3). If an opioid is used, it is recommended that it is not pethidine.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>For symptomatic ureteral stones, urgent SWL as first-line treatment is a feasible option (9).</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In acute stone episodes, pain relief should be initiated immediately.</td>
<td>A</td>
</tr>
<tr>
<td>Whenever possible, an NSAID should be the first drug of choice.</td>
<td>A</td>
</tr>
</tbody>
</table>

4.1.2 Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 5.3.

For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and risk of recurrent pain (8,10,11). Although diclofenac can affect renal function in patients with already reduced function, it has no effect in patients with normal kidney function (LE: 1b) (12).

In a double-blind, placebo-controlled trial, recurrent pain episodes of stone colic were significantly fewer in patients treated with NSAIDs (as compared to no NSAIDs) during the first 7 days of treatment (11).

Daily α-blockers reduce recurrent colic (LE: 1a) (Section 5.3) (13,14).

If analgesia cannot be achieved medically, drainage, using stenting or percutaneous nephrostomy, or stone removal, should be performed.
4.1.3 **Recommendations for analgesia during renal colic**

<table>
<thead>
<tr>
<th>First choice: start with an NSAID, e.g. diclofenac*, indomethacin or ibuprofen**.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second choice: hydromorphone, pentazocine or tramadol.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Use α-blockers to reduce recurrent colics. 1a A

*Affects glomerular filtration rate (GFR) in patients with reduced renal function (15) (LE: 2a).

**Recommended to counteract recurrent pain after ureteral colic.

4.1.4 **References**


4.2 **Management of sepsis in obstructed kidney**

The obstructed kidney with all signs of urinary tract infection (UTI) is a urological emergency. Urgent decompression is often necessary to prevent further complications in infected hydronephrosis secondary to
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stone-induced, unilateral or bilateral renal obstruction.

The optimal method of decompression has yet to be established (1-3). However, it is known that compromised delivery of antibiotics into the obstructed kidney means that the collecting system must be drained to encourage resolution of infection.

4.2.1 Decompression
Currently, there are two options for urgent decompression of obstructed collecting systems:

• placement of an indwelling ureteral catheter;
• percutaneous placement of a nephrostomy catheter.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good-quality evidence to suggest that ureteric stenting has more complications than percutaneous nephrostomy (1,4,5).

Only two RCTs (2,5) have assessed decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteric stent insertion are less well described (1).

Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy (6,7).

Emergency nephrectomy may become necessary in highly complicated cases to eliminate further complications.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For sepsis with obstructing stones, the collecting system should be urgently decompressed, using percutaneous drainage or ureteral stenting.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Definitive treatment of the stone should be delayed until sepsis is resolved.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

4.2.2 Further measures
Following urgent decompression of the obstructed and infected urinary collecting system, both urine- and blood samples should be sent for culture-antibiogram sensitivity testing, and antibiotics should be initiated immediately thereafter. The regimen should be re-evaluated in the light of the culture-antibiogram test. Intensive care might become necessary.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect urine for antibiogram test following decompression.</td>
<td>A*</td>
</tr>
<tr>
<td>Start antibiotics immediately thereafter (+ intensive care if necessary).</td>
<td></td>
</tr>
<tr>
<td>Re-evaluate antibiotic regimen following antibiogram findings</td>
<td></td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

4.2.3 References
5. **STONE RELIEF**

When deciding between active stone removal and conservative treatment with medical expulsive therapy (MET), it is important to consider all the patients’ circumstances that may affect treatment decisions (1).

5.1 **Observation of ureteral stones**

5.1.1 **Stone-passage rates**

There are only limited data about spontaneous stone passage according to size (2,3). A meta-analysis of 328 patients harbouring ureteral stones < 10 mm investigated the likelihood of ureteral stone passage (Table 10) (2). These studies had limitations including non-standardisation of stone size measurement, and lack of analysis of stone position, stone-passage history, and time to stone passage.

<table>
<thead>
<tr>
<th>Stone size</th>
<th>Average time to pass</th>
<th>Percentage of passages (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mm (n = 224)</td>
<td>68% (46-85%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 mm (n = 104)</td>
<td>47% (36-58%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 2 mm</td>
<td>31 days</td>
<td></td>
</tr>
<tr>
<td>2-4 mm</td>
<td>40 days</td>
<td></td>
</tr>
<tr>
<td>4-6 mm</td>
<td>39 days</td>
<td></td>
</tr>
</tbody>
</table>

95% of stones up to 4 mm pass within 40 days (3).

**Recommendations**

In patients with newly diagnosed ureteral stones < 10 mm, and if active removal is not indicated (Chapter 6), observation with periodic evaluation is an optional initial treatment.

Such patients may be offered appropriate medical therapy to facilitate stone passage during observation.*

*see Section 5.3, Medical expulsive therapy (MET).

5.2 **Observation of kidney stones**

Observation of kidney stones, especially in calices, depends on their natural history (Section 6.2.1).

**Statement**

It is still debatable whether kidney stones should be treated, or whether annual follow-up is sufficient for asymptomatic caliceal stones that have remained stable for 6 months.

**Recommendations**

Kidney stones should be treated in case of growth, formation of de novo obstruction, associated infection, and acute or chronic pain.

Comorbidity and patient preference need to be taken into consideration when making treatment decisions.

If kidney stones are not treated, periodic evaluation is needed.

* Upgraded based on panel consensus.
5.3  **Medical expulsive therapy (MET)**

Drugs that expel stones might act by relaxing ureteral smooth muscle through inhibition of calcium channel pumps or α-1 receptor blockade (4,5).

MET should only be used in patients who are comfortable with this approach and when there is no obvious advantage from immediate active stone removal.

Meta-analyses have shown that patients with ureteral stones treated with α-blockers or nifedipine are more likely to pass stones with fewer episodes of colic than those not receiving such therapy (4,5).

**Statement LE**
There is good evidence that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain (4-16).

### 5.3.1 Medical agents

Tamsulosin is one of the most commonly used α-blockers (4,6,17-20). However, one small study has suggested that tamsulosin, terazosin and doxazosin are equally effective, indicating a possible class effect (21). This is also indicated by several trials demonstrating increased stone expulsion using doxazosin (4,21,22), terazosin (21,23), alfuzosin (24-27) naftopidil (28,29), and silodosin (30,31).

**Statement LE**
Several trials have demonstrated an α-blocker class effect on stone expulsion rates. 1b

With regard to the class effect of calcium-channel blockers, only nifedipine has been investigated (LE = 1a) (4,9-11,32,33).

Administration of tamsulosin and nifedipine is safe and effective in patients with distal ureteral stones with renal colic. However, tamsulosin is significantly better than nifedipine in relieving renal colic and facilitating and accelerating ureteral stone expulsion (11,32,33).

Based on studies with a limited number of patients (34,35) (LE 1b), no recommendation for the use of corticosteroids in combination with α-blockers in MET can be made.

**Statement LE**
There is no evidence to support the use of corticosteroids as monotherapy for MET. Insufficient data exist to support the use of corticosteroids in combination with α-blockers as an accelerating adjunct (3,21,34,35).

### Recommendations for MET

<table>
<thead>
<tr>
<th>Recommendations for MET</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For MET, α-blockers are recommended.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Patients should be counseled about the attendant risks of MET, including associated drug side effects, and should be informed that it is administered off-label**.</td>
<td>A*</td>
<td></td>
</tr>
<tr>
<td>Patients, who elect for an attempt at spontaneous passage or MET, should have well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Patients should be followed once between 1 and 14 days to monitor stone position and be assessed for hydronephrosis.</td>
<td>4</td>
<td>A*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>†</td>
</tr>
<tr>
<td>*</td>
</tr>
<tr>
<td>**</td>
</tr>
</tbody>
</table>

5.3.2  **Factors affecting success of medical expulsive therapy (tamsulosin)**

#### 5.3.2.1 Stone size

Due to the high likelihood of spontaneous passage of stones up to ~5 mm, MET is less likely to increase the stone-free rate (SFR) (5,36-39) (LE: 1b). However, MET does reduce the need for analgesics (4,6) (LE: 1a).

5.3.2.2  **Stone location**

The vast majority of trials have investigated distal ureteral stones (4). One RCT has assessed the effect of tamsulosin on spontaneous passage of proximal ureteral calculi 5-10 mm. The main effect was to encourage stone migration to a more distal part of the ureter (40) (LE: 1b).
5.3.2.3 **Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)**
Clinical studies and several meta-analyses have shown that MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs and reduce analgesic requirements (7,12,41-49) (LE: 1a).

5.3.2.4 **Medical expulsive therapy after ureteroscopy**
MET following holmium:YAG laser lithotripsy increases SFRs and reduces colic episodes (50) (LE: 1b).

5.3.2.5 **Medical expulsive therapy and ureteral stents (Section 5.6.2.1.8)**

5.3.2.6 **Duration of medical expulsive therapy treatment**
Most studies have had a duration of 1 month or 30 days. No data are currently available to support other time-intervals.

5.3.3 **References**


5.4 Chemolytic dissocation of stones

Oral or percutaneous irrigation chemolysis of stones or their fragments can be useful first-line therapy. It may also be an adjunct to SWL, percutaneous nephrolithotomy (PNL), ureterorenoscopy (URS) or open surgery to support elimination of small residual fragments, considering that its use as first-line therapy may take several weeks to be effective.

Combined treatment with SWL and chemolysis is a minimally invasive option for patients with partial or complete infection staghorn stones who are not eligible for PNL. Stone fragmentation leads to increased stone surface area and improved efficacy of chemolitholysis.

Chemolysis is possible only for the stone compositions listed below, therefore, knowledge of stone composition is mandatory before treatment.

5.4.1 Percutaneous irrigation chemolysis

Percutaneous irrigation chemolysis may be an option for infection- and uric acid stones (1,2).

<table>
<thead>
<tr>
<th>Stone composition</th>
<th>Refs.</th>
<th>Irrigation solution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Struvite</td>
<td>1-6</td>
<td>10% hemiacidrin, pH 3.5-4, Suby's G</td>
<td>Combination with SWL for staghorn stones. Risk of cardiac arrest due to hypermagnesaemia.</td>
</tr>
<tr>
<td>Carbon apatite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brushite</td>
<td>7</td>
<td>Hemiacidrin Suby's G</td>
<td>Can be considered for residual fragments.</td>
</tr>
<tr>
<td>Cystine</td>
<td>8-13</td>
<td>Trihydroxymethyl aminomethane (THAM; 0.3 or 0.6 mol/L), pH 8.5-9.0, N-acetylcyesteine (200 mg/L)</td>
<td>Takes significantly longer time than for uric acid stones. Used for elimination of residual fragments.</td>
</tr>
<tr>
<td>Uric acid</td>
<td>10,14-18</td>
<td>THAM (0.3 or 0.6 mol/L), pH 8.5-9.0</td>
<td>Oral chemolysis is the preferred option.</td>
</tr>
</tbody>
</table>

Irrigation chemolysis appears to the panel to be used rarely, probably because of the complexity of the technique and the possible side effects.

5.4.2 Oral chemolysis

Oral chemolitholysis is efficient only for uric acid calculi, and is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate (3-6).

When chemolitholysis is planned, the pH should be adjusted to 6.5-7.2. Within this range chemolysis is more effective at a higher pH, which, however, might lead to calcium phosphate stone formation.

In case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated (7). A combination of alkalinisation with tamsulosin seems to achieve the highest SFRs for distal ureteral stones (8).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The dosage of alkalisating medication must be modified by the patient according to urine pH, which is a direct consequence of such medication.</td>
<td>A</td>
</tr>
<tr>
<td>Dipstick monitoring of urine pH by the patient is required at regular intervals during the day. Morning urine must be included.</td>
<td>A</td>
</tr>
<tr>
<td>The physician should clearly inform the patient of the significance of compliance.</td>
<td>A</td>
</tr>
</tbody>
</table>
5.4.3 References


5.5 Extracorporeal shock wave lithotripsy (SWL)

Introduction of SWL in the early 1980s dramatically changed the management of urinary tract stones. The development of new lithotripters, modified indications, and treatment principles has also completely changed urolithiasis treatment. Modern lithotripters are smaller and usually included in uroradiological tables. They ensure application of SWL and other associated diagnostic and ancillary procedures.

More than 90% of stones in adults might be suitable for SWL treatment (1-3). However, success depends on the efficacy of the lithotripter and the following factors:
• size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Chapter 6);
• patient’s habitus (Chapter 6);
• performance of SWL (best practice, see below).

Each of these factors has an important influence on retreatment rate and final outcome of SWL.

5.5.1 Contraindications of extracorporeal shock wave lithotripsy

There are several contraindications to the use of extracorporeal SWL, including:
• pregnancy, due to the potential effects on the foetus (4);
• bleeding diatheses, which should be compensated for at least 24 h before and 48 h after treatment (5);
• uncontrolled UTIs;
• severe skeletal malformations and severe obesity, which prevent targeting of the stone;
• arterial aneurysm in the vicinity of the stone (6);
• anatomical obstruction distal to the stone.

5.5.2 Stenting before carrying out extracorporeal shock wave lithotripsy

5.5.2.1 Stenting in kidney stones

Routine use of internal stents before SWL does not improve SFR (LE: 1b) (7). A JJ stent reduces the risk of renal colic and obstruction, but does not reduce formation of steinstrasse or infective complications (8).

However, stone particles may pass along stents while urine flows in and around the stent. This usually prevents obstruction and loss of ureteral contractions. Occasionally, stents do not efficiently drain purulent or mucoid material, increasing the risk of obstructive pyelonephritis. If fever occurs and lasts for a few days despite proven correct stent position, the stent must be removed and replaced by a new JJ stent or a percutaneous nephrostomy tube, even when US does not reveal any dilatation. (panel consensus)
5.5.2.2  Stenting in ureteral stones
The 2007 AUA/EAU Guidelines on the management of ureteral calculi state that routine stenting is not recommended as part of SWL (9). When the stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain (10).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine stenting is not recommended as part of SWL treatment of ureteral stones.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

5.5.3  Best clinical practice

5.5.3.1  Pacemaker
Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken; patients with implanted cardioverter defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters (11).

5.5.3.2  Shock wave rate
Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFR (12-16). Tissue damage increases with shock wave frequency (17-19).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The optimal shock wave frequency is 1.0-1.5 Hz.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

5.5.3.3  Number of shock waves, energy setting and repeat treatment sessions
The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves.

Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment (20), which prevents renal injury (21). Animal studies (22) and a prospective randomised study (23) have shown better SFRS (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used (24,25).

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within 1 day for ureteral stones).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical experience has shown that repeat sessions are feasible (within 1 day for ureteral stones)</td>
<td>4</td>
</tr>
</tbody>
</table>

5.5.3.4  Improvement of acoustic coupling
Proper acoustic coupling between the cushion of the treatment head and the patient’s skin is important. Defects (air pockets) in the coupling gel reflect 99% of shock waves. A defect of only 2% in the gel layer covering the cushion reduces stone fragmentation by 20-40% (26). US gel is probably the optimum agent available for use as a lithotripsy coupling agent (27). To reduce air pockets, the gel should be applied to the water cushion straight from the container, rather than by hand (28).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure correct use of the coupling gel because this is crucial for effective shock wave transportation.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

5.5.3.5  Procedural control
Results of treatment are operator dependent, and better results are obtained by experienced urologists. During the procedure, careful imaging control of localisation contributes to outcome quality (29).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain careful fluoroscopic and/or ultrasonographic monitoring during the procedure.</td>
<td>4</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.
5.5.3.6 Pain control
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions (30-32).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use proper analgesia because it improves treatment results by limiting induced movements and excessive respiratory excursions.</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

5.5.3.7 Antibiotic prophylaxis
No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) (33,34).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case of infected stones or bacteriuria, antibiotics should be given prior to SWL.</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

5.5.3.8 Medical expulsive therapy after extracorporeal shock wave lithotripsy
MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs, as well as reduce additional analgesic requirements (35-45) (Section 5.3.2.3).

5.5.4 Complications of extracorporeal shock wave lithotripsy
Compared to PNL and ureteroscopy, there are fewer overall complications with SWL (46,47) (Table 12).

Table 12: SWL-related complications (1,4,46-48)

<table>
<thead>
<tr>
<th>Complications</th>
<th>%</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to stone fragments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinstrasse</td>
<td>4 - 7</td>
<td>49-51</td>
</tr>
<tr>
<td>Regrowth of residual fragments</td>
<td>21 - 59</td>
<td>52</td>
</tr>
<tr>
<td>Renal colic</td>
<td>2 - 4</td>
<td>48</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriuria in non-infection stones</td>
<td>7.7 - 23</td>
<td>52,53</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 - 2.7</td>
<td>52,53</td>
</tr>
<tr>
<td>Tissue effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma, symptomatic</td>
<td>&lt; 1</td>
<td>1,54</td>
</tr>
<tr>
<td>Haematoma, asymptomatic</td>
<td>4 - 19</td>
<td>1,54</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>11 - 59</td>
<td>52,55</td>
</tr>
<tr>
<td>Morbid cardiac events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver, spleen haematoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached (9,61-63).

5.5.5 References


5.6 Endourology techniques

5.6.1 Percutaneous nephrolithotomy (PNL)

Since the 1980s PNL has been developed as the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available and the selection is mainly based on the surgeon’s own preference. Standard access tracts are 24-30 F. So called “Mini-PNL” was introduced initially for paediatric use, but has also become popular in adults. Usually, the term Mini-PNL is used for access sheaths < 18 F, however, the terminology has not been standardised. The benefits of such miniaturised instruments remain controversial (1,2).

5.6.1.2 Intracorporeal lithotripsy

Several methods for intracorporal lithotripsy are available (the devices are discussed in Section 5.6.2.2.7). During PNL, ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser has become the standard, as for ureteroscopy (3). Electrohydraulic lithotripsy (EHL) is highly effective but is no longer considered as a first-line technique, due to frequent collateral damage (4).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonic, ballistic and Ho:YAG devices are recommended for intracorporeal lithotripsy during PNL.</td>
<td>A*</td>
</tr>
<tr>
<td>When using flexible instruments, the Ho:YAG laser is currently the most effective device.</td>
<td></td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

5.6.1.3 Extraction tools

Stones or stone fragments are extracted from the kidney through the access sheath of the nephroscope using forceps or baskets. Nitinol (nickel-titanium alloy) baskets provide additional advantages compared with steel wire baskets, such as increased flexibility. Tipless versions of nitinol baskets are also available for use in calices.

5.6.1.4 Best clinical practice

5.6.1.4.1 Contraindications

All contraindications for general anaesthesia apply. Patients receiving anticoagulant therapy must be monitored carefully pre- and postoperatively. Anticoagulant therapy must be discontinued before PNL (5).

Other important contraindications include:

- untreated UTI;
- atypical bowel interposition;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 8.2).

5.6.1.4.2 Preoperative imaging

Preprocedural evaluations are summarised in Chapter 3. In particular for PNL, US or CT of the kidney and the surrounding structures can provide information about interpositioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung) (6).
Preprocedural imaging, including contrast medium where possible or retrograde study when starting the procedure, is mandatory to assess stone comprehensiveness, view the anatomy of the collecting system, and ensure safe access to the kidney stone.

*A* Upgraded based on panel consensus.

5.6.1.4.3 Positioning of the patient
Traditionally, the patient is positioned prone for PNL. The supine position is also possible, with or without flank upholstery. Both positions are equally safe. The advantages of the supine position for PNL are (7,8):

- shorter operating time;
- possibility of simultaneous retrograde transurethral manipulation;
- more convenient position for the operator;
- easier anaesthesia.

Although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and operating table.

5.6.1.4.4 Puncture
Colon interposition in the access tract of PNL can lead to colon injuries. Although rare, such injuries are more likely when operating on the left kidney. Preoperative CT or intraoperative US allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury (9-11).

5.6.1.4.5 Dilatation
Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilator. The difference in outcomes is less related to the technology used than to the experience of the surgeon (12).

5.6.1.4.6 Nephrostomy and stents
The decision about whether or not to place a nephrostomy tube at the end of the PNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intraoperative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported (13-16).

In uncomplicated cases, tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) PNL procedures provide a safe alternative.

5.6.1.6 Management of complications
The most common postoperative complications associated with PNL are fever and bleeding, urinary leakage, and problems due to residual stones. A recent review on complications following PNL used the validated Dindo-modified Clavien System and showed a normal (uncomplicated) postoperative course in 76.7% of patients (Clavien 0) (25) (Table 13). See also the EAU Guidelines on Reporting and Grading of Complications after Surgical Procedures (17).
Table 13: Complications following PNL

<table>
<thead>
<tr>
<th>Complications</th>
<th>Transfusion</th>
<th>Embolisation</th>
<th>Urinoma</th>
<th>Fever</th>
<th>Sepsis</th>
<th>Thoracic complication</th>
<th>Organ injury</th>
<th>Death</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Range)</td>
<td>(0-20%)</td>
<td>(0-1.5%)</td>
<td>(0-1%)</td>
<td>(0-32.1%)</td>
<td>(0.3-1.1%)</td>
<td>(0-11.6%)</td>
<td>(0-1.7%)</td>
<td>(0-0.3%)</td>
<td>1a</td>
</tr>
<tr>
<td>N = 11,929</td>
<td>7%</td>
<td>0.4%</td>
<td>0.2%</td>
<td>10.8%</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Urinary leakage and stone clearance can be viewed endoscopically and by X-ray analysis. In doubtful cases, complications can be minimised by performing standard rather than totally tubeless PNL.

Perioperative fever can occur, even with a sterile preoperative urinary culture and perioperative antibiotic prophylaxis, because the kidney stones themselves may be a source of infection. Intraoperative kidney stone culture may therefore help to select postoperative antibiotics (18,19). Intraoperative kidney stone culture may therefore help to select postoperative antibiotics (18,19). Intraoperative irrigation pressure < 30 mm Hg and unobstructed postoperative urinary drainage may be important factors in preventing postoperative sepsis. Well-positioned or specially designed access sheaths can prevent high intrapelvic irrigation pressure (20).

Bleeding after PNL may be treated by brief clamping of the nephrostomy tube. Super-selective embolic occlusion of the artery may become necessary in case of severe bleeding.

5.6.2 Ureterorenoscopy (URS) (including retrograde access to renal collecting system)

URS has dramatically changed the management of ureteral calculi. Major technical improvements include endoscope miniaturisation, enhanced optical quality and tools, and introduction of disposables. The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter (21). Major technological progress has been achieved for retrograde intrarenal surgery [RIRS (flexible URS)], with improved deflection mechanisms, better durability, and recently, digital optical systems (22-24). Initial experience with digital scopes has demonstrated shorter operation times due to the improvement in image quality (25-27). In Europe, RIRS is mainly used for the renal collecting system and - in cases with difficult anatomy - the upper ureter.

5.6.2.1 Best clinical practice in ureterorenoscopy (URS)

5.6.2.1.1 Preoperative work-up and preparations

Before the procedure, the following information should be sought and actions taken (LE: 4):

- patient history;
- physical examination, because anatomical and congenital abnormalities may complicate or prevent retrograde stone manipulation;
- thrombocyte aggregation inhibitors/anticoagulants (antiplatelet drugs) should be discontinued if possible, however URS can be performed in patients with bleeding disorders, with a moderate increase in complications (5,28);
- imaging.

**Recommendation**

<table>
<thead>
<tr>
<th>Short-term antibiotic prophylaxis should be administered (27).</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE: 4</td>
</tr>
<tr>
<td>GR: A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

5.6.2.1.2 Contraindications

Apart from general problems, for example, with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications. Specific problems such as ureteral strictures may prevent successful retrograde stone management.

5.6.2.1.3 Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible. Instrument miniaturisation means that intravenous sedation can be used to achieve the same outcome (29).

Intravenous sedation with miniaturised instruments is especially suitable for female patients with distal ureteral stones. However, kidney movement is more pronounced with local or intravenous anaesthesia, which may hinder RIRS.
Antegrade URS is an option for large, impacted proximal ureteral calculi (30) (Section 6.5.3).

5.6.2.1.4 Safety aspects
Fluoroscopic equipment must be available in the operating room. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it (31,32). A safety wire prevents false passage in case of perforation, and ensures that a JJ stent can be inserted in difficult situations, thus avoiding more significant complications.

Retrograde access to the upper urinary tract is usually obtained under endoscopic guidance.

Balloon and plastic dilators are available if necessary. If insertion of a flexible URS is difficult, prior rigid ureteroscopy can be helpful for optical dilatation. If ureteral access is not possible, insertion of a JJ stent followed by URS after 7-14 days offers an alternative procedure.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placement of a safety wire is recommended.</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

5.6.2.1.5 Ureteral access sheaths
Hydrophilic-coated ureteral access sheaths, which are available in different calibres (inner diameter from 9 F upwards), can be inserted via a guide wire, with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy multiple access to the upper urinary tract and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreasing intrarenal pressure, and potentially reducing operating time (33,34).

Ureteral access sheaths allow continuous outflow of irrigation fluid, which improves visual quality and maintains a low-pressure system (35,36). The insertion of ureteral access sheaths may lead to ureteral damage, however, no data on long-term consequences are available (37). Use of ureteral access sheaths depends on the surgeon’s preference.

5.6.2.1.6 Stone extraction
The aim of URS is complete stone removal (especially ureteric stones). “Smash and go” strategies should be limited to the treatment of large renal stones.

Stones can be extracted by endoscopic forceps or baskets. Forceps allow safe release of stone fragments if they become stuck within the ureter, but extraction takes longer than when using baskets. Only baskets made of nitinol can be used for RIRS (38).

<table>
<thead>
<tr>
<th>Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitinol baskets preserve the tip deflection of flexible ureterorenoscopes, and the tipless design reduces the risk of mucosal injury.</td>
</tr>
<tr>
<td>Nitinol baskets are the only baskets suitable for use in RIRS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone extraction using a basket without endoscopic visualisation of the stone (blind basketing) should not be performed.</td>
<td>4</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones that need disintegration within the lower renal pole, it may help to displace them into a more accessible calyx (Section 6.4.2) (43).

5.6.2.1.7 Intracorporeal lithotripsy
The most effective lithotripsy system is the Ho:YAG laser, which has become the gold standard for ureteroscopy and flexible nephroscopy (Section 5.6.1.2), because it is effective for all stone types (3,39-41). Pneumatic and US systems can be used with high disintegration efficacy in rigid URS (42-44). However, stone migration into the kidney is a common problem, which can be prevented by placement of special tools proximal of the stone (45).
Recommendation

Ho:YAG laser lithotripsy is the preferred method for (flexible) URS.

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

5.6.2.1.8 Stenting before and after URS

Routine stenting is no longer necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces complications (46).

Most urologists routinely insert a JJ stent following URS, although several randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher postoperative morbidity (47-49). A ureteric catheter with a shorter indwelling time (1 day) may be used as well, with similar results (50).

Stents should be inserted in patients who are at increased risk of complications (e.g., residual fragments, bleeding, perforation, UTIs, or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known. Most urologists favour 1-2 weeks after URS. Patients should be followed up with a plain abdominal film (KUB), CT or US.

α-Blockers reduce the morbidity of ureteral stents and increase tolerability (51). A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin (52).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In uncomplicated URS, a stent need not be inserted.</td>
<td>1a</td>
</tr>
<tr>
<td>An α-blocker can reduce stent-related symptoms.</td>
<td>1a</td>
</tr>
</tbody>
</table>

5.6.2.2 Complications

The overall complication rate after URS is 9-25% (21,53) (Table 14). Most are minor and do not require intervention. Ureteral avulsion and strictures used to be greatly feared, but nowadays are rare in experienced hands (< 1%). Previous perforations are the most important risk factor for complications.

Table 14: Complications of URS*

<table>
<thead>
<tr>
<th>Intraoperative complications</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal injury</td>
<td>1.5</td>
</tr>
<tr>
<td>Ureteral perforation</td>
<td>1.7</td>
</tr>
<tr>
<td>Significant bleeding</td>
<td>0.1</td>
</tr>
<tr>
<td>Ureteral avulsion</td>
<td>0.1</td>
</tr>
<tr>
<td>Early complications</td>
<td>6.0</td>
</tr>
<tr>
<td>Fever or urosepsis</td>
<td>1.1</td>
</tr>
<tr>
<td>Persistent haematuria</td>
<td>2.0</td>
</tr>
<tr>
<td>Renal colic</td>
<td>2.2</td>
</tr>
<tr>
<td>Late complications</td>
<td>0.2</td>
</tr>
<tr>
<td>Ureteral stricture</td>
<td>0.1</td>
</tr>
<tr>
<td>Persistent vesicoureteral reflux</td>
<td>0.1</td>
</tr>
</tbody>
</table>


5.6.3 References


5.7 Open and laparoscopic surgery for removal of renal stones

5.7.1 Open surgery

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open stone surgery, which is now often a second- or third-line treatment option needed in only 1.0-5.4% of cases (1-5). The incidence of open stone surgery is ~1.5% of all stone removal interventions in developed countries, and in developing countries, it has dropped from 26% to 3.5% in recent years (3,5).

However, open surgery is still needed for the most difficult stones, which supports the importance of maintaining proficiency, skills and expertise in open renal and ureteral surgical techniques such as extended pyelolithotomy, pyelonephrolithotomy, anatrophic nephrolithotomy, multiple radial nephrotomy, partial nephrectomy, and renal surgery under hypothermia (6-10) (Table 15).

Recently, intraoperative B-mode scanning and Doppler sonography (11,12) have been used to identify avascular areas in the renal parenchyma that are close to the stone or dilated calices. This allows removal of large staghorn stones by multiple small radial nephrotomy, without loss of kidney function.

The efficacy of open surgery compared to less-invasive therapy in terms of SFRs, is based on historical data, but no comparative studies are available (13-16).

5.7.1.1 Indications for open surgery

There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL or combined PNL and SWL. If a reasonable number of percutaneous approaches are not likely to be successful, or if multiple, endourological approaches have been performed unsuccessfully, open surgery may be a valid treatment option.
Table 15: Indications for open surgery

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex stone burden.</td>
</tr>
<tr>
<td>Failure of SWL, PNL, or ureteroscopic procedure.</td>
</tr>
<tr>
<td>Intrarenal anatomical abnormalities: infundibular stenosis; stone in the</td>
</tr>
<tr>
<td>calyceal diverticulum (particularly in an anterior calyx); obstruction of</td>
</tr>
<tr>
<td>the ureteropelvic junction; and stricture if endourologic procedures have</td>
</tr>
<tr>
<td>failed or are not promising.</td>
</tr>
<tr>
<td>Morbid obesity.</td>
</tr>
<tr>
<td>Skeletal deformity, contractures and fixed deformities of hips and legs.</td>
</tr>
<tr>
<td>Comorbidity.</td>
</tr>
<tr>
<td>Concomitant open surgery.</td>
</tr>
<tr>
<td>Non-functioning lower pole (partial nephrectomy), non-functioning kidney</td>
</tr>
<tr>
<td>(nephrectomy).</td>
</tr>
<tr>
<td>Patient choice following failed minimally invasive procedures; the patient</td>
</tr>
<tr>
<td>may prefer a single procedure and avoid the risk of needing more than one</td>
</tr>
<tr>
<td>PNL procedure.</td>
</tr>
<tr>
<td>Stone in an ectopic kidney where percutaneous access and SWL may be</td>
</tr>
<tr>
<td>difficult or impossible.</td>
</tr>
<tr>
<td>For the paediatric population, the same considerations apply as for adults</td>
</tr>
</tbody>
</table>

5.7.2 Laparoscopic surgery

Laparoscopic urological surgery is increasingly replacing open surgery. Today laparoscopic surgery is used to remove renal and ureteric stones in certain situations, including complex stone burden, failed previous SWL and/or endourological procedures, anatomical abnormalities or morbid obesity, and planned nephrectomy of a stone-containing non-functioning kidney. Although surgical pyelolithotomy is rarely indicated (Table 16), laparoscopic removal of solitary large renal pelvic (17) as well as anterior caliceal diverticular stones is possible in selected cases (18). Stone-free rates are reported to be equal to PNL, but complications are more frequent, using laparoscopic retroperitoneal pyelolithotomy (17). Additionally, as a less-invasive option, laparoscopic anatrophic nephrolithotomy has been found to be effective for the removal of complex staghorn stones; however, PNL is still the method of choice and laparoscopic stone removal should be reserved for selected cases (19,20).

Laparoscopic ureterolithotomy is relatively easy, with SFRs up to 100% provided expertise is available (21-24). It can replace open surgery in most situations (15,16). Retroperitoneal and transperitoneal laparoscopic access to all portions of the ureter has been reported (24-30), although laparoscopic ureterolithotomy in the distal ureter is less successful than in the middle and proximal ureter, but the size of the stone does not appear to influence outcome. Although highly effective, laparoscopic ureterolithotomy is not first-line therapy in most cases because of its invasiveness, longer recovery time, and greater risk of associated complications compared to SWL and URS (21-24) (Table 16).

5.7.2.1 Table 16: Indications for laparoscopic stone surgery

| Indications for laparoscopic kidney-stone surgery include:                |
| • Complex stone burden                                                  |
| • Failed previous SWL and/or endourological procedures                  |
| • Anatomical abnormalities                                              |
| • Morbid obesity                                                        |
| • Nephrectomy in case of non-functioning kidney.                        |
| Indications for laparoscopic ureteral stone surgery include:            |
| • Large impacted ureteral stones                                        |
| • In cases of concurrent conditions requiring surgery                   |
| • When other non-invasive or low-invasive procedures have failed        |
| • For upper ureteral calculi, laparoscopic urolithomy has the highest    |
|   stone-free rate compared to URS and SWL (31) (LE: 1b).               |
Laparoscopic or open surgical stone removal may be considered in rare cases in which SWL, URS, and percutaneous URS fail or are unlikely to be successful.

When expertise is available, laparoscopic surgery should be the preferred option before proceeding to open surgery. An exception is complex renal stone burden and/or stone location.

For ureterolithotomy, laparoscopy is recommended for large impact stones or when endoscopic lithotripsy or SWL has failed.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic or open surgical stone removal may be considered in rare cases in which SWL, URS, and percutaneous URS fail or are unlikely to be successful.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>When expertise is available, laparoscopic surgery should be the preferred option before proceeding to open surgery. An exception is complex renal stone burden and/or stone location.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>For ureterolithotomy, laparoscopy is recommended for large impact stones or when endoscopic lithotripsy or SWL has failed.</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

5.7.3 References


http://www.ncbi.nlm.nih.gov/pubmed/17263607


6. INDICATION FOR ACTIVE STONE REMOVAL AND SELECTION OF PROCEDURE

Although kidney stones might be asymptomatic, ureteral stones cause acute renal colic in most cases. Treatment decisions for upper urinary tract calculi are based on several general aspects such as stone composition, stone size, and symptoms.
6.1 **Indications for active removal of ureteral stones (1-3)**
- Stones with low likelihood of spontaneous passage.
- Persistent pain despite adequate analgesic medication.
- Persistent obstruction.
- Renal insufficiency (renal failure, bilateral obstruction, or single kidney).

6.2 **Indications for active removal of kidney stones (4)**
- Stone growth.
- Stones in high-risk patients for stone formation.
- Obstruction caused by stones.
- Infection.
- Symptomatic stones (e.g., Pain or haematuria).
- Stones > 15 mm.
- Stones < 15 mm if observation is not the option of choice.
- Patient preference.
- Comorbidity.
- Social situation of the patient (e.g., Profession or travelling).

6.2.1 **Natural history of caliceal stones**
Natural history of small, non-obstructing asymptomatic lower pole calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, and timing and type of intervention.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Although the question of whether caliceal stones should be treated is still unanswered, stone growth, de novo obstruction, associated infection, and acute and/or chronic pain are indications for treatment (4-6).</td>
<td>3</td>
</tr>
</tbody>
</table>

Glowacki et al. have reported that the risk of a symptomatic episode or need for intervention was ~10% per year, with a cumulative 5-year event probability of 48.5% (7). In a recent retrospective study, 77% of asymptomatic patients with renal stones of all sizes experienced disease progression, with 26% requiring surgical intervention (8).

In a retrospective study, Hubner and Porpaczy have assumed that 83% of caliceal calculi require intervention within the first 5 years of diagnosis (9). Inci et al. have investigated lower pole caliceal stones, and observed that within a follow-up period of 52.3 months, nine (33.3%) patients had increased stone size, and three (11%) required intervention (10).

However, in a prospective RCT with 2.2 years clinical follow-up, Keeley et al. have reported no significant difference between SWL and observation when they compared asymptomatic caliceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life, renal function, or hospital admission (11). Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported (7,9,12).

In a follow-up period of almost 5 years after SWL, Osman et al. have demonstrated that 21.4% of patients with small residual fragments needed treatment. A similar figure is given by Re buck et al. Although these studies are based on residuals after SWL and URS respectively, they may serve as information about natural history of renal stones (13,14).

Excellent SFRs and pain relief have been reported after removal of small caliceal stones by SWL, PNL or URS, which indicates the need for removal of symptomatic caliceal stones (12-14).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For asymptomatic caliceal stones in general, active surveillance with annual follow-up of symptoms and stone status (KUB radiography, US, or NCCT) is an option for 2-3 years, whereas intervention should be considered after this period provided patients are adequately informed.</td>
<td>C</td>
</tr>
<tr>
<td>Observation might be associated with a greater risk of necessitating more invasive procedures.</td>
<td>C</td>
</tr>
</tbody>
</table>
6.2.2 References


6.3 General recommendations and precautions for stone removal

6.3.1 Infections

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days, via a stent or percutaneous nephrostomy, before starting stone removal.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture or urinary microscopy is mandatory before any treatment is planned.</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.
6.3.2 **Anticoagulation and stone treatment**
Patients with a bleeding diathesis, or receiving anticoagulation, should be referred to an internist for appropriate therapeutic measures before and during stone removal (1-3). In patients with an uncorrected bleeding diathesis, the following are contraindicated:

- SWL;
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery (4-6).

Although SWL is feasible and safe after correction of underlying coagulopathy (7-9), URS might offer an alternative approach and is associated with less morbidity. In contrast to ESWL and PNL, in URS the problem of coagulation disorders is less pronounced.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation therapy including salicylates should be stopped before stone removal.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>If intervention for stone removal is essential and salicylate therapy should not be interrupted, retrograde ureterorenoscopy is the preferred treatment of choice.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.3.3 **Obesity**
Obesity can cause a higher risk due to anaesthesiological measurements, and a lower success rate after SWL and PNL (Section 5.5).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case of severe obesity, URS is a more promising therapeutic option than SWL.</td>
<td>2b</td>
</tr>
</tbody>
</table>

6.3.4 **Hard stones**
Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard (10). Percutaneous nephrolithotomy or RIRS are alternatives for removal of large SWL-resistant stones.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider the stone composition before deciding on the method of removal (based on patients history, former stone analysis of the patient or HU in unenhanced CT. Stones with medium density &gt; 1,000 HU on NCCT are less likely to be disintegrated by SWL) (10).</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

6.3.5 **Radiolucent stones**
Stones composed of uric acid, but not sodium or ammonium urate, can be dissolved by oral chemolysis. Differentiation is done by urinary pH measurement (Section 5.4.2). Postoperative monitoring of radiolucent stones during therapy is the domain of US, however repeat NCCT might be necessary.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careful monitoring of radiolucent stones during/after therapy is imperative.</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

6.3.6 **Steinstrasse**
Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, which does not pass within a reasonable period of time, and interferes with the passage of urine (11,12). Steinstrasse occurs in 4-7% cases of SWL (13), and the major factor in steinstrasse formation is stone size (14).

Insertion of a ureteral stent before SWL prevents formation of steinstrasse only in stones > 15 mm in diameter (15). Symptoms of steinstrasse include flank pain, fever, nausea and vomiting, bladder irritation, or it may be asymptomatic. A major problem of steinstrasse is ureter obstruction, which can be silent in 23% of cases (16) and lead to kidney failure (17). Anuria occurs in 5% of cases of steinstrasse in treatment of solitary kidneys (16).

When steinstrasse is asymptomatic, conservative treatment is an initial option, depending on patient preference and willingness to comply with close surveillance. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention (18,19).
Table 17: Treatment of steinstrasse

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>LE</th>
<th>Symptomatic</th>
<th>LE</th>
<th>Symptomatic + fever</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MET</td>
<td>1b</td>
<td>1. URS</td>
<td>3</td>
<td>1. PCN</td>
<td>1</td>
</tr>
<tr>
<td>2. SWL</td>
<td>3</td>
<td>1. PCN</td>
<td>3</td>
<td>2. Stent</td>
<td>2</td>
</tr>
<tr>
<td>3. URS</td>
<td>3</td>
<td>1. SWL</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Stent</td>
<td>3</td>
</tr>
</tbody>
</table>

Numbers 1, 2 and 3 in Asymptomatic column indicate first, second and third choice. See note; LE in Table 17 would then have to be priority.

Statements

Medical expulsion therapy increases the stone expulsion rate of steinstrasse (15). 1b

When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.

SWL is indicated in asymptomatic and symptomatic cases, with no evidence of UTI, when large stone fragments are present (19).

Ureteroscopy is equally effective as SWL for treatment of steinstrasse (20,21).

Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without UTI.

Recommendations

<table>
<thead>
<tr>
<th>Percutaneous nephrostomy is indicated for steinstrasse associated with urinary tract infection/fever.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shockwave lithotripsy is indicated for steinstrasse when large stone fragments are present.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Ureteroscopy is indicated for symptomatic steinstrasse and treatment failure.</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

References

6.4 Selection of procedure for active removal of kidney stones

6.4.1 Stones in renal pelvis or upper/middle calices

Shockwave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. Although PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size (1-4). Shockwave lithotripsy achieves excellent SFRs for stones up to 20 mm, except for those at the lower pole (3,5). Therefore, SWL remains the first method of choice for such stones. Larger stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and has the risk of ureteral obstruction (colic or steinstrasse) with the need for adjunctive procedures (Figure 1) (6). Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm, for which SFR is decreasing, and staged procedures have become necessary (7,8). However, RIRS can be successful in experienced hands in high-volume centres (4,9).

The following can impair successful stone treatment by SWL:
- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 18) (7,8,10-14).

Further anatomical parameters cannot yet be established. The value of supportive measures such as inversion, vibration or hydration remains under discussion (7,8).

Table 18: Unfavourable factors for SWL success (10-16)

<table>
<thead>
<tr>
<th>Factors that make SWL less likely</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Shockwave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).</td>
<td></td>
</tr>
<tr>
<td>Steep infundibular-pelvic angle.</td>
<td></td>
</tr>
<tr>
<td>Long lower pole calyx (&gt; 10 mm).</td>
<td></td>
</tr>
<tr>
<td>Narrow infundibulum (&lt; 5 mm).</td>
<td></td>
</tr>
</tbody>
</table>

Shockwave lithotripsy for the lower pole is often disappointing, therefore, endourological procedures (PNL and RIRS) are recommended for stones > 15 mm. If there are negative predictors for SWL, PNL and RIRS might be a reasonable alternative, even for smaller calculi.

Retrograde renal surgery seems to have comparable efficacy to SWL (5,6). Recent clinical experience with last-generation ureterorenoscopes has suggested an advantage of URS over SWL, but at the expense of greater invasiveness (17,18). Depending on operator skills, stones up to 3 cm can be treated efficiently by RIRS (9,17,19-22). In complex stone cases, a combined antegrade and retrograde approach may be indicated (23-25). However, staged procedures are frequently required.

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWL remains the method of first choice for stones &lt; 2 cm within the renal pelvis and upper or middle calices. Larger stones should be treated by PNL.</td>
<td>B*</td>
</tr>
<tr>
<td>Flexible URS cannot be recommended as first-line treatment, especially for stones &gt; 1.5 cm in the renal pelvis and upper or middle calices, for which SFR after RIRS is decreasing, and staged procedures become necessary.</td>
<td>B*</td>
</tr>
<tr>
<td>For the lower pole, PNL or RIRS is recommended, even for stones &gt; 1.5 cm, because the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).</td>
<td>B*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus

SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy; SFR = stone free rate; RIRS = retrograde renal surgery
Figure 1: Treatment algorithm for renal calculi

Kidney stone
(all but lower pole stone 10-20 mm)

> 20 mm
1. PNL
2. RiRS or SWL

10-20 mm
SWL or Endourology

< 10 mm
1. SWL or RiRS
2. PNL

Lower pole stone
> 20 mm and < 10 mm: like above

10-20 mm
Favourable factors for SWL
(see table 19)

Yes
SWL or Endourology

No
1. Endourology
2. SWL

In complex stone cases, open or laparoscopic approaches are possible alternatives (see appropriate chapters).

6.4.3 References


6.5  Selection of procedure for active removal of ureteral stones

6.5.1  Methodology

Stone free rates were analysed for SWL and URS. If the study reported the SFR after all primary procedures, that rate was used for analysis. If not, and the study reported the SFR after the first procedure, then that rate was used. The Panel aimed to present an estimate of the number of primary procedures and the associated SFRs. There is a lack of uniformity in reporting the time to stone-free status, thereby limiting the ability to comment on the timing of this parameter.

6.5.2  Extracorporeal shock wave lithotripsy and ureteroscopy

For proximal stones, no difference in overall SFRs between SWL and URS was detected. However, after stratifying for stone size, in proximal ureteral stones < 10 mm (n = 1,285), SWL had a higher SFR than URS had. For stones > 10 mm (n = 819), URS had superior SFRs. This can be attributed to the fact that proximal ureteral stones treated with URS did not vary significantly with size, whereas the SFR following SWL negatively correlated with stone size.

For all mid-ureteral stones, URS appears superior to SWL, but after stratification for stone size, the small number of patients limits the significance. For all distal stones, URS yields better SFRs overall, compared to other methods for active stone removal, independent of stone size.

6.5.2.1  Stone free rates (SFRs)

Table 19 shows the results of a meta-analysis of SFRs. The results are presented as medians of the posterior distribution (best central estimate) with 95% confidence intervals (CIs). This represents an update of the EAU/AUA Collaborative Guidelines Project (1). Outcomes show no significant changes.

<table>
<thead>
<tr>
<th>Stone location and size</th>
<th>SWL</th>
<th>URS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>SFR/95% CI</td>
</tr>
<tr>
<td>Distal ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>7217</td>
<td>74% (73-75)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>966</td>
<td>74% (57-87)</td>
</tr>
<tr>
<td>Mid ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>1684</td>
<td>86% (80-91)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>966</td>
<td>74% (57-87)</td>
</tr>
<tr>
<td>Proximal ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>1697</td>
<td>73% (71-75)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>44</td>
<td>84% (65-95)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>76% (36-97)</td>
</tr>
<tr>
<td></td>
<td>6682</td>
<td>82% (81-83)</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>967</td>
<td>89% (87-91)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>481</td>
<td>70% (66-74)</td>
</tr>
</tbody>
</table>

Unfortunately, RCTs comparing these treatments have been lacking. However, the posterior distributions from the meta-analysis can be subtracted, which yields a distribution for the difference between the treatments. If the CI does not include zero, then the result can be considered to be significantly different. This operation is mathematically justifiable but operationally risky: if the patients receive different treatments or the outcome measures are different, the results might be meaningless. Nonetheless, the SFRs for URS remained significantly better than those for SWL for distal ureteral stones < 10 mm and > 10 mm and for proximal ureteral stones > 10 mm. The SFRs for mid-ureteral stones did not differ significantly between URS and SWL.
Although there are not sufficient data to compare flexible and rigid URS statistically for proximal ureteral stones, favourable SFRs have been reported using RIRS (87%) or rigid or semi-rigid URS (77%) (1). SFRs have probably continued to improve with the distribution and technical improvement of RIRS.

6.5.2.2 Complications
Although URS is effective for ureteric calculi, it has greater potential for complications. In the current endourological era, with access to newer and smaller rigid and flexible instruments, and use of small-calibre intracorporeal lithotripsy devices, the complication rate and morbidity of ureteroscopy have been significantly reduced (6).

Patients should be informed that URS has a better chance of achieving stone-free status with a single procedure, but has higher complication rates [Sections 5.5.4 (Complications of SWL) and 5.6.2.2.9 (Complications of URS)].

6.5.3 Percutaneous antegrade ureteroscopy
Percutaneous antegrade removal of ureteral stones is a consideration in selected cases. For example, for very large (> 15 mm diameter) impacted stones in the proximal ureter between the ureteropelvic junction and the lower border of the fourth lumbar vertebra (7-10), or when the ureter is not amenable to retrograde manipulation (11-13). With SFRs of 85-100%, its superiority to standard techniques has been evaluated (7,10,11,14,15). The complication rate is low, and no different than for any other percutaneous procedure. However, percutaneous antegrade removal of ureteral stones is associated with longer operative times, hospital stay, and time to return to normal activities (10). (11-13).

Recommendations
Percutaneous antegrade removal of ureteral stones is an alternative when SWL is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.

<table>
<thead>
<tr>
<th>Table 20: Recommended treatment options (if indicated for active stone removal) (GR A*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone location and size</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Proximal ureter &lt; 10 mm</td>
</tr>
<tr>
<td>Proximal ureter &gt; 10 mm</td>
</tr>
<tr>
<td>Distal ureter &lt; 10 mm</td>
</tr>
<tr>
<td>Distal ureter &gt; 10 mm</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

6.5.4 Other methods for ureteral stone removal
Few studies have reported laparoscopic stone removal (Section 5.7.2), and open surgery (Section 5.7.1). These procedures are usually reserved for special cases, therefore, the reported data could not be used to compare procedures with each other or with SWL or URS. These more invasive procedures have yielded high SFRs.

6.5.5 References
7. RESIDUAL STONES

7.1 Clinical evidence

Residual fragments are commonly seen in the kidney (mostly in the lower calix) after SWL and sometimes after intracorporeal lithotripsy. Reports on residual fragments vary between institutions, according to imaging method. However, the clinical value of detecting very small concretions remains debatable.

The clinical problem of residual kidney stones is related to the risk of developing:

- new stones from such nidi (heterogeneous nucleation);
- persistent UTI;
- dislocation of fragments with/without obstruction and symptoms (1-6).
Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones (3-5).

Patients with residual fragments or stones should be followed up regularly to monitor disease course.

Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones. In a 2.2-year follow-up of 53 patients, 78% with stone fragments at 3 months after treatment experienced stone progression. The SFR was 20%, and the remaining 2% had stable disease (7). For all stone compositions, 21-59% of patients with residual stones required treatment within 5 years. Fragments > 5 mm are more likely than smaller ones to require intervention (2,3,5,8).

### Table 21: Recommendations for the treatment of residual fragments

<table>
<thead>
<tr>
<th>Residual fragments, stones (largest diameter)</th>
<th>Symptomatic residuals</th>
<th>Asymptomatic residuals</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4-5 mm</td>
<td>Stone removal</td>
<td>Reasonable follow-up (dependent on risk factors)</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>&gt; 6-7 mm</td>
<td>Stone removal</td>
<td></td>
<td>7.2</td>
<td></td>
</tr>
</tbody>
</table>

#### 7.2 Therapy

Residual fragments after PNL can be avoided by a second look using the existing percutaneous tract 1-3 days after the first procedure (9). To facilitate further clearance, medical and physical adjunctive therapy can be suggested.

The indications for active stone removal and selection of the procedure are based on the same criteria as for primary stone treatment (Chapter 6) and includes repeat SWL (10).

If intervention is not required, medical therapy according to stone analysis, patient risk group, and metabolic evaluation might help to prevent regrowth of residual fragments (11-14).

**Statement LE**

For well-disintegrated stone material in the lower calix, an inversion therapy with simultaneous mechanical percussion maneuver under enforced diuresis may facilitate stone clearance (14).

**Recommendation LE GR**

After SWL and URS, and in the presence of residual fragments, MET is recommended using an α-blocker to improve fragment clearance.

**References**


8. MANAGEMENT OF URINARY STONES AND RELATED PROBLEMS DURING PREGNANCY

Urolithiasis during pregnancy is a diagnostic and therapeutic challenge. In most cases, it becomes symptomatic in the second or third trimester (1-4).

8.1 Diagnostic imaging

Diagnostic options in pregnant women are limited due to the possible teratogenic, carcinogenic, and mutagenic risk of foetal radiation exposure. The risk for the child crucially depends on gestational age and amount of radiation delivered. X-ray imaging during the first trimester should be reserved for diagnostic and therapeutic situations in which alternative imaging methods have failed (1,2,5,6).

Ultrasound (when necessary using change in renal resistive index and transvaginal/transabdominal US with a full bladder) has become the primary radiological diagnostic tool when evaluating pregnant patients suspected of renal colic (7,8).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal physiological changes in pregnancy can mimic ureteral obstruction, therefore, US may not help to differentiate dilatation properly and has a limited role in acute obstruction.</td>
<td>3</td>
</tr>
</tbody>
</table>

X-ray imaging options in pregnancy are: limited excretory urography and NCCT (considering the higher dose of radiation exposure).

Magnetic resonance urography (MRU) can be used to define the level of urinary tract obstruction, and to visualize stones as a filling defect. MRU studies avoid ionising radiation and iodinated contrast medium.
However, findings are non-specific and there is little experience using this imaging modality during pregnancy (9-11).

### 8.2 Management

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, obstetrician and urologist.

Approximately 70-80% of the symptomatic stones pass spontaneously. If spontaneous passage does not occur, or if complications develop (e.g., induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary. Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation (20-23). Ureteroscopy has become a reasonable alternative in these situations (12-19). Although feasible, retrograde endoscopic and percutaneous stone removal procedures during pregnancy remain an individual decision and should be performed only in experienced centres (20-24).

Pregnancy remains an absolute contraindication for SWL.

#### Statements

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>If intervention becomes necessary, placement of a ureteral stent or a percutaneous nephrostomy tube are readily available primary options.</td>
<td>3</td>
</tr>
<tr>
<td>Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.</td>
<td>2a</td>
</tr>
<tr>
<td>Regular follow-up until final stone removal is necessary due to the higher encrustation tendency of stents during pregnancy.</td>
<td></td>
</tr>
</tbody>
</table>

#### Recommendation

Conservative management should be the first-line treatment for all non-complicated cases of urolithiasis in pregnancy (except those that have clinical indications for intervention).

#### References


9. MANAGEMENT OF STONE PROBLEMS IN CHILDREN

Rates of urolithiasis have increased in developed countries, and there has been a shift in the age group experiencing a first stone episode (1-3). More than 1% of all urinary stones are seen in patients aged < 18 years. As a result of malnutrition and racial factors, paediatric urolithiasis remains an endemic disease in some areas (e.g., Turkey and the Far East); elsewhere, the rates are similar to those observed in developed countries (4-11).

9.1 Aetiology

Paediatric patients forming urinary stones have a high risk of recurrence, therefore, standard diagnostic procedures for high-risk patients apply (Chapters 2.6 and 11).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In paediatric patients, the most common non-metabolic disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties (11,12).</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all paediatric patients, complete metabolic evaluation based on stone analysis (if available) is necessary.</td>
<td>A</td>
</tr>
<tr>
<td>All efforts should be made to collect stone material that then should be analysed to classify the stone type.</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgrade following panel consensus.

9.2 Diagnostic imaging

When selecting diagnostic procedures to identify urolithiasis in paediatric patients, it should be remembered that these patients might be uncooperative, require anaesthesia, or be sensitive to ionising radiation (13).

9.2.1 Ultrasound

Ultrasound (US) is the primary imaging technique (13) in paediatrics. Its advantages are absence of radiation and no need for anaesthesia. Ultrasound (US) provides information about the presence, size and location of a stone, and the grade of dilatation/obstruction of the urinary collecting system and the severity of nephrocalcinosis. It also indicates anatomical abnormalities.

Colour Doppler US shows differences in the ureteric jet (14) and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction (15).

Nevertheless, US fails to identify stones in > 40% of paediatric patients (16-19) (LE: 4), and provides no information about renal function.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>US is the first choice for imaging in children and should include the kidney, filled bladder, and adjoining portions of the ureter (14,20).</td>
<td>2a</td>
</tr>
</tbody>
</table>

9.2.2 Plain films (KUB radiography)

KUB radiography can help to identify stones and their radiopacity, and facilitate follow-up.

9.2.3 Intravenous urography (IVU)

Intravenous urography is an important diagnostic tool. However, the need for contrast medium injection is a major drawback. The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) (21).

9.2.4 Helical computed tomography (CT)

Recent CT protocols have been shown to reduce radiation exposure significantly (22). The principle of ALARA (as low as reasonable achievable) should always be observed. In adults it has a sensitivity of 94-100% and specificity of 92-100% (23).

In children, only 5% of stones escape detection by NCCT (14,23,24). Sedation or anaesthesia is rarely needed with modern high-speed CT apparatus (11).
9.2.5  Magnetic resonance urography (MRU)
Magnetic resonance urography cannot be used to detect urinary stones. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology (25).

9.2.6  Nuclear imaging
99mTc-dimercaptosuccinyl acid scanning provides information about cortical abnormalities such as scarring, but does not aid primary diagnosis of urolithiasis. Diuretic renography with injection of a radiotracer (MAG3 [Mercaptacetyltriglycin] or DPTA [Diethylentriaminpentaacetat]) and furosemide can be used to demonstrate renal function, identify obstruction in the kidney after injection of furosemide, and indicate the anatomical level of the obstruction (11,14).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In children, US is the first-line imaging modality when suspecting a stone.</td>
<td>B</td>
</tr>
<tr>
<td>If US does not provide the required information, KUB radiography (or NCCT) should be performed.</td>
<td>B</td>
</tr>
</tbody>
</table>

US = ultrasound; KUB = kidney, ureter, bladder; NCCT = non-contrast enhanced computed tomography.

9.3  Stone removal
Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL (26). For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. Anticipation of the expected stone composition should be taken into account when selecting the appropriate procedure for stone removal (cystine stones are more resistant to SWL).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous passage of a stone is more likely in children than adults (6,11,12).</td>
<td>4</td>
</tr>
</tbody>
</table>

9.3.1  Medical expulsive therapy (MET) in children
Medical expulsive therapy in children has already been discussed in Section 5.3.2.6. Although the use of α-blockers is very common in adults, there are insufficient data to demonstrate their safety and efficacy in children (27).

9.3.2  Extracorporeal shock wave lithotripsy

SFRs of 67-93% in short-term and 57-92% in long-term follow-up studies have been reported. In children, compared with adults, SWL can achieve more effective disintegration of large stones, together with swifter and uncomplicated discharge of large fragments (32-34). Stones located in calices, as well as abnormal kidneys, and large stones, are more difficult to disintegrate and clear. The likelihood of urinary obstruction is higher in such cases, and children should be followed closely for the prolonged risk of urinary tract obstruction. The retreatment rate is 13.9-53.9%, and the need for ancillary procedures and/or additional interventions is 7-33% (32-34,36).

The need for general anaesthesia during SWL depends on patient age and the lithotripter used. General or dissociative anaesthesia is administered in most children aged < 10 years, to avoid patient and stone motion and the need for repositioning (32,36). With modern lithotriptors, intravenous sedation or patient-controlled analgesia have been used in selected cooperative older children (37) (LE: 2b). There are concerns regarding the safety and potential biological effects of SWL on immature kidneys and surrounding organs in children. However, during short- and long-term follow-up, no irreversible functional or morphological side effects of high-energy shock waves have been demonstrated. In addition, when the potential deterioration of renal function is taken into account (although transient), restricting the number of shock waves and the energy used during each treatment session helps protect the kidneys (38-41).

If the stone burden requires a ureteral stent, alternative procedures should be considered. Ureteral stents are seldom needed following SWL of upper tract stones, ureteral pre-stenting decreases the SFR after initial treatment (28,30-32).
In children, the indications for SWL are similar to those in adults, however, they pass fragments more easily.

Children with renal stones of a diameter up to 20 mm (~300 mm²) are ideal candidates for SWL.

### 9.3.3 Endourological procedures

Improvement in intracorporeal lithotripsy devices and development of smaller instruments facilitate PNL and URS in children.

#### 9.3.3.1 Percutaneous nephrolithotripsy (PNL)

Preoperative evaluation and indications for PNL in children are similar to those in adults. Although PNL is performed as monotherapy in most cases, it can be used as an adjunctive procedure. Availability of appropriate-size instruments and US guidance mean that age is not a limiting factor, and PNL can now be performed safely by experienced operators, with less radiation exposure, even for large and complex stones (42-46). SFRs are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS (42,43).

For paediatric patients, the indications for PNL are similar to those in adults. 1a

In children, PNL is recommended for treatment of renal pelvic or caliceal stones with a diameter > 20 mm (~300 mm²).

#### 9.3.3.2 Ureteroscopy

Although SWL still is the first-line treatment for most ureteral stones, it is unlikely to be successful for stones > 10 mm in diameter, or for impacted, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult (47-50).

If SWL is not promising, ureteroscopy can be used. With the clinical introduction of smaller-calibre instruments, this modality has become the treatment of choice for medium and larger distal ureteric stones in children (48-50).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 5.6.2.2.7).

For intracorporeal lithotripsy, the same devices as in adults can be used (Ho:Yag laser, pneumatic and US lithotriptors).

Flexible ureteroscopy has become an efficacious treatment for paediatric upper urinary tract stones. It might be particularly effective for treatment of proximal ureteral calculi and for stones < 1.5 cm in the lower pole calices (56-58).

#### 9.3.4 Open or laparoscopic surgery

Most stones in children can be managed by SWL and endoscopic techniques (59). Therefore, the rate of open procedure has dropped significantly (60-64). In some situations, open surgery is inevitable. Indications for surgery include: failure of primary therapy for stone removal; very young children with complex stones; congenital obstruction that requires simultaneous surgical correction; severe orthopaedic deformities that limit positioning for endoscopic procedures; and abnormal kidney position (29,31,44,45). Open surgery can be replaced by laparoscopic procedures in experienced hands (62-64).

### 9.4 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. In case of obstructive pathology in association with the established metabolic abnormalities, treatment should not be delayed. Children are in the high-risk group for stone recurrence (Chapter 11).
9.5 References


10. STONES IN URINARY DIVERSION AND OTHER VOIDING PROBLEMS

10.1 Management of stones in patients with urinary diversion

10.1.1 Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir (1-3). Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation (4) (Chapter 2.6). One study has shown that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at 5 years (5).

10.1.2 Management

Some patients with smaller upper-tract stones can be treated effectively with SWL (6,7). However, in the majority, well-established endourological techniques are necessary to achieve stone-free status (8).

An endoscopic approach might be difficult or impossible in individuals with long, tortuous conduits or with invisible ureter orifices.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade URS is the alternative.</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNL is the preferred treatment for removal of large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach or that are not amenable to SWL.</td>
<td>A*</td>
</tr>
</tbody>
</table>

PNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy.
For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. The same applies for continent urinary diversion where trans-stomal manipulations must be performed carefully to avoid disturbance of the continence mechanism (9).

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of an overlying bowel, which could make this approach unsafe (10), and if present, an open surgical approach should be considered.

10.1.3 Prevention
Recurrence risk is high in these patients (5). Close follow-up and metabolic evaluation are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyperdiuresis or regular irrigation of continent reservoirs (11).

10.1.4 References

10.2 Management of stones in patients with neurogenic bladder
10.2.1 Aetiology, clinical presentation and diagnosis
Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, pelvicaliectasis, vesicoureteric reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect (1). The main issues are urinary stasis and infection (Chapter 2.6). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed (2,3).

Diagnosis of stones may be difficult and late in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction (4). Difficulties in self-catheterisation should lead to suspicion of bladder calculi.
Imaging studies are needed (US, CT) to confirm clinical diagnosis prior to surgical intervention.

10.2.2 Management
Management of calculi in patients with neurogenic bladder is similar to that described in Section 10.1.

In MMC (myelomeningocele-) patients, latex allergy is common, therefore, appropriate measures need to be taken regardless of the treatment (5). Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table.

The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols (6).

For efficient long-term stone prevention in patients with neurogenic bladder, correction of the metabolic disorder, appropriate infection control, and restoration of normal storing/voiding function of the bladder are needed.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In myelomeningocele patients, latex allergy is common so that appropriate measures need to be taken regardless of the treatment.</td>
<td>B</td>
</tr>
</tbody>
</table>

10.2.3 References

10.3 Management of stones in transplanted kidneys
10.3.1 Aetiology and clinical presentation
Transplant patients depend on their solitary kidney for renal function. Impairment causing urinary stasis/obstruction therefore requires immediate intervention or drainage of the transplanted kidney. Risk factors in these patients are multifold:
- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyperfiltration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism (1) are biochemical risk factors.

Stones in kidney allografts have a incidence of 0.2-1.7% (2-4).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive, US or NCCT should be performed to rule out calculi (5).</td>
<td>4</td>
<td>B</td>
</tr>
</tbody>
</table>

US = ultrasound; NCCT = non-contrast enhanced computed tomography.
10.3.2 **Management**

Treatment decisions for selecting the appropriate technique for stone removal from a transplanted kidney are difficult. Although management principles are similar to those applied in other single renal units (6-9), additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal position of the organ, directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and holmium laser has made ureteroscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs (12-14). Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity (15-17).

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.</td>
<td></td>
</tr>
<tr>
<td>SWL for small calyceal stones is an option with minimal complication risk, but localisation of the stone can be challenging and SFRs are poor (10,11).</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with transplanted kidneys, all contemporary treatment modalities, including shockwave therapy, (flexible) ureteroscopy, and percutaneous nephrolithotomy are management options.</td>
<td>B</td>
</tr>
<tr>
<td>Metabolic evaluation should be completed after stone removal.</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

10.3.3 **References**


10.4 Special problems in stone removal

### Table 22: Special problems in stone removal

<table>
<thead>
<tr>
<th>Problem</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caliceal diverticulum stones</td>
<td>SWL, PNL (if possible) or RIRS. Can also be removed using laparoscopic retroperitoneal surgery (1-5). Patients may become asymptomatic due to stone disintegration (SWL) whilst well-disintegrated stone material remains in the original position due to narrow caliceal neck.</td>
</tr>
<tr>
<td>Horseshoe kidneys</td>
<td>Can be treated in line with the options described above (6.) Passage of fragments after SWL might be poor.</td>
</tr>
<tr>
<td>Stones in pelvic kidneys</td>
<td>SWL, RIRS or laparoscopic surgery. For obese patients, the options are SWL, PNL, RIRS or open surgery.</td>
</tr>
<tr>
<td>Stones formed in a continent reservoir</td>
<td>Section 10.1. Each stone problem must be considered and treated individually.</td>
</tr>
<tr>
<td>Patients with obstruction of the ureteropelvic junction</td>
<td>When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. URS together with endopyelotomy with Ho:YAG. Incision with an Acucise balloon catheter might be considered, provided the stones can be prevented from falling into the pelviureteral incision (7-10).</td>
</tr>
</tbody>
</table>

10.5 References

11. METABOLIC EVALUATION AND RECURRENT PREVENTION

11.1 General metabolic considerations for patient work-up

11.1.1 Evaluation of patient risk

After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 2).

For correct classification, two items are mandatory:
- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (Section 3.2).

Figure 2: Assignment of patients to low- or high-risk groups for stone formation


Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The different stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-dihydroxyadenine;
- drug stones;
- unknown composition.

11.1.2 Urine sampling
Specific metabolic evaluation requires collection of two consecutive 24-h urine samples (1-3). The collecting bottles should be prepared with 5% thymol in isopropanol or stored at ≤ 8°C during collection with the risk of spontaneous crystallisation in the urine (4). Preanalytical errors can be minimised by carrying out urinalysis immediately after collection. Alternatively boric acid (10 g powder per urine container) can also be used. The collecting method should be chosen in close cooperation with the particular laboratory. Urine pH should be assessed during collection of freshly voided urine four times daily (5) using sensitive pH-dipsticks or pH-meter.

HCl can be used as a preservative in special situations to prevent precipitation of calcium oxalate and calcium phosphate. However, in samples preserved with HCl, pH measurement is impossible and uric acid precipitates immediately. Alkalisation is needed to dissolve urate crystals if urate excretion is of interest (6).

Spot urine samples are an alternative method of sampling, particularly when 24-h urine collection is difficult, for example, in non-toilet trained children (7,8). Spot urine studies normally link the excretion rates to creatinine (8,9), but these are limited because the results may vary with collection time and patients’ sex, body weight and age.

11.1.3 Timing of specific metabolic work-up
For the initial specific metabolic work-up, the patient should stay on a self determined diet under normal daily conditions and should ideally be stone free. A minimum of 20 days is recommended (3 months suggested) between stone expulsion or removal and 24-h urine collection (4,10).

Follow-up studies are necessary in patients receiving recurrent stone prophylaxis (1). The first follow-up 24-h urine measurement should be at 8-12 weeks after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-h urine measurements if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-h urine evaluation every 12 months.

The panel realise that on this issue there is only very limited published evidence.

11.1.4 Reference ranges of laboratory values
Tables 23-26 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.
Table 23: Normal laboratory values for blood parameters in adults

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>20-100 μmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.5 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.0-2.5 mmol/L (total calcium)</td>
</tr>
<tr>
<td></td>
<td>1.12-1.32 mmol/L (ionised calcium)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>119-380 μmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>98-112 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.81-1.29 mmol/L</td>
</tr>
</tbody>
</table>

Blood gas analysis

<table>
<thead>
<tr>
<th></th>
<th>Reference range</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td></td>
</tr>
<tr>
<td>pO₂</td>
<td>80-90 mmHg</td>
<td></td>
</tr>
<tr>
<td>pCO₂</td>
<td>35-45 mmHg</td>
<td></td>
</tr>
<tr>
<td>HCO₃</td>
<td>22-26 mmol/L</td>
<td></td>
</tr>
<tr>
<td>BE</td>
<td>± 2 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

BE = base excess (loss of buffer base to neutralise acid).

11.1.5 Risk indices and additional diagnostic tools

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in urine:

- APCaOxindex (11,12);
- EQUIL, a computer program to calculate relative supersaturations (13-15);
- Bonn Risk Index (16-18).

Another approach to risk assessment is the Joint Expert Speciation System (JESS), which is based on an extensive database of physiochemical constants and is similar to the EQUIL (19). However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing and the benefit remains controversial.

Table 24: Normal laboratory values for urinary parameters in adults

<table>
<thead>
<tr>
<th>Urinary Parameters</th>
<th>Reference ranges and limits for medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Constantly &gt; 5.8</td>
</tr>
<tr>
<td></td>
<td>Constantly &gt; 7.0</td>
</tr>
<tr>
<td></td>
<td>Constantly ≤ 5.8</td>
</tr>
<tr>
<td>Specific weight</td>
<td>&gt; 1.010</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt; 7-13 mmol/day females</td>
</tr>
<tr>
<td></td>
<td>13-18 mmol/day males</td>
</tr>
<tr>
<td>Calcium</td>
<td>&gt; 5.0 mmol/day</td>
</tr>
<tr>
<td></td>
<td>≥ 8.0 mmol/day</td>
</tr>
<tr>
<td>Oxalate</td>
<td>&gt; 0.5 mmol/day</td>
</tr>
<tr>
<td></td>
<td>0.45-0.85 mmol/day</td>
</tr>
<tr>
<td></td>
<td>≥ 1.0 mmol/day</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&gt; 4.0 mmol/day (women), 5 mmol/day (men)</td>
</tr>
<tr>
<td>Citrate</td>
<td>&lt; 2.5 mmol/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td>&lt; 3.0 mmol/day</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>&gt; 35 mmol/day</td>
</tr>
<tr>
<td>Ammonium</td>
<td>&gt; 50 mmol/day</td>
</tr>
<tr>
<td>Cystine</td>
<td>&gt; 0.8 mmol/day</td>
</tr>
</tbody>
</table>
Table 25: Normal values for spot urine samples: creatinine ratios (solute/creatinine) (20)

<table>
<thead>
<tr>
<th>Parameter/Patient age</th>
<th>Ratio of solute to creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium mol/mol</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>1-3 years</td>
<td>&lt; 1.5</td>
</tr>
<tr>
<td>1-5 years</td>
<td>&lt; 1.1</td>
</tr>
<tr>
<td>5-7 years</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>&gt; 7 years</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td></td>
<td>Oxalate mmol/mol</td>
</tr>
<tr>
<td>0-6 months</td>
<td>&lt; 325-360</td>
</tr>
<tr>
<td>7-24 months</td>
<td>&lt; 132-174</td>
</tr>
<tr>
<td>2-5 years</td>
<td>&lt; 98-101</td>
</tr>
<tr>
<td>5-14 years</td>
<td>&lt; 70-82</td>
</tr>
<tr>
<td>&gt; 16 years</td>
<td>&lt; 40</td>
</tr>
<tr>
<td></td>
<td>Citrate mol/mol</td>
</tr>
<tr>
<td>0-5 years</td>
<td>&gt; 0.25</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>&gt; 0.15</td>
</tr>
<tr>
<td></td>
<td>Magnesium mol/mol</td>
</tr>
<tr>
<td>&gt; 0.63</td>
<td>&lt; 0.13</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&lt; 0.56 mg/dl (33 ìmol/l) per GFR (ratio x plasma creatinine)</td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td></td>
</tr>
</tbody>
</table>

Table 26: Urinary excretion of soluble excretion in 24-h urine samples**

<table>
<thead>
<tr>
<th>Calcium excretion</th>
<th>Citrate excretion</th>
<th>Cystine excretion</th>
<th>Oxalate excretion</th>
<th>Urate excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>All age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1 mmol/kg/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 mg/kg/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All age groups</td>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1.9 mmol/1.73 m²/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 365 mg/1.73 m²/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1.6 mmol/1.73 m²/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 310 mg/1.73 m²/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 10 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 55 μmol/1.73 m³/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 13 mg/1.73 m³/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 200 μmol/1.73 m³/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 48 mg/1.73 m³/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 10 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 5 mmol/1.73 m³/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 40 mg/1.73 m³/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 70 μmol/kg/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 13 mg/kg/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 1 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 55 μmol/kg/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 9.3 mg/kg/24 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**24h urine parameters are diet and gender dependent and may vary geographically.

11.1.6 References

http://books.nap.edu/catalog/10490.html

11.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 27. The main focus of these is normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment and based on stone analysis.
### Table 27: General preventive measures

| Fluid intake (drinking advice) | Fluid amount: 2.5-3.0 L/day  
| Circadian drinking  
| Neutral pH beverages  
| Diuresis: 2.0-2.5 L/day  
| Specific weight of urine: < 1010 |
| Nutritional advice for a balanced diet | Balanced diet*  
| Rich in vegetable and fibre  
| Normal calcium content: 1-1.2 g/day  
| Limited NaCl content: 4-5 g/day  
| Limited animal protein content: 0.8-1.0 g/kg/day |
| Lifestyle advice to normalise general risk factors | BMI: 18-25 kg/m² (target adult value, not applicable to children)  
| Stress limitation measures  
| Adequate physical activity  
| Balancing of excessive fluid loss |

*Caution: The protein need is age-group dependent, therefore protein restriction in childhood should be handled carefully.*

*Avoid excessive consumption of vitamin supplements.*

### 11.2.1 Fluid intake

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated (1,2). The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate (3). If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased (4,5).

### 11.2.2 Diet

A common sense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, but without any excesses (6).

**Fruits, vegetables and fibres:** fruit and vegetable intake should be encouraged because of the beneficial effects of fibre (7). The alkaline content of a vegetarian diet also increases urinary pH.

**Oxalate:** excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load (3), particularly in patients who have high oxalate excretion.

**Vitamin C:** although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial (8-10). However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

**Animal protein** should not be taken in excess (11,12) and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

**Calcium intake** should not be restricted unless there are strong reasons because of the inverse relationship between dietary calcium and stone formation (13). The daily requirement for calcium is 1000 to 1200 mg/day (14). Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate (12,15-17).

**Sodium:** the daily sodium (NaCl) intake should not exceed 3-5 g. High intake adversely affects urine composition:

- calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to loss of bicarbonate;
- increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein (11,12). A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women (13,18). There have been no prospective clinical trials on the role of sodium restriction as an independent variable in
reducing the risk of stone formation.

Urate: intake of urate-rich food should be restricted in patients with hyperuricosuric calcium oxalate (19-21) and uric acid (16) stones. Intake should not exceed 500 mg/day.

11.2.3 Lifestyle
Lifestyle factors may influence the risk of stone formation, for example, overweight and obesity (22-24). Another risk factor is arterial hypertension (25,26).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The aim should be to obtain a 24-h urine volume ≥ 2.5 L.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>Oxalate restriction</td>
<td>2b</td>
</tr>
<tr>
<td>High sodium excretion</td>
<td>Restricted intake of salt</td>
<td>1b</td>
</tr>
<tr>
<td>Small urine volume</td>
<td>Increased fluid intake</td>
<td>1b</td>
</tr>
<tr>
<td>Urea level indicating a high intake of animal protein</td>
<td>Avoid excessive intake of animal protein</td>
<td>1b</td>
</tr>
</tbody>
</table>

11.2.4 References


11.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

11.3.1 Introduction

Pharmacological treatment is necessary in patients at high risk for recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 28 highlights the most important characteristics of commonly used medication.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Rationale</th>
<th>Dose</th>
<th>Specifics and side effects</th>
<th>Stone type</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline citrates</td>
<td>Alkalinisation</td>
<td>5-12 g/d (14-36 mmol/d)</td>
<td>Daily dose for alkalinisation depends on urine pH.</td>
<td>Calcium oxalate Uric acid Cystine</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>Hypocitraturia</td>
<td>Children: 0.1-0.15 g/kg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibition of calcium oxalate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>crystallisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Hyperuricosuria</td>
<td>100-300 mg/d</td>
<td>100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction</td>
<td>Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine</td>
<td>7-9</td>
</tr>
<tr>
<td></td>
<td>Hyperuricaemia</td>
<td>Children: 1-3 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Enteric hyperoxaluria</td>
<td>500 mg/d</td>
<td>Intake 30 min before the meals</td>
<td>Calcium oxalate</td>
<td>10-13</td>
</tr>
<tr>
<td>Captopril</td>
<td>Cystinuria</td>
<td>75-150 mg</td>
<td>Second-line option due to significant side effects</td>
<td>Cystine</td>
<td>14,15</td>
</tr>
<tr>
<td>I-Methionine</td>
<td>Acidification</td>
<td>600-1500 mg/d</td>
<td>Hypercalciuria, bone demineralization, systemic acidosis. No long-term therapy.</td>
<td>Infection stones Ammonium urate Calcium phosphate</td>
<td>1,16, 17</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Isolated hypomagnesuria</td>
<td>200-400 mg/d</td>
<td>Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.</td>
<td>Calcium oxalate</td>
<td>18-21</td>
</tr>
<tr>
<td></td>
<td>Enteric hyperoxaluria</td>
<td>Children: 6 mg/kg/d</td>
<td></td>
<td></td>
<td>low evidence</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Alkalinisation Hypocitraturia</td>
<td>4.5 g/d</td>
<td></td>
<td>Calcium oxalate Uric acid Cystine</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Primary hyperoxaluria</td>
<td>Initial dose 5 mg/kg/d</td>
<td>Polyneuropathia</td>
<td>Calcium oxalate</td>
<td>22-24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max. 20 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide (Hydrochlorothiazide)</td>
<td>Hypercalciuria</td>
<td>25-50 mg/d</td>
<td>Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia</td>
<td>Calcium oxalate Calcium phosphate</td>
<td>1,18,25-36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 0.5-1 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiopronin</td>
<td>Cystinuria</td>
<td>Initial dose 250 mg/d</td>
<td>Risk for tachyphylaxis and proteinuria.</td>
<td>Cystine</td>
<td>37-42</td>
</tr>
<tr>
<td></td>
<td>Active decrease of urinary cystine levels</td>
<td>Max. 2000 mg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11.3.2 References


11.4 Calcium oxalate stones
The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Section 2.6.

11.4.1 Diagnosis
Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) (and vitamin D) in case of increased calcium levels.

Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium.

11.4.2 Interpretation of results and aetiology
The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 3 (1-26).
Calcium oxalate stone

Basic evaluation

24 h urine collection

Hyperoxaluria

Hyperuricosuria

Hypomagnesuria

Hypercitraturia

Hypercalcuria

Figure 3: Diagnostic and therapeutic algorithm for calcium oxalate stones

1 Be aware of excess calcium excretion 2 d: day(24h) 3 No magnesium therapy for patients with renal insufficiency
The most common metabolic abnormality associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagnesuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ for different ethnic groups (1).

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- "Acidic arrest" (urine pH constantly < 6) may promote co-crystallisation of uric acid and calcium oxalate. Similarly, increased uric acid excretion (> 4 mmol/day in adults or > 12 mg/kg/day in children) can act as a promoter.
- Urine pH levels constantly > 5.8 in the day profile indicate renal tubular acidosis (RTA), provided urinary tract infection (UTI) has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (Section 11.6.4).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (< 2.5 mmol/day) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m²/day in children) confirms hyperoxaluria.
  - primary hyperoxaluria (oxalate excretion mostly ≥ 1 mmol/day), appears in three genetically determined forms;
  - secondary hyperoxaluria (oxalate excretion ≥ 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
  - mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

11.4.3 **Specific treatment**

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 3 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones (2-26).

11.4.4 **Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition**

<table>
<thead>
<tr>
<th>Urinary risk factor</th>
<th>Suggested treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Thiazide + potassium citrate</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>Oxalate restriction</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Enteric hyperoxaluria</td>
<td>Potassium citrate</td>
<td>3-4</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Calcium supplement</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Oxalate absorption</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Hypocitraturia</td>
<td>Potassium citrate</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>High sodium excretion</td>
<td>Restricted intake of salt</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Small urine volume</td>
<td>Increased fluid intake</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Urea level indicating a high intake of animal protein</td>
<td>Avoid excessive intake of animal protein</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>No abnormality identified</td>
<td>High fluid intake</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

11.4.5 **References**


11.5 Calcium phosphate stones

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is given in Section 2.6.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite: Carbonate apatite crystallisation occurs at pH ≥ 6.8 and may be associated with infection.

Brushite crystallises at an optimum pH of 6.5-6.8, at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI.

Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

11.5.1 Diagnosis

Diagnosis requires blood analysis for: creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), and PTH (in case of increased calcium levels). Urinalysis includes measurement of: volume, urine pH profile, specific weight, calcium, phosphate and citrate.

11.5.2 Interpretation of results and aetiology

General preventive measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.

Figure 4: Diagnostic and therapeutic algorithm for calcium phosphate stones

11.5.3 Pharmacological therapy (1-9)

HPT and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using

Hydrochlorothiazide

- Initially 25 mg/d
- Up to 50 mg/d

L-methionine

- 200-500 mg 3 times daily
thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be helpful however is not commonly used and needs monitoring for systemic acidosis development. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

### Recommendations for the treatment of calcium phosphate stones

<table>
<thead>
<tr>
<th>Urinary risk factor</th>
<th>Suggested treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Thiazide</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Inadequate urine pH</td>
<td>Acidification</td>
<td>3-4</td>
<td>C</td>
</tr>
<tr>
<td>UTI</td>
<td>Antibiotics</td>
<td>3-4</td>
<td>C</td>
</tr>
</tbody>
</table>

11.5.4 References


11.6 Disorders and diseases related to calcium stones

11.6.1 **Hyperparathyroidism** (1-10)

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Kidney stones occur in approximately 20% of patients with primary HPT. The clinical appearance of HPT typically comprises bone loss, gastric ulcers and urolithiasis. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcemia and hypercalciuria. Serum calcium may be mildly elevated and serum PTH within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting. Stones of PTH patients may contain both calcium oxalate and calcium phosphate.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. Primary HPT can only be cured by surgery.

11.6.2 **Granulomatous diseases** (11,12)

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcemia and hypercalciuria secondary to increased calcitriol production. The later is independent of PTH control, leading to increased calcium absorption in the gastrointestinal tract and suppression of PTH. Treatment focusses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. It should be reserved to the specialist.
11.6.3  **Primary hyperoxaluria** (13-19)
Patients with primary hyperoxaluria (PH) should be referred to specialised centres, because successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5-4.0 L/day in adults (children 1.5 L/m² body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyperdiuresis, alkaline citrates and magnesium. However, in end-stage renal failure, primary PH requires simultaneous liver-kidney transplantation.

Treatment regimens are:
• Pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
• Alkaline citrate: 9-12 g/day in adults, 0.1-0.15 meq/kg/day in children;
• Magnesium: 200-400 mg/day (no magnesium in case of renal insufficiency).

<table>
<thead>
<tr>
<th>Urinary risk factor</th>
<th>Suggested treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperoxaluria</td>
<td>Pyridoxine</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

11.6.4  **Enteric hyperoxaluria** (20-28)
Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection and malabsorptive bariatric surgery and in Crohn’s disease and pancreas insufficiency. Intestinal loss of fatty acids is combined with loss of calcium. The normal complex formation between oxalate and calcium is therefore disturbed and oxalate absorption is increased. In addition to hyperoxaluria, these patients usually present with hypocitraturia because of loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, and stone formation.

Specific preventive measures are:
• restricted intake of oxalate-rich foods;
• restricted fat intake;
• calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine (20,21);
• sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
• alkaline citrates to raise urinary pH and citrate.

<table>
<thead>
<tr>
<th>Urinary risk factor</th>
<th>Suggested treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric hyperoxaluria</td>
<td>Potassium citrate</td>
<td>3-4</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Calcium supplement</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Oxalate absorption</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Small urine volume</td>
<td>Increased fluid intake</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

11.6.5  **Renal tubular acidosis** (29-31)
Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 5 outlines the diagnosis of RTA. Table 29 shows acquired and inherited causes of RTA.
An alternative Ammonium Chloride loading test using NH₄Cl load with 0.05 g/kg body weight over 3 days might provide similar results and may be better tolerated by the patient (31).

RTA can be acquired or inherited. Reasons for acquired RTA can be obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalciuria and primary parathyroidism, and drug-induced (e.g. zonisamide). Table 29 shows the inherited causes of RTA.

**Table 29: Inherited causes of renal tubular acidosis**

<table>
<thead>
<tr>
<th>Type - inheritance</th>
<th>Gene/gene product/function</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td>SLC4A1/AE1/Cl-bicarbonate exchanger</td>
<td>Hypercalciuria, hypokalaemia, osteomalacia</td>
</tr>
<tr>
<td>Autosomal recessive with hearing loss</td>
<td>ATP6V1B1/B1 subunit of vacuolar H-ATPase/proton secretion</td>
<td>Hypercalciuria, hypokalaemia, rickets</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>ATP6V0A4/A4 subunit of vacuolar H-ATPase/proton secretion</td>
<td>Hypercalciuria, hypokalaemia, rickets</td>
</tr>
</tbody>
</table>

The main therapeutic aim is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 30). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.
Table 30: Pharmacological treatment of renal tubular acidosis

<table>
<thead>
<tr>
<th>Biochemical risk factor</th>
<th>Rationale for pharmacological therapy</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Calcium excretion &gt; 8 mmol/day</td>
<td>Hydrochlorothiazide, - in adults, 25 mg/day initially, up to 50 mg/day - in children, 0.5-1 mg/kg/day</td>
</tr>
<tr>
<td>Inadequate urine pH</td>
<td>Intracellular acidosis in nephron</td>
<td>Alkaline citrate, 9-12 g/day divided in 3 dosages OR Sodium bicarbonate, 1.5 g, 3 times daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary risk factor</th>
<th>Suggested treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal RTA</td>
<td>Potassium citrate</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Thiazide + potassium citrate</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

11.6.6 Nephrocalcinosis (32,33)

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with kidney stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent’s disease Bartter’s syndrome and Medullary sponge kidney. The many causes of NC means there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, while minimising the biochemical risk factors.

11.6.6.1 Diagnosis

Diagnosis requires the following blood analysis: PTH (in case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis. Urinalysis should investigate: urine pH profile (minimum 4 times daily), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

11.6.7 References


11.7 Uric acid and ammonium urate stones
All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence (1). Uric acid nephrolithiasis is responsible for approximately 10% of kidney stones (2). They are associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs, gout or catabolism (3). Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), increased acic acid intake (high animal protein intake), or increased base loss (diarrhoea) (3).

Ammonium urate stones are extremely rare, comprising < 1% of all types of urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), potassium deficiency, hypokalemia and malnutrition.

Suggestions on uric acid and ammonium urate nephrolithiasis are based on level III and IV evidence.

11.7.1 Diagnosis
Figure 6 shows the diagnostic and therapeutic algorithm for uric acid and ammonium urate stones.

Blood analysis requires measurement of creatinine, potassium and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. Urine culture is needed in case of ammonium urate stones.

11.7.2 Interpretation of results
Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 5.8) promotes uric acid crystallisation.

Hyperuricosuria is defined as uric acid excretion ≥ 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation.

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by: urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones (7,8).

Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration and ammonium being present to serve as cation (4-6).

11.7.3 Specific treatment
General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction of their daily diet. Figure 6 describes pharmacological treatment (1-15).
Figure 6: Diagnostic and therapeutic algorithm for uric acid and ammonium urate stones

**Urate containing stones**

**Uric acid stone**

Basic evaluation

"Uric acid arrest" Urine pH < 6

Alcaline citrate 9-12 g/d^2^
Or Sodium bicarbonate 1.5 g tid

Dose depends on targeted urine pH

Prevention urine pH 6.2-6.8

Chemolysis urine pH 6.5-7.2^*^

**Ammonium urate stone**

Basic evaluation

Urine pH > 6.5

UTI

L-methionine 200-500 mg tid Target urine-pH 5.8-6.2

Correction of factors predisposing amm.urate stone formation

Hyperuricosuria

> 4.0 mmol/d

Allopurinol 100 mg/d

> 4.0 mmol/d and Hyperuricemia > 380 µmol

Allopurinol 100-300 mg/d

1 d: day (24h)

^* A higher pH may lead to calcium phosphate stone formation.

### References

11.8 Struvite and infection stones
All infection-stone formers are deemed at high risk of recurrence.

Struvite stones represent 2-15% of the stones sent for analysis. Stones that contain struvite may originate de novo or grow on pre-existing stones, which are infected with urea-splitting bacteria (1,2). There are several factors predisposing patients to struvite stone formation (Table 31) (3,4).

11.8.1 Diagnosis
Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.

**Interpretation**
Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate. Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 32). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 (4,6,7). Proteus mirabilis accounts for more than half of all urease-positive UTIs (8,9).

11.8.2 Specific treatment
General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal (10), short- or long-term antibiotic treatment (11), urinary acidification using methionine (12) or ammonium chloride (13), and urease inhibition (14,15). For severe infections, acetohydroxamic acid may be an option (14,15) (Figure 1), however it is not licensed/available in all European countries.

11.8.3 Recommendations for therapeutic measures of infection stones

<table>
<thead>
<tr>
<th>Recommendations for therapeutic measures</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical removal of the stone material as completely as possible</td>
<td>3,4</td>
<td>A*</td>
</tr>
<tr>
<td>Short-term antibiotic course</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Long-term antibiotic course</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Urinary acidification: ammonium chloride, 1 g 2 or 3 times daily</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Urinary acidification: methionine, 200-500 mg, 1-3 times daily</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Urease inhibition</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

* upgraded following panel consensus.
11.8.4 References


Table 31: Factors predisposing to struvite stone formation

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td>Spinal cord injury/paralysis</td>
</tr>
<tr>
<td>Continent urinary diversion</td>
</tr>
<tr>
<td>Heal conduit</td>
</tr>
<tr>
<td>Foreign body</td>
</tr>
<tr>
<td>Stone disease</td>
</tr>
<tr>
<td>Indwelling urinary catheter</td>
</tr>
<tr>
<td>Urethral stricture</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Bladder diverticulum</td>
</tr>
<tr>
<td>Cystocele</td>
</tr>
<tr>
<td>Caliceal diverticulum</td>
</tr>
<tr>
<td>Ureteropelvic junction obstruction</td>
</tr>
</tbody>
</table>

Table 32: Most important species of urease-producing bacteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Bacteria</th>
</tr>
</thead>
</table>
| Obligate urease-producing bacteria (> 98 %) | • Proteus spp.  
• Providencia rettgeri  
• Morganella morganii  
• Corynebacterium urealyticum  
• Ureaplasma urealyticum |
| Facultative urease-producing bacteria   | • Enterobacter gergoviae  
• Klebsiella spp.  
• Providencia stuartii  
• Serratia marcescens  
• Staphylococcus spp. |

CAUTION: 0-5% of strains of *Escherichia coli*, *Enterococcus spp.* and *Pseudomonas aeruginosa* may produce urease.
11.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies (1,2). All cystine stone formers are deemed at high risk of recurrence.

11.9.1 Diagnosis

Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

**Interpretation**

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of phenotype or genotype of the cystinuric patient, the clinical manifestations are the same (3).
- There is no role for genotyping patients in the routine management of cystinuria (4-6).
- Reductive therapy targets the disulphide binding in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria (7).
- The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/L, with a sensitivity of 72% and specificity of 95%. False-positive results in
patients with Fanconi’s syndrome, homocystinuria, or those taking various drugs, including ampicillin or sulfa-containing medication (8,9).

- Quantitative 24-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis. Levels above 30 mg/day are considered abnormal (10-13).

### 11.9.2 Specific treatment

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine, however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day (14).

A high level of diuresis is of fundamental importance, aiming for a 24-h urine volume of ≥ 3 L (15,16). A considerable fluid intake evenly distributed throughout the day is necessary.

#### 11.9.2.1 Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cystine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m² body surface area in children.

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cysteine.

*Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example, when nephritic syndrome develops, or poor compliance, especially with long-term use.*

After carefully considering the risk of early tachyphylaxis, putting into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day or in the case of recurring stone formation, notwithstanding other preventive measures.

Ascorbic acid (as effervescent tablets) can be used when cystine excretion is < 3.0 mmol/day. However, it has uncertain, limited reductive power and is estimated to lower urinary cystine levels by ~20% (17). The effectiveness and use of ascorbic acid as a standard therapeutic regimen are controversial (18).

Results for the angiotensin-converting enzyme inhibitor, captopril, are controversial, and hypotonus and hyperkalaemia are possible side effects (19-23). Captopril remains a second-line option, for use when tiopronin is not feasible or unsuccessful.
Figure 8: Metabolic management of cystine stones

**Therapeutic measures**

<table>
<thead>
<tr>
<th>Therapeutic measure</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine dilution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High fluid intake recommended so that 24-h urine volume exceeds 3 L. Intake should be ≥ 150 mL/h.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td><strong>Alkalisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For cystine excretion &lt; 3 mmol/day: potassium citrate 3-10 mmol 2 or 3 times daily, to achieve pH &gt; 7.5.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td><strong>Complex formation with cystine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with cystine excretion &gt; 3 mmol/day, or when other measures are insufficient: tiopronin, 250-2000 mg/day. Captopril, 75-150 mg/d, remains a second-line option if tiopronin is not feasible or unsuccessful.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

**References**


11.10 2,8-dihydroxyadenine stones and xanthine stones (1)
All 2,8-dihydroxyadenine and xanthine stone formers are considered to be at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones.

11.10.1 2,8-dihydroxyadenine stones
A genetically determined defect of adenine phosphoribosyl transferase causes high urinary excretion of poorly soluble 2,8-dihydroxyadenine. High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring.

11.10.2 Xanthine stones
Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

11.10.3 Fluid intake and diet
Recommendations for general preventive measures apply. Pharmacological intervention is difficult, therefore, high fluid intake ensures optimal specific weight levels of urine < 1.010. A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

11.11 Drug stones (2)
Drug stones are induced by pharmacological treatment (3,4) (Table 33). Two types exist:
• stones formed by crystallised compounds of the drug;
• stones formed due to unfavourable changes in urine composition under drug therapy.

Table 33: Compounds that cause drug stones

<table>
<thead>
<tr>
<th>Active compounds crystallising in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol/oxypurinol</td>
</tr>
<tr>
<td>Amoxicillin/ampicillin</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Quinolones</td>
</tr>
<tr>
<td>Ephedrine</td>
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<tr>
<td>Indinavir</td>
</tr>
<tr>
<td>Magnesium trisilicate</td>
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<tr>
<td>Sulphonamides</td>
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<tr>
<td>Triamterene</td>
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<tr>
<td>Zonisamide</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Substances impairing urine composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Allopurinol</td>
</tr>
<tr>
<td>Aluminium magnesium hydroxide</td>
</tr>
<tr>
<td>Ascorbic acid</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Furosemide</td>
</tr>
<tr>
<td>Laxatives</td>
</tr>
<tr>
<td>Methoxyflurane</td>
</tr>
<tr>
<td>Vitamin D</td>
</tr>
<tr>
<td>Topiramate</td>
</tr>
</tbody>
</table>

11.12 Unknown stone composition (5)
An accurate medical history is the first step towards identifying risk factors (Table 34).

Diagnostic imaging begins with ultrasound examination of both kidneys to establish whether the patient is stone free. Stone detection by ultrasound should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia is additionally screened.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are
signs of infection.

Constant urine pH < 5.8 in the daily profile indicates acidic arrest, which may promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded.

Microscopy of urinary sediment can help to discover rare stone types, because crystals of 2,8-dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease. In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine, with a sensitivity of 72% and specificity of 95%. False-positive results are possible in patients with Fanconi’s syndrome or homocystinuria, or in those taking various drugs, including ampicillin or sulfa-containing medication (6,7).

Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow. However, if any expelled stone material is available, it should be analysed by diagnostic confirmation or correction.

Table 34: Investigating patients with stones of unknown composition

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Rationale for investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>• Stone history (former stone events, family history)</td>
</tr>
<tr>
<td></td>
<td>• Dietary habits</td>
</tr>
<tr>
<td></td>
<td>• Medication chart</td>
</tr>
<tr>
<td>Diagnostic imaging</td>
<td>• Ultrasound in case of a suspected stone</td>
</tr>
<tr>
<td></td>
<td>• Unenhanced helical CT</td>
</tr>
<tr>
<td></td>
<td>(Determination of Hounsfield units provides information about the possible stone composition)</td>
</tr>
<tr>
<td>Blood analysis</td>
<td>• Creatinine</td>
</tr>
<tr>
<td></td>
<td>• Calcium (ionised calcium or total calcium + albumin)</td>
</tr>
<tr>
<td></td>
<td>• Uric acid</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>• Urine pH profile (measurement after each voiding, minimum 4 times daily)</td>
</tr>
<tr>
<td></td>
<td>• Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight</td>
</tr>
<tr>
<td></td>
<td>• Urine culture</td>
</tr>
<tr>
<td></td>
<td>• Microscopy of urinary sediment (morning urine)</td>
</tr>
<tr>
<td></td>
<td>• Cyanide nitroprusside test (cystine exclusion)</td>
</tr>
</tbody>
</table>

Further examinations depend on the results of the investigations listed above

11.13 References
12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

BFMZ  bendroflumethiazide
BMI  body mass index
CI  credible intervals
CT  computed tomography
DPTA  diethylene triamine pentaacetic acid (radiotracer)
EAU  European Association of Urology
GR  grade of recommendation
HCTZ  hydrochlorothiazide
HIRU  Health Information Research Unit
Ho:YAG  holmium:yttrium-aluminium-garnet [laser]
HPT  hyperparathyroidism
INR  international normalised ratio
IRS  infrared spectroscopy
IVU  intravenous urography
JESS  joint expert speciation system
KUB  Kidney ureter bladder
LE  level of evidence
MAG 3  mercapto acetyltriglycine (radiotracer)
MET  medical expulsive therapy
MMC  myelomeningocele
MRU  magnetic resonance urography
NC  nephrocalcinosis
NCCT  non-contrast enhanced computed tomography
NSAIDs  non-steroidal anti-inflammatory drugs
PCN  percutaneous nephrostomy
PH  primary Hyperoxaluria
PNL  percutaneous nephrolithotomy
PTH  parathyroid hormone
PTT  partial thrombolastin time
RCT  randomised controlled trial
RIRS  retrograde renal surgery
RTA  renal tubular acidoisis
SFR  stone free rate
SIGN  Scottish Intercollegiate Guidelines Network
SWL  (extracorporeal) shock wave lithotripsy
THAM  tris-hydroxymethyl-aminomethane
UPJ  ureteropelvic junction
URS  ureterorenoscopy
US  ultrasound
UTI  urinary tract infection
XRD  X-ray diffraction

Conflict of interest
All members of the Urolithiasis Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. METHODOLOGY

1.1 Introduction
A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) has prepared these guidelines to make a document available that may help to increase the quality of care for children with urological problems.

This compilation document addresses a number of common clinical pathologies in paediatric urological practice, but covering the entire field of paediatric urology in a single guideline document is unattainable, nor practical.

The majority of urological clinical problems in children are distinct and in many ways different to those in adults. This publication intends to outline a practical and preliminary approach to paediatric urological problems. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres where paediatric urology practice has been fully established and a multidisciplinary approach is available.

For quite some time, paediatric urology has informally developed, expanded, matured and established its diverse body of knowledge and expertise and may now be ready to distinguish itself from its parent specialties. Thus, paediatric urology has recently emerged in many European countries as a distinct subspecialty of both urology and paediatric surgery, and presents a unique challenge in the sense that it covers a large area with many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come. We now have new techniques for the treatment of reflux, our techniques for the treatment of complex congenital anomalies have substantially improved, and totally new technologies for bladder replacement and laparoscopic procedures have been developed.

1.2 Data identification and evidence sources
The guidelines were compiled based on current literature following a systematic review using MEDLINE. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies.

Due to the limited availability of large randomised controlled trials (RCTs) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems - this document will largely be a consensus document. Also, there is clearly a need for continuous re-evaluation of the information presented in the current document.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, also taking individual circumstances and patient and parent preferences into account.

1.3 Level of evidence and grade of recommendation
The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from Sackett, et al. (1).
It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as ‘upgraded based on panel consensus’. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.

### Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett, et al. (1).

### 1.4 Publication history


Standard procedure for EAU publications includes an annual scoping search to guide updates. An ultra-short reference document is being published alongside this publication. All documents are available, free access, through the EAU website Uroweb [http://www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/online-guidelines/).

#### 1.4.1 Summary of updated and new information

New literature has been included and a limited revision applied for chapters:
- Chapter 2: Phimosis
- Chapter 4: Hydrocele
- Chapter 5: Acute scrotum in children.
- Chapter 8: Varicocele in children and adolescents
- Chapter 10: Daytime lower urinary tract conditions
- Chapter 11: Monosymptomatic enuresis
- Chapter 12: Management of neurogenic bladder in children.
- Chapter 13: Dilatation of the upper urinary tract (ureteropelvic junction and ureterovesical junction obstruction)
- Chapter 14: Vesicoureteral reflux in children
- Chapter 15: Urinary stone disease
- Chapter 17: Disorders of sex development”. Former chapter 9 -“micropenis” has been incorporated.
- Chapter 20: Post-operative fluid management in children
- Chapter 21: Post-operative pain management in children

A complete update was achieved for chapters:
- Chapter 3: Cryptorchidism
- Chapter 6: Hypospadias; the management algorithm has been updated.

**New topic included in this 2012 print**
- Paediatric urological Trauma (Chapter 19)

### 1.5 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: [http://www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/online-guidelines/).
2. PHIMOSIS

2.1 Background
At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in only about 50% of boys; this rises to approximately 89% by the age of 3 years. The incidence of phimosis is 8% in 6 to 7-year-olds and just 1% in males aged 16-18 years (1). Phimosis is either primary (physiological) with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans. Phimosis has to be distinguished from normal agglutination of the foreskin to the glans, which is a physiological phenomenon (2).

The paraphimosis must be regarded as an emergency situation: retraction of a too narrow prepuce behind the glans penis into the glanular sulcus may constrict the shaft and lead to oedema. It interferes with perfusion distally from the constrictive ring and brings a risk of consecutive necrosis.

2.2 Diagnosis
The diagnosis of phimosis and paraphimosis is made by physical examination.

If the prepuce is not retractable or only partly retractable and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenulum breve. A fraenulum breve leads to a ventral deviation of the glans once the foreskin is retracted. If the tip remains narrow and glanular adhesions were separated, than the space is filled with urine during voiding causing the foreskin to balloon outward.

The paraphimosis is characterised by retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

2.3 Treatment
Treatment of phimosis in children is dependent on the parents' preferences and can be plastic or radical circumcision after completion of the second year of life. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision). However, this procedure carries the potential for recurrence of the phimosis (3). In the same session, adhesions are released and an associated fraenulum breve is corrected by fraenulotomy. Meatoplasty is added if necessary.

An absolute indication for circumcision is secondary phimosis. The indications in primary phimosis are recurrent balanoposthitis and recurrent urinary tract infections in patients with urinary tract abnormalities (4-7) (LE: 2; GR: B). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A recent metaanalysis could not find any risk in uncircumcised patient without a history of phimosis (8). Contraindications for circumcision are coagulopathy, an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, because the foreskin may be required for a reconstructive procedure (8,10).

Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason (11-14) (LE: 2; GR B). As a conservative treatment option of the primary phimosis, a corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 20-30 days with a success rate of more than 90 %. (15-18) (LE: 1; GR: A). A recurrence rate up to 17 % can be expected (19). This
treatment has no side effects and the mean bloodspot cortisol levels are not significantly different from an untreated group of patients (20) (LE: 1). The hypothalamic-pituitary-adrenal axis was not influenced by local corticoid treatment (21). Agglutination of the foreskin does not respond to steroid treatment (16) (LE: 2).

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band may be helpful to release it (22) (LE: 4; GR: C). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

2.4 Conclusions and recommendations on phimosis

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Treatment for phimosis usually starts after two years of age or according to parents’ preference.</td>
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<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>In primary phimosis, conservative treatment with a corticoid ointment or cream has a success rate more than 90%.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>In primary phimosis, recurrent balanoposthitis and recurrent UTI in patients with urinary tract abnormalities are indications for active intervention.</td>
<td>2</td>
<td>A</td>
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<tr>
<td>Secondary phimosis is an absolute indication for circumcision.</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>Paraphimosis is an emergency situation and treatment must not be delayed. If manual reposition fails, a dorsal incision of the constrictive ring is required.</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>Routine neonatal circumcision to prevent penile carcinoma is not indicated.</td>
<td>2</td>
<td>B</td>
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2.5 References


3. CRYPTORCHIDISM

3.1 Background
At 1 year of age, nearly 1% of all full-term male infants have cryptorchidism, which is the commonest congenital anomaly affecting the genitalia of newborn male infants (1). The most useful classification of cryptorchidism is into palpable and non-palpable testes, and clinical management is decided by the location and presence of the testes.
- Retractile testes require only observation because they may become ascendant. Although they have completed their descent, a strong cremasteric reflex may cause their retention in the groin (2).
- Bilateral, non-palpable testes and any suggestion of sexual differentiation problems (e.g. hypospadias) require urgent, mandatory endocrinological and genetic evaluation (3) (LE: 3; GR: B).

3.2 Diagnosis
Physical examination is the only way of differentiating between palpable or non-palpable testes. There is no benefit in performing ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) or angiography.

Clinical examination includes a visual description of the scrotum and assessment of the child in both the supine and crossed-leg positions. The examiner should inhibit the cremasteric reflex with his/her non-dominant hand, immediately above the symphysis in the groin region, before touching or reaching for the scrotum. The groin region may be “milked” towards the scrotum in an attempt to move the testis into the scrotum. This manoeuvre also allows an inguinal testis to be differentiated from enlarged lymph nodes that could give the impression of an undescended testis. A retractile testis can generally be brought into the scrotum, where it will remain until a cremasteric reflex (touching the inner thigh skin) retracts it into the groin (4).

A unilateral, non-palpable testis and an enlarged contralateral testis suggest testicular absence or
atrophy, but this is not a specific finding and does not preclude surgical exploration. An inguinal, non-palpable testis requires specific visual inspection of the femoral, penile and perineal regions to exclude an ectopic testis. Diagnostic laparoscopy is the only examination that can reliably confirm or exclude an intra-abdominal, inguinal and absent/vanishing testis (non-palpable testis) (5). Before carrying out laparoscopic assessment, examination under general anaesthesia is recommended because some, originally non-palpable, testes become palpable under anaesthetic conditions.

3.3 Treatment
Treatment should be done as early as possible around 1 year of age, starting after 6 months and finishing preferably at 12 months of age, or 18 months at the latest (6-9). This timing is driven by the final adult results on spermatogenesis and hormone production, as well as the risk for tumours.

3.3.1 Medical therapy
Medical therapy using human chorionic gonadotrophin (hCG) or gonadotrophin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, with maximum success rates of 20% (10,11). However, it must be taken into account that almost 20% of descended testes have the risk of reascending later.

Hormonal therapy for testicular descent has lower success rates, the higher the undescended testis is located. A total dose of 6000-9000 U hCG is given in four doses over a period of 2-3 weeks, depending on weight and age, along with GnRH, given for 4 weeks as a nasal spray at a dose of 1.2 mg/day, divided into three doses per day.

Medical treatment may be beneficial before surgical orchidofuniculolysis and orchidopexy (dosage as described earlier) or afterwards (low intermittent dosages), in terms of increasing the fertility index, which is a predictor for fertility in later life (12). Long-term follow-up data are still awaited. Nonetheless, it has been reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood. Therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend it on a routine basis because there is not sufficient evidence for a beneficial effect of hormonal treatment before or after surgery. However, this statement relied only on data from hormonal treatment using hCG (13).

3.3.2 Surgery
Palpable testis
Surgery for a palpable testis includes orchidofuniculolysis and orchidopexy, via an inguinal approach, with success rates of up to 92% (14). It is important to remove and dissect all cremasteric fibres to prevent secondary retraction. Associated problems, such as an open processus vaginalis, must be carefully dissected and closed. It is recommended that the testis is placed in a subdartos pouch. With regard to sutures, there should be no fixation sutures or they should be made between the tunica vaginalis and the dartos musculature. The lymph drainage of a testis that has undergone surgery for orchidopexy has been changed from iliac drainage to iliac and inguinal drainage (important in the event of later malignancy). Scrotal orchidopexy can also be an option in less-severe cases and when performed by surgeons with experience using that approach.

Non-palpable testis
Inguinal surgical exploration with possible laparoscopy should be attempted for non-palpable testes. There is a significant chance of finding the testis via an inguinal incision. In rare cases, it is necessary to search into the abdomen if there are no vessels or vas deferens in the groin. Laparoscopy is the best way of examining the abdomen for a testis. In addition, either removal or orchidofuniculolysis and orchidopexy can be performed via laparoscopic access (15).

For boys aged ≥ 10 years with an intra-abdominal testis, with a normal contralateral testis, removal is an option because of the theoretical risk of later malignancy. In bilateral intra-abdominal testes, or in boys younger than 10 years, a one-stage or two-stage Fowler-Stephens procedure can be performed. In the event of a two-stage procedure, the spermatic vessels are laparoscopically clipped or coagulated proximal to the testis to allow development of collateral vasculature (16). The second-stage procedure, in which the testis is brought directly over the symphysis and next to the bladder into the scrotum, can also be performed by laparoscopy 6 months later. The testicular survival rate in the one-stage procedure varies between 50 and 60%, with success rates increasing up to 90% for the two-stage procedure (17,18). Microvascular autotransplantation can also be performed with a 90% testicular survival rate. However, the procedure requires skilled and experienced surgeons (18).

3.4 Prognosis
Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as
those with bilateral descended testes. Boys with bilateral undescended testes have lower fertility and paternity rates.

Boys with an undescended testis have an increased risk of developing testicular malignancy. Screening both during and after puberty is therefore recommended for these boys. A Swedish study, with a cohort of almost 17,000 men who were treated surgically for undescended testis and followed for ~210,000 person-years, showed that treatment for undescended testis before puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchidopexy before 13 years of age was 2.23 when compared with the Swedish general population; this increased to 5.40 for those treated at ≥ 13 years (19). A systematic review and meta-analysis of the literature have also concluded that prepubertal orchidopexy may decrease the risk of testicular cancer and that early surgical intervention is indicated in children with cryptorchidism (20).

Boys with retractile testes do not need medical or surgical treatment, but require close follow-up until puberty.

3.5  Recommendations for cryptorchidism

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Boys with retractile testes do not need medical or surgical treatment, but require close follow-up until puberty.</td>
<td>2</td>
<td>A</td>
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<tr>
<td>Surgical orchidolysis and orchidopexy should be concluded at the age of 12 months, or 18 months the latest.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>In case of non-palpable testes and no evidence of disorders of sex development, laparoscopy still represents the gold standard because it has almost 100% sensitivity and specificity in identifying an intra-abdominal testis as well as the possibility for subsequent treatment in the same session.</td>
<td>1a</td>
<td>A</td>
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<tr>
<td>Hormonal therapy, either in an adjuvant or neo-adjuvant setting, is not standard treatment. Patients have to be evaluated on an individual basis.</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>For an intra-abdominal testis in a 10-year-old boy or older, with a normal contralateral testis, removal is an option because of the theoretical risk of a later malignancy.</td>
<td>3</td>
<td>B</td>
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</tbody>
</table>

3.6  References
4. HYDROCELE

4.1 Background
Hydrocele is defined as a collection of fluid between the parietal and visceral layer of tunica vaginalis (1).
Pathogenesis of hydrocele is based on an imbalance between the secretion and reabsorption of this fluid.
This is in contrast with inguinal hernia, which is defined as the protrusion of a portion of organs or tissues through the abdominal wall (2). Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele alone or connected with other intrascrotal pathology (hernia). The exact time of spontaneous closure of the processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults (3). If complete obliteration of the processus vaginalis occurs with patency of midportion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are encountered in newborns as well (4). Non-communicating hydroceles are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation or may appear as a recurrence after primary repair of a communicating hydrocele.
4.2 Diagnosis
The classic description of a communicating hydrocele is that of a hydrocele that vacillates in size, and is usually related to activity. It may be diagnosed by history and physical investigation. Transillumination of the scrotum makes the diagnosis in the majority of cases, keeping in mind that fluid-filled intestine and some prepubertal tumours such as teratomas may transilluminate as well (5,6). If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually non-tender. If there are any doubts about the character of an intrascrotal mass, scrotal ultrasound should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler ultrasound studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

4.3 Treatment
In the majority of infants, the surgical treatment of hydrocele is not indicated within the first 12-24 months because of the tendency for spontaneous resolution (LE: 2; GR: B) (7). Little risk is taken by initial observation because progression to hernia is rare and does not result in incarceration (7). Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology (LE: 2; GR: B) (8,9). Persistence of a simple scrotal hydrocele beyond 24 months of age may be an indication for surgical correction. However, there is no evidence that this type of hydrocele risks testicular damage. The question of contralateral disease should be addressed by both history and physical examination at the time of initial consultation (LE: 2) (10). In late-onset hydrocele, suggestive of a non-communicating hydrocele, there is a reasonable chance of spontaneous resolution (75%) and expectant management of 6-9 months is recommended (11).

In the paediatric age group, the operation consists of ligation of patent processus vaginalis via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed (1,6,8) (LE: 4; GR: C). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3; GR: B). Sclerosing agents should not be used because of the risk for chemical peritonitis in communicating processus vaginalis peritonei (6,8) (LE: 4; GR: C). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

4.4 Recommendations for the management of hydrocele

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
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<tbody>
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<td>In the majority of infants, surgical treatment of hydrocele is not indicated within the first 12-24 months due to the tendency for spontaneous resolution. Little risk is taken by initial observation because progression to hernia is rare.</td>
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</tr>
<tr>
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<td>4</td>
<td>C</td>
</tr>
<tr>
<td>In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision. Sclerosing agents should not be used because of the risk for chemical peritonitis.</td>
<td>4</td>
<td>C</td>
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</tbody>
</table>

4.5 References


5. ACUTE SCROTUM IN CHILDREN

5.1 Background
Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis (1-6). Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic disease (e.g. Henoch-Schönlein purpura) (7-19).

Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testes occurs over a wider age range. Acute epididymitis affects two age groups: < 1 year and 12-15 years (5,20,21). Acute epididymitis is found most often (37-64.6%) in boys with acute scrotum (1-4). One study predicted the annual incidence of epididymitis as about 1.2 per 1,000 children (22).

5.2 Diagnosis
Patients usually present with scrotal pain. The duration of symptoms is shorter in testicular torsion (69% present within 12 h) compared to torsion of the appendix testes (62%) and acute epididymitis (31%) (5,6,20).

In the early phase, location of the pain can lead to diagnosis. Patients with acute epididymitis experience a tender epididymis, whereas patients with testicular torsion are more likely to have a tender testicle, and patients with torsion of the appendix testis feel isolated tenderness of the superior pole of the testis (20).

An abnormal position of the testis is more frequent in testicular torsion than epididymitis (20). Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion (21,23) (LE:3; GR: C).

Fever occurs often in epididymitis (11-19%). The classical sign of a “blue dot” was found only in 10-23% of patients with torsion of the appendix testis (4,6,21,24).

In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone (1-6,21,24).

A positive urine culture is only found in a few patients with epididymitis (3,21,24,25). It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

Doppler ultrasound is useful to evaluate acute scrotum, with 63.6-100% sensitivity and 97-100% specificity, and a positive predictive value of 100% and negative predictive value 97.5% (26-31) (LE: 3).

The use of Doppler ultrasound may reduce the number of patients with acute scrotum undergoing scrotal exploration, but it is operator-dependent and can be difficult to perform in prepubertal patients (29,32). It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion: persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% had normal or increased testicular vascularity (29). Better results were reported using high-resolution ultrasonography (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% (29,33) (LE: 2; GR: C).
Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to ultrasound (34-37). These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergency intervention (24).

The diagnosis of acute epididymitis in boys is mainly based on clinical judgement and adjunctive investigation. However, it should be remembered that findings of secondary inflammatory changes in the absence of evidence of an extra-testicular nodule by Doppler ultrasound might suggest an erroneous diagnosis of epididymitis in children with torsion of appendix testes (38).

Prepubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable (3,21,22).

5.3  **Treatment**

5.3.1  **Epididymitis**

In prepubertal boys, the aetiology is usually unclear, with an underlying pathology of about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection (22,39). Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3; GR: C). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required (40).

Torsion of the appendix testis can be managed conservatively (LE: 4; GR: C). During the six-week-follow-up, clinically and with ultrasound, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain (27).

5.3.2  **Testicular torsion**

Manual detorsion of the testis is done without anaesthesia. It should initially be done by outwards rotation of the testis unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination (41) (LE: 3; GR: C). Doppler ultrasound may be used for guidance (42).

Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including 11 patients who had reported pain relief after manual detorsion (41,43).

5.3.3  **Surgical treatment**

Testicular torsion is an urgent condition, which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting (44). Severe testicular atrophy occurred after torsion for as little as 4 h when the turn was > 360°. In cases of incomplete torsion (180-360°), with symptom duration up to 12 h, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion > 360° and symptom duration > 24 h (45).

Early surgical intervention with detorsion (mean torsion time < 13 h) was found to preserve fertility (46). Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 h of symptom onset. In patients with testicular torsion > 24 h, semi-elective exploration is necessary (44,45) (LE: 3). There is still controversy on whether to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, in order to preserve contralateral function and fertility after testicular torsion of long duration (> 24 h).

A recent study in humans found that sperm quality was preserved after orchiectomy and orchidopexy in comparison to normal control men, although orchietomy resulted in better sperm morphology (47). During exploration, fixation of the contralateral testis is also performed. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no common recommendation about the preferred type of fixation and suture material; however, many urologists currently use a Dartos pouch orchidopexy (48).

External cooling before exploration and several medical treatments seem effective in reducing ischaemia-reperfusion injury and preserving the viability of the torsed and the contralateral testis (49-53).

5.4  **Prognosis**

5.4.1  **Fertility**

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20%.
5.4.2 Subfertility
Subfertility is found in 36-39% of the patients after torsion. Semen analysis may be normal in only 5-50% in long-term follow-up (44). Early surgical intervention (mean torsion time < 13 h) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 h) followed by orchiectomy jeopardised fertility (46).

One study identified sperm antibodies in the semen of patients with testicular torsion and correlated antibody levels with infertility, while others have failed to confirm these results (44,47). Anderson, et al. found pre-existing contralateral testis abnormalities in biopsies performed at the time of surgery and did not detect any case of sperm antibodies after testicular torsion (46).

5.4.3 Androgen levels
A study in rats showed a long-term reduction in testicular androgen production after testicular torsion. This effect was considered to be caused by reperfusion/oxidative stress in the testis (45). Even though the levels of FSH, LH and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion (47).

5.4.4 Testicular cancer
There may be a 3.2-fold increased risk of developing a testis tumour 6-13 years after torsion. However, two of nine reported cases had torsion of a tumour-bearing testis and four had a tumour in the contralateral testis (44).

5.4.5 Nitric oxide
A study in rats found that spermatic cord torsion did not lead to impairment in nitric oxide (NO)-mediated relaxant responses of the isolated penile bulb (54).

5.5 Perinatal torsion
Perinatal torsion of the testis most often occurs prenatally. After birth, perinatal torsion occurs in 25%. Bilateral torsion comprises 11-21% of all perinatal cases (55). Most cases are extravaginal in contrast to the usual intravaginal torsion, which occurs during puberty. Intrauterine torsion may present as:
• testicular nubbin;
• small and hard testis;
• normal-sized and hard testis;
• acute scrotum.

Torsion occurring in the first postnatal month presents with signs of acute scrotum. The clinical signs correlate well with surgical and histological findings and thus define the need and urgency to explore the history (56). Doppler ultrasound can be an additional diagnostic tool. The diagnostic sensitivity for testicular torsion is high, although the specificity is unknown for neonates. Doppler ultrasound may also be used to exclude congenital testicular neoplasm (57). Neonates with acute scrotal signs as well as bilateral cases should be treated as surgical emergencies (56,58).

In cases of postnatal torsion, one study reported 40% of testes were salvaged with emergency exploration (59). The contralateral scrotum should also be explored because of the risk of asynchronous contralateral testicular torsion in as many as 33% of cases (58).

5.6 Recommendations acute scrotum in children

<table>
<thead>
<tr>
<th>LE</th>
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<tbody>
<tr>
<td><strong>Acute scrotum</strong> is a paediatric urological emergency and intervention should not be delayed.</td>
<td>3  C</td>
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<tr>
<td>Neonates with acute scrotum, and bilateral cases, should be treated as surgical emergencies. In neonates, the contralateral scrotum should also be explored.</td>
<td>3  C</td>
</tr>
<tr>
<td>Doppler ultrasound is a highly effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.</td>
<td>3  C</td>
</tr>
<tr>
<td>High-resolution ultrasonography is better for direct visualisation of spermatic cord twisting.</td>
<td>3  C</td>
</tr>
<tr>
<td>Torsion of the appendix testis can be managed conservatively but in equivocal cases and in patients with persistent pain, surgical exploration is indicated.</td>
<td>3  C</td>
</tr>
<tr>
<td>Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 h of symptom onset.</td>
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</tr>
</tbody>
</table>
5.7 References


25. Murphy FL, Fletcher L, Pease P. Early scrotal exploration in all cases is the investigation and intervention of choice in the acute paediatric scrotum. Pediatr Surg Int 2006 May;22(5):413-6.


http://radiology.rsna.org/cgi/content/abstract/207/1/223


6. HYPOSPADIAS

6.1 Background
Hypospadias can be defined as hypoplasia of the tissues forming the ventral aspect of the penis beyond the division of the corpus spongiosum. Hypospadias is usually classified based on the anatomical location of the proximally displaced urethral orifice:
- Distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most common type of hypospadias)
- Intermediate-middle (penile).
- Proximal-posterior (penoscrotal, scrotal, perineal).

The pathology may be much more severe after skin release.

6.1.1 Risk factors
Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental (1) (LE: 2b):
- An additional member with hypospadias is found in 7% of families (2).
- Endocrine disorders can be detected in a very few cases.
- Babies of young or old mothers and babies with a low birth weight have a higher risk of hypospadias (2).
- A significant increase in the incidence of hypospadias over the last 20 years suggests a role for environmental factors (hormonal disruptors and pesticides) (3-6). This information has been questioned recently (7).
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in the offspring (8) (LE: 2a).

6.2 Diagnosis
Patients with hypospadias should be diagnosed at birth (except for the megameatus intact prepuce variant).

Diagnosis includes a description of the local findings:
- Position, shape and width of the orifice
- Presence of atretic urethra and division of corpus spongiosum
- Appearance of the preputial hood and scrotum
- Size of the penis
- Curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:
- Cryptorchidism (in up to 10% of cases of hypospadias)
- Open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, requires a complete genetic and endocrine work-up immediately after birth to exclude intersexuality, especially congenital adrenal hyperplasia.

Urine trickling and ballooning of the urethra require exclusion of meatal stenosis.

The incidence of anomalies of the upper urinary tract does not differ from the general population, except in very severe forms of hypospadias (3,4).

6.3 Treatment
Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision-making.
The functional indications for surgery are:
- Proximally located meatus
- Ventrally deflected urinary stream
- Meatal stenosis
- Curved penis.

The cosmetic indications, which are strongly linked to the psychology of the parent or the patient’s future psychology, are:
- Abnormally located meatus
- Cleft glans
- Rotated penis with abnormal cutaneous raphe
- Preputial hood
- Penoscrotal transposition
- Split scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the parents is crucial.

The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the neomeatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance of the boy’s genitalia (3,4) (LE: 4) (Figure 1).

The use of magnifying spectacles and special fine synthetic absorbable suture materials (6/0-7/0) are required. As in any penile surgery, an exceptional prudence should be adopted with the use of cautery. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome. Pre-operative hormonal treatment with local or parenteral application of testosterone, dihydrotestosterone or beta-chorionic gonadotropin can be helpful in patients with a small penis or for repeat surgery. In order to prevent healing complications, it is recommended to postpone the surgery for 3 months after completion of hormonal therapy (9) (LE: 2b).

6.3.1 **Age at surgery**
The age at surgery for primary hypospadias repair is usually 6-18 (24) months (3) (LE: 4). However, earlier repair between 4 and 6 months of age has been reported recently (LE: 3) (10).

6.3.2 **Penile curvature**
If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% of patients (11). The urethral plate has well vascularized connective tissue and does not cause curvature in most cases. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty or ventral corporotomies with or without grafting (12,13) (LE: 2b).

6.3.3 **Preservation of the well-vascularized urethral plate**
The mainstay of hypospadias repair is preservation of the well-vascularized urethral plate and its use for urethral reconstruction has become the mainstay of hypospadias repair (14). Mobilization of the corpus spongiosum /urethral plate and the bulbar urethra decreases the need for urethral plate transection (11,13,15) (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended that a midline-relaxing incision of the plate, followed by reconstruction according to the Snodgrass-Orkiszewski technique, is performed in distal hypospadias, as well as in proximal hypospadias (although the complication rate is higher) (16-21).

The onlay technique is preferred in proximal hypospadias and in cases with a plate that is unhealthy or too narrow (11). For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement, etc.) (22) (LE: 2b).

If the continuity of the urethral plate cannot be preserved, a modification of the tubularised flap, such as a tube-onlay or an inlay-onlay flap, is used to prevent urethral stricture (23,24) (LE: 3). In this situation, as well as in severe scrotal or penoscrotal hypospadias, the Koyanagi technique or two-stage procedure may be preferable (25-28).

If preputial or penile skin is not available, or has signs of balanitis xerotica obliterans, a buccal mucosa graft is used in an onlay or two-stage repair (29-31) (LE: 3). The use of inlay skin grafts may allow an increased number of single-stage repairs to be performed (32).
6.3.4 **Re-do hypospadias repairs**

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual needs of the patient.

**Figure 1: Algorithm for the management of hypospadias**

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**D.S.D. = disorders of sexual differentiation; GAP = glans approximation procedure; TIP = tubularized incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.**

6.3.5 **Urethral reconstruction**

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum may be used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. However, in the TIP repair, the parents should be advised that the use of a preputial dartos flap reduces the fistula rate (17,21) (LE: 2).

6.3.6 **Urine drainage and wound dressing**

Urine is drained with a transurethral dripping stent, or with a suprapubic tube. Some surgeons use no drainage after distal hypospadias repair. A circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures (33) (LE: 4). Postoperative prophylaxis is associated with a lower complication rate (34) (LE: 1b).

A large variation in the duration of stenting and dressing is described. No recommendation can be given due to the low level of evidence.

6.3.7 **Outcome**

A literature review on distal TIP urethroplasty found significant clinical heterogeneity with some limitations in the comparability of the data; one should expect a predictable outcome with complication rates below 10% (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) (35). A systematic review of the Mathieu and TIP repairs of distal hypospadias found a similar incidence of fistula (3.4-3.6%), and a higher incidence of meatal stenosis in TIP (30% versus 0.6% in Mathieu) after 6-12 months follow-up (36).

The complication rate of TIP and onlay repairs of primary severe hypospadias is similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty (11). A staged buccal mucosa graft requires redo grafting in 13% of patients, after the second stage more than one third of patients have
complications, most of these with some degree of graft fibrosis (37).
Ventral corporeal grafting for severe penile curvature gives good long-term results and safety for erectile
function is reported (LE 2) (38,39).

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions
and recurrent penile curvature.

Overall, between 7% and 67% of patients operated on for hypospadias end up with an obstructive
flow (24.6% in TIP). These children should be followed until adulthood to clarify the clinical significance of this
obstructive flow. Spontaneous improvement has been described (40,41) (LE: 2a).

Adolescents and adults, who have undergone hypospadias repair in childhood, have a slightly higher rate of
dissatisfaction with penile size, especially proximal hypospadias patients, but their sexual behaviour is not
different from that in control subjects (42,43) (LE: 2a/2b). The later corrective surgery is completed, the more
likely the patients may become insecure with regard to gender-role behaviour (44,45) (LE: 2b).

6.4 Conclusions and recommendations

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The age at surgery for primary hypospadias repair is usually 6-18 (24) months.</td>
<td>4</td>
</tr>
</tbody>
</table>
| The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate
size, to bring the neomeatus to the tip of the glans, if possible, and to achieve an overall acceptable
cosmetic appearance. | 4 |
| After hypospadias repair, sexual functions are usually well preserved. | 2 |

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
</table>
| At birth, isolated hypospadias has to be differentiated from disorders of sex development which are
mostly associated with cryptorchidism or micropenis. | A |
| Differentiation between functionally necessary (functional indications) and aesthetically feasible
operative procedures (psychological, cosmetic indications) is important for therapeutic decision-
making. As all surgical procedures carry the risk of complications and thorough pre-operative
counselling of the parents is crucial. | B |
| Original and modified tubularised incised plate urethroplasty has become the most popular type of
surgery for distal hypospadias; the onlay urethroplasty or two-stage procedures are used in more
severe hypospadias. For the algorithm see Fig. 1. | B |
| After hypospadias repairs, long-term follow-up is necessary, up to adolescence, to detect urethral
stricture, voiding dysfunction and recurrent penile curvature. | A |

6.5 References


7. CONGENITAL PENILE CURVATURE

7.1 Background
Penile curvature may be ventral, dorsal or lateral. Most of ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies (1). Similarly, the dorsal curvature is mostly associated with epispadias (2). Isolated penile curvature is not frequent with an incidence of 0.6% (3) (LE: 2). The curvature is caused by asymmetry of the cavernous bodies (1,4).

Curvature over 30 degrees is considered clinically significant; curvature over 60 degrees may interfere with satisfactory sexual intercourse in adulthood (5) (LE: 4).

7.2 Diagnosis
Diagnosis is made during hypospadias or epispadias repair using an artificial erection (6). The isolated anomaly is usually not recognised until later in childhood because the appearance of the penis is normal. The curvature is only observed during erections.

7.3 Treatment
The treatment is surgical. An artificial erection is used to determine the degree of curvature and to check the symmetry after the repair (6).

In hypospadias, chordee related to the tethering of the ventral skin and to the spongiosal pillars is first released. Only in a few cases the penile curvature is caused by a short urethral plate, which should be cut.

To repair the corporeal angulation in the isolated curvature or curvature associated with hypospadias, different techniques of plication of corpora cavernosa (orthoplasty) are used (5).

In epispadias, a combination of complete release of the urethral body from the corpora and a different kind of corporoplasty with or without corporotomy is usually necessary to achieve a straight penis (7,8).

7.4 References

8. VARICOCELE IN CHILDREN AND ADOLESCENTS

8.1 Background
Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under 10 years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are least common; they are usually noted only when
bilateral varicoceles are present and seldom occur as an isolated finding (1-3).

Varicocele develops during accelerated body growth by a mechanism that is not clearly understood. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found. However, studies correlating a hypoplastic testicle with poor sperm quality reported controversial results (4,5). A recent study has shown that in late adolescence the contralateral right testis is smaller in boys with varicocele than in boys that are not affected, and comparison of testicle sizes may not reflect long-term testicular well-being (6) (LE: 2).

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents (7,8) (LE: 2). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels (9) (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise (10). The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy (4,5,11) (LE: 1).

8.2 Diagnosis

Varicocele is mostly asymptomatic, rarely causing pain at this age. It may be noticed by the patient or parents, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre.

Varicocele is classified into 3 grades:
- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance) (12).

The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler colour flow mapping in the supine and upright position (13). Venous reflux detected on ultrasound only is classified as subclinical varicocele. The ultrasound examination includes assessment of the testicular volume to discriminate testicular hypoplasia. In adolescents, a testis that is smaller by more than 2 mL or 20% compared to the other testis is considered to be hypoplastic (14) (LE: 2).

In order to assess testicular injury in adolescents with varicocele, supranormal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) responses to the luteinizing hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients (11,15).

8.3 Therapy

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:
- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques (16-19).

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic artery at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic magnification) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring (16-18,20). The recurrence rate is usually less than 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test (9,16,17,20) (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs (16,18,21,22). Angiographic occlusion of the internal spermatic veins also meets these requirements. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins (23-25). However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique. Available data on failure rates combine anatomical inaccessibility and recurrence (1,24-25) (LE: 2).

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. The recommended indication criteria for varicocelectomy in children and adolescents are (1):
- varicocele associated with a small testis;
• additional testicular condition affecting fertility;
• bilateral palpable varicocele;
• pathological sperm quality (in older adolescents);
• symptomatic varicocele.

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available (6).

Repair of a large varicocele, physically or psychologically causing discomfort, may be also considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4).

8.4 Conclusions and recommendations
Varicocele becomes more frequent at the beginning of puberty and is found in 14-20% of adolescents. Fertility problems are expected in 20% of them.

Varicocele is examined in the standing position and classified into 3 grades. Venous reflux is diagnosed using Doppler colour flow mapping in the supine and upright position. In up to 70% of patients with grade II and III varicocele, left testicular volume loss was found; in late adolescence the contralateral right testis may become smaller as well.

8.5 References
   http://www.ncbi.nlm.nih.gov/pubmed/11275726

9. URINARY TRACT INFECTIONS IN CHILDREN

9.1 Introduction
Urinary tract infection (UTI) represents the most common bacterial infection in children < 2 years of age. In neonates, the symptoms differ in many aspects from those in UTIs in infants and children. The prevalence is higher; there is a male predominance; infections not caused by Escherichia coli are more frequent; and there is a higher risk of urosepsis (1-4).

The incidence of UTIs varies depending on age and sex. One meta-analysis showed that, in the first
3 months of life, UTIs were present in 7.5% of girls, 2.4% (CI: 1.4-3.5) of circumcised boys, and 20.1% (CI: 16.8-23.4) of uncircumcised boys, who presented with fever (2). In the first year of life, UTIs are more common in boys (3.7%) than in girls (2%). Later, the incidence changes and ~3% of pre-pubertal girls and 1% of pre-pubertal boys are diagnosed with UTIs (2-7).

*E. coli* is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial. In the latter, *Klebsiella pneumoniae*, *Enterobacter* spp., *Enterococcus* spp., *Pseudomonas* spp. and *Candida* spp. are more frequent than in community-acquired UTIs. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia in around 12% (8), however, it is less frequent in community-acquired than in nosocomial UTI (8,9).

9.2 **Classification**

There are five widely used classification systems according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

9.2.1 **Classification according to site**

**Lower urinary tract (cystitis)** is an inflammatory condition of the urinary bladder with general signs and symptoms including dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

**Upper urinary tract (pyelonephritis)** is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (> 38 °C), chills, costovertebral angle or flank pain, and tenderness. Older children may report cystitis symptoms along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

9.2.2 **Classification according to episode** (10)

First infection: the first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage (11). Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection.

In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract [inadequate therapy, inadequate antimicrobial urinary concentration (poor renal concentration/gastrointestinal malabsorption), and infection involving multiple organisms with differing antimicrobial susceptibilities].

Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae in papillary necrosis, urachal cyst, urethral diverticulum, periurethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

Reinfection: each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is *E. coli*, which occurs in many different serotypes. Therefore, recurrent *E. coli* UTI does not equate to infection with the same organism.

9.2.3 **Classification according to severity**

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI.

In severe UTI, infection is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

9.2.4 **Classification according to symptoms**

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response.

In symptomatic bacteriuria, symptoms associated with UTI include irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.
9.2.5 **Classification according to complicating factors** (12)

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal urinary tract. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of their bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract.

In complicated UTI, all neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent from their location. Functional obstruction often results from lower urinary tract dysfunction of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux. Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities (13). If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

9.3 **Diagnosis**

9.3.1 **Medical history**

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or postnatal ultrasound screening); family history; and whether there is constipation or presence of lower urinary tract symptoms.

9.3.2 **Clinical signs and symptoms**

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice, hyperecstibility and without any fever). UTI is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic (14,15). Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are > 2 years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

9.3.3 **Physical examination**

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

9.4 **Urine sampling, analysis and culture**

Urine sampling should be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis as well as culture affects the rate of contamination, which influences interpretation of the results. Especially in early infancy it can be challenging and depends on the mode of urine sampling (16,17).

9.4.1 **Urine sampling**

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever.

In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine in this age group:

1. **Plastic bag attached to the cleaned genitalia.**
   This technique is most often used in daily practice. It is helpful when the culture result is negative. Also, if the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria, UTI can be excluded without the need for confirmatory culture (18). However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found (19,20).

2. **Clean-catch urine collection.**
   The infant is placed in the lap of a parent or member of the nursing staff, who holds a sterile foil bowl underneath the infant’s genitalia. The infant is offered oral fluids and urine collection is awaited (21). This is time consuming and requires proper instruction of the parents. However, there seems to be a good correlation between the results of urine culture obtained by this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% (21,22).
(3) Bladder catheterisation.
Especially in boys, transurethral catheterisation is traumatic and bears the risk of nosocomial infection, but in experienced hands, this technique may be an alternative to SPA (23). In a prospective study using bladder catheterisation in febrile children aged ≥ 36 months, contamination was defined by multiple pathogens, non-pathogens, or colony counts < 10,000 cfu/mL. Ten percent of the children had true UTI and 14% of the cultures were contaminated. Univariate analysis of potential predictors identified age < 6 months, difficult catheterisation, and uncircumcised boys (24).

(4) Suprapubic bladder aspiration.
This is the most sensitive method to obtain an uncontaminated urine sample in this age group (24-26). Using ultrasound to assess bladder filling simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to ~97% (25,26). Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation (27). However, bladder puncture causes more pain than catheterisation in infants < 2 months old (28).

In older, toilet-trained children, who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the periurethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trail (29).

If the clinical situation necessitates, and for differential diagnosis of sepsis, it is most appropriate to obtain an adequate urine sample by catheterisation or SPA (22). In infants, a bag can only be used if the dipstick is negative, otherwise the urine should be obtained through catheterisation or SPA. This is also recommended in children, who are severely ill and a UTI needs to be excluded or confirmed. Blood sampling is dependent on the clinical situation.

9.4.2 Urinalysis
There are three methods that are commonly used for urinalysis:

(1) Dipsticks.
These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria requires approximately 4 h in the bladder (22,30). However, nitrite is not a very sensitive marker for infants, who empty their bladder frequently, and not all urinary pathogens reduce nitrate to nitrite. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results) (1,22).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (Range), %</th>
<th>Specificity (Range), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte esterase test</td>
<td>83 (67-94)</td>
<td>78 (64-92)</td>
</tr>
<tr>
<td>Nitrite test</td>
<td>53 (15-82)</td>
<td>98 (90-100)</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite test positive</td>
<td>93 (90-100)</td>
<td>72 (58-91)</td>
</tr>
<tr>
<td>Microscopy, WBCs</td>
<td>73 (32-100)</td>
<td>81 (45-98)</td>
</tr>
<tr>
<td>Microscopy, bacteria</td>
<td>81 (16-99)</td>
<td>83 (11-100)</td>
</tr>
<tr>
<td>Leucocyte esterase test, nitrite test or microscopy positive</td>
<td>99.8 (99-100)</td>
<td>70 (60-92)</td>
</tr>
</tbody>
</table>

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(2) Microscopy.
This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of 5 white blood cells (WBCs) per high-power field (25 WBC/μL) (27). In uncentrifuged urine, ≥ 10 WBC/μL has been demonstrated to be sensitive for UTI (31) and this could perform well in clinical situations (32). However, this is rarely done in an outpatient setting.
Flow imaging analysis technology. This is being used increasingly to classify particles in uncentrifuged urine specimens (33). The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods (22).

9.4.3 Urine culture
After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is recommended.

It is unclear what represents a significant UTI. In severe UTI, > 10^5 cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs (34). The classical definition of > 10^3 cfu/mL of voided urine is still used to define a significant UTI (35,36). The recent American Academy of Pediatric Guidelines on Urinary tract infection suggest that the diagnosis should be on the basis of the presence of both pyuria and at least 50,000 cfu. However, some studies have shown that, in voided specimens, < 10^4 organisms may indicate a significant UTI (37,38). If urine is obtained by catheterisation, 1,000-50,000 cfu/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

Table 4: Criteria for UTI in children (adapted from the EAU Guideline on Urological Infections [39])

<table>
<thead>
<tr>
<th>Urine specimen from suprapubic bladder puncture</th>
<th>Urine specimen from bladder catheterisation</th>
<th>Urine specimen from midstream void</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any number of cfu/mL (at least 10 identical colonies)</td>
<td>≥ 1,000-50,000 cfu/mL</td>
<td>≥ 10^4 cfu/mL with symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 10^5 cfu/mL without symptoms</td>
</tr>
</tbody>
</table>

Pyuria without bacteriuria (sterile pyuria) may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by Mycobacterium tuberculosis or Chlamydia trachomatis.

9.5 Therapy

9.5.1 Administration route
The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged < 2 months, parenteral antibiotic therapy is recommended. Electrolyte disorders with hyponatremia and hyperkalaemia can occur in these cases (13). Combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or respectively a third-generation cephalosporin achieves excellent therapeutic results (high efficacy of aminoglycosides, respectively cephalosporines against common uropathogens; enterococcus gap is closed with Ampillicin). Compared to the division in two doses, a daily single dose of aminoglycosides is safe and effective (13,40,41).

The choice of agent is also based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity testing of the isolated uropathogen (22). Especially in infancy, not all available antibiotics are approved by the national health authorities. In uncomplicated nephritis, both oral and parenteral treatment can be considered, because both are equally effective in children without urinary tract abnormalities.

Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI (41-43).

9.5.2 Duration of therapy
Adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (1-3 days) are inferior to those of 7-4-day courses (22). In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture (8,13). In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA (dimercaptosuccinic acid) scan (44). Some recent studies using exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) have demonstrated that this is equivalent to the usual 2-4 days intravenous therapy followed by oral treatment (40,45-47). Similar data have been shown for amoxicillin-clavulanate (48), however, these antibiotics are associated with increasing rates of resistance. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised (49).

In complicated UTI, uropathogens other than E. coli, such as Proteus mirabilis, Klebsiella spp., Pseudomonas aeruginosa, enterococci and staphylococci, are more often to be anticipated (13). Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubic cystostomy or percutaneous nephrostomy) might be required in case of failure of conservative treatment in obstructive uropathy.
Acute focal bacterial nephritis (lobar nephronia) is a localised bacterial infection of the kidney that presents as an inflammatory mass without abscess formation. This may represent a relatively early stage of renal abscess. For the majority of children, the pathogenesis is related to ascending infection due to pre-existing uropathy, especially vesicorenal reflux or urinary obstruction (megaureter). Prolonged intravenous antibiotic treatment is sufficient in most cases (50), and intravenous and oral therapy tailored to the pathogen identified in culture is recommended (51).

9.5.3 **Antimicrobial agents**

**Table 5: Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children***

<table>
<thead>
<tr>
<th>Chemotherapeutics</th>
<th>Daily dosage</th>
<th>Application</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3a, e.g. cefotaxime</td>
<td>100-200 mg/kg</td>
<td>i.v. in 2-3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 3-6 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3b, e.g. ceftazidime</td>
<td>100-150 mg/kg</td>
<td>i.v. in 2-3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 2-6 g)</td>
<td>75 mg/kg</td>
<td>i.v. in 1 D</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3a, e.g. cefotaxime</td>
<td>100-200 mg/kg</td>
<td>i.v. in 2-3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 3-6 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3b, e.g. ceftazidime</td>
<td>100-150 mg/kg</td>
<td>i.v. in 2-3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 2-6 g)</td>
<td>75 mg/kg</td>
<td>i.v. in 1 D</td>
<td></td>
</tr>
<tr>
<td><strong>Oral cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3, e.g. cefitobuten</td>
<td>9 mg/kg</td>
<td>p.o. in 1-2 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 0,4 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3, e.g. cefixime</td>
<td>8-12 mg/kg</td>
<td>p.o. in 1-2 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 0,4 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2, e.g. cepodoxime proxetil</td>
<td>8-10 mg/kg</td>
<td>p.o. in 2 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 0,4 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2, e.g. cefuroximexetil</td>
<td>20-30 mg/kg</td>
<td>p.o. in 3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 0,5-1 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1, e.g. cefadroxil</td>
<td>50-100 mg/kg</td>
<td>p.o. in 2-3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 1,5-4 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trimethoprim or</strong></td>
<td>5-6 mg/kg</td>
<td>p.o. in 2 D</td>
<td></td>
</tr>
<tr>
<td><strong>Trimethoprim/sulfamethoxazole</strong></td>
<td>5-6 mg/kg</td>
<td>p.o. in 2 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 320 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>100-200 mg/kg</td>
<td>i.v. in 3 D</td>
<td>Ampicillin and Amoxicillin are not eligible for calculated therapy</td>
</tr>
<tr>
<td>(Adolesc.: 3-6 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>50-100 mg/kg</td>
<td>i.v. in 3-4 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 1,5-6 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin/clavulanic acid (parenteral)</strong></td>
<td>60-100 mg/kg</td>
<td>i.v. in 3 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 3,6-6,6 g)</td>
<td>45-60 mg/kg</td>
<td>i.v. in 3 D</td>
<td></td>
</tr>
<tr>
<td>(Amoxicillin-fraction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 1500 + 375 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Piperacillin</strong></td>
<td>300 mg/kg</td>
<td>i.v. in 3-4 D</td>
<td></td>
</tr>
<tr>
<td><strong>Tobramycin</strong></td>
<td>5 mg/kg</td>
<td>i.v. in 1 D</td>
<td>Drug monitoring</td>
</tr>
<tr>
<td>(Adolesc.: 3-5 mg/kg, max. 0,4 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>5 mg/kg</td>
<td>i.v. in 1 D</td>
<td></td>
</tr>
<tr>
<td>(Adolesc.: 3-5 mg/kg, max. 0,4g)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ciprofloxacin | Children and adolesc. (1-17 years of age): 20-30 mg/kg (max. D: 400 mg) (parenterally) | i.v. in 3 D | Approved in most European countries as second- or third line medication for complicated UTIs, „reserve-antibiotic“!
| | Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally) | p.o. in 2 D | |

Nitrofurantoin | 3-5 mg | p.o. in 2 D | Contraindicated in the case of renal insufficiency

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Dosage for adolescents in paracentesis, if differing.

1 Infants 2 D, children 1-12 ys. 3 D.

Table 6: Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Proposal</th>
<th>Application</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis during the first 0-6 months of life</td>
<td>Ceftazidime + Ampicillin(^1) or Aminoglycoside + Ampicillin(^1)</td>
<td>3-7 days parenterally, for at least 2 days after defervescence, then oral therapy(^2)</td>
<td>10 (-14) days Newborns 14-21 days</td>
</tr>
<tr>
<td>Uncomplicated pyelonephritis after 6 months of age</td>
<td>Cephalosporin group 3(^2)</td>
<td>Orally (initially parenterally, if necessary)</td>
<td>(7-)10 days</td>
</tr>
<tr>
<td>Complicated pyelonephritis/ urosepsis (all ages)</td>
<td>Ceftazidime + Ampicillin(^1) or Aminoglycoside + Ampicillin(^1)</td>
<td>7 days parenterally, then oral therapy(^2)</td>
<td>10-14 days</td>
</tr>
</tbody>
</table>

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\(^1\) after receipt of microbiological findings (pathogen, resistance) adaptation of therapy.

\(^2\) i.v.: e.g. cefotaxime; orally: e.g. cefpodoxime proxetil, ceftibuten, cefixime.

Table 7: Recommendations for antibacterial treatment in cystitis und cystourethritis (Dosages for children up to 12 years of age)*

<table>
<thead>
<tr>
<th>Chemotherapeutics</th>
<th>Daily dosage</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cephalosporins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1, e.g. cefaclor</td>
<td>50 (-100) mg/kgbw</td>
<td>p.o. in 2-3 D</td>
</tr>
<tr>
<td>Group 1, e.g. cefalexin</td>
<td>50 mg/kgbw</td>
<td>p.o. in 3-4 D</td>
</tr>
<tr>
<td>Group 2, e.g. cefuroximaxetil</td>
<td>20-30 mg/kgbw</td>
<td>p.o. in 2 D</td>
</tr>
<tr>
<td>Group 2, e.g. cefpodoxime proxetil</td>
<td>8-10 mg/kgbw</td>
<td>p.o. in 2 D</td>
</tr>
<tr>
<td>Group 3, e.g. ceftibuten</td>
<td>9 mg/kgbw</td>
<td>p.o. in 1 D</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>5-6 mg/kgbw</td>
<td>p.o. in 2 D</td>
</tr>
</tbody>
</table>
Trimethoprim/sulfamethoxazole 5-6 mg/kgbw /TMP-fraction) p.p. in 3 D

Amoxicillin/clavulanic acid 37.5-75 mg/kgbw (Amoxicillin-fraction) p.o. in 3 D

Nitrofurantoin 3-5 mg/kgbw p.o. in 2 D

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9.5.4 Chemoprophylaxis
Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage. Some recently published prospective, randomised studies do not support the efficacy of antibacterial prophylaxis (53-56). The Australian PRIVENT study demonstrated risk reduction using trimethoprim-sulfamethoxazole in children from birth to 18 years of age who had at least one symptomatic UTI (19% of the placebo group and 13% of the antibiotic group) (46) (see also Chapter 15).

Table 8: Drugs for antibacterial prophylaxis*

<table>
<thead>
<tr>
<th>Substance**</th>
<th>Prophylactic dosage (mg/kgbw/d)</th>
<th>Limitations in young infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim</td>
<td>1</td>
<td>until 6 weeks of age</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1</td>
<td>Until 3 months of age</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>10</td>
<td>No age limitations</td>
</tr>
<tr>
<td>Cefixim</td>
<td>2</td>
<td>Preterms and newborns</td>
</tr>
<tr>
<td>Ceftibuten</td>
<td>2</td>
<td>***</td>
</tr>
<tr>
<td>Cefuroximacetil</td>
<td>5</td>
<td>***</td>
</tr>
</tbody>
</table>

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** Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.

*** In Germany, ceftibuten is not approved for infants < 3 months old.

9.6 Monitoring of UTI
With successful treatment, urine usually becomes sterile after 24 h, and leukocyturia normally disappears within 3-4 days. Normalisation of body temperature can be expected within 24-48 h after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate ultrasound examination is recommended in these cases.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as reliable serum marker for early prediction of renal parenchymal inflammation with first febrile UTI (57). In patients with febrile UTI, serum electrolytes and blood cell counts should be obtained.

9.7 Imaging
9.7.1 Ultrasound
Renal and bladder ultrasonography is strongly recommended in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in ~15% of cases, and 1-2% have abnormalities that require prompt action (e.g., additional evaluation, referral, or surgery) (22). In other studies, renal ultrasound revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed vesicoureteral reflux (VUR) in 27% of cases (9). Dilating VUR is missed by ultrasound in around one third of cases (58). Post-void residual urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI.

9.7.2 Radionuclide scanning
Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated well with the presence of dilating reflux and the risk of further pyelonephritis episodes, break-through-infections
(59) and future renal scarring. DMSA scanning may be used as a first-line diagnostic procedure based on observations that dilating VUR occurs in almost all children with abnormal DMSA scan (58,60). These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning (61).

9.7.3 Voiding cystourethrography
Voiding cystourethrography is still the gold standard to exclude or confirm VUR. Due to the risk of renal scarring, VCUG is recommended after the first episode of febrile UTI in boys and girls. The timing of VCUG does not influence the presence or severity of VUR (62,63). Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity (64). Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after urinary tract infection (see Chapter 15).

9.8 Bladder and bowel dysfunction
Bladder and bowel dysfunction are risk factors for which each child with UTI should be screened upon presentation. Normalisation of micturition disorders or bladder overactivity is important to lower the rate of UTI recurrence. If there are signs of bladder and/or bowel dysfunction at infection-free intervals, further diagnosis and effective treatment are strongly recommended (65-68). Treatment of constipation leads to a decrease in UTI recurrence (69-71). Therefore, exclusion of bladder and bowel dysfunction is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of a dysfunctional elimination syndrome.

9.9 Conclusions and recommendations for UTI in children

**Conclusions**

Urinary tract infection represents the most common bacterial infection in children < 2 years of age. The incidence varies depending on age and sex.

Classifications can be made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

The number of colony forming units (cfu) in the urine culture can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs. The classical definition of > 105 cfu/mL of voided urine is still used to define a significant UTI.

**Recommendations**

<table>
<thead>
<tr>
<th>Diagnosis includes medical history, clinical signs and symptoms (signs of a UTI may be vague and unspecific in small children) as well as a physical examination (including a general examination as well as the genitalia).</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion of bladder and bowel dysfunction is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of a dysfunctional elimination syndrome.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urine sampling</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine sampling with plastic bags are commonly used in daily practice. They are helpful only when the dipstick and / or the culture result are negative. There is high risk of false positive results.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Clean-catch of urine could be an acceptable technique for obtaining urine only in toilet-trained children.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Bladder catheterisation is traumatic especially in boys. It may be an alternative to suprapubic bladder aspiration.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Suprapubic bladder aspiration is the most sensitive method to obtain an uncontaminated urine sample in an infant.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipsticks yield rapid results, but should be used with caution in infants who empty their bladder frequently as conversion of nitrates to nitrites by bacteria requires approximately 4 h.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Microscopic investigation is the standard method of assessing pyuria after centrifugation, but it is rarely done in an outpatient setting.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Flow imaging analysis is increasingly used to classify particles in uncentrifuged urine, The numbers of WBCs, squamous epithelial cells and red cells correlate well with manual methods.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g., urinary obstruction).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral therapy is advised when there is clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated UTI.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged &lt; 2 months, parenteral antibiotic therapy is recommended. In an emergency setting, i.v. fluid replacement is necessary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes of short courses (1-3 days) are inferior to those of 7-4-day courses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral therapy with a third-generation cephalosporin (e.g., cefixime or cefitiben) may be equivalent to the usual 2-4 days intravenous therapy followed by oral treatment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In complicated UTI, parenteral treatment with broad-spectrum antibiotics is indicated.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Imaging |
| Renal and bladder ultrasonography is strongly recommended in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. |
| Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage. If it is positive, reflux may be present. |
| VCUG is the gold standard to exclude or confirm VUR. Due to the risk of renal scarring, it is recommended after the first episode of febrile UTI in boys and girls. The timing of VCUG does not influence the presence or severity of VUR. |

9.10 References


http://www.ncbi.nlm.nih.gov/pubmed/18623125


10. DAYTIME LOWER URINARY TRACT CONDITIONS

10.1 Background
Following the new terminology document by the International Children's Continence Society (ICCS), ‘daytime lower urinary tract (LUT) conditions’ is the new term used to group together functional incontinence problems in children (1). After any possible underlying uropathy or neuropathy has been excluded, a problem of incontinence in children is grouped into the category of ‘daytime LUT conditions’. Night-time wetting is known as ‘enuresis’.

Although exact data are unavailable, it is clear that the incidence of daytime LUT conditions is increasing. The changes in toilet training and toilet habits associated with a modern lifestyle have been blamed for the increase in incidence, but with little evidence. Rather, it is that modern life and higher hygiene standards have probably resulted in incontinence problems receiving more attention, so that an increase in prevalence could probably be attributed to an increased awareness. There exists a wide variation in reported prevalence ranging from 2% to 20% (2-6). This wide variation might reflect the variation in definitions used.

10.2 Definition
Daytime LUT conditions are conditions that present with lower urinary tract symptoms (LUTS), including urge, incontinence, weak stream, hesitancy, frequency and urinary tract infections, but without overt uropathy or neuropathy.

Normal bladder storage and voiding involves low pressure and adequate bladder volume filling. This is followed by a continuous detrusor contraction, which results in complete bladder emptying, associated with an adequate relaxation of the sphincter complex. Normal urine storage by the bladder and evacuation are controlled by a complex interaction between the spinal cord, brain stem, midbrain and higher cortical structures, associated with a complex integration of sympathetic, parasympathetic and somatic innervations (7).

It is understandable that this complex control mechanism is likely to be susceptible to developing different types of dysfunction. Various functional disorders of the detrusor-sphincter complex may occur during the sophisticated early development of normal mechanisms of micturition control. Voiding dysfunction is therefore thought to be the expression of incomplete or delayed maturation of the bladder sphincter complex.

Normal daytime control of bladder function matures between 2 and 3 years of age, while nighttime control is normally achieved between 3 and 7 years of age (8). There are two main groups of voiding
dysfunction, namely, filling-phase dysfunctions and voiding-phase dysfunctions.

10.2.1 **Filling-phase dysfunctions**
In filling-phase dysfunctions, the detrusor can be overactive, as in *overactive bladder (OAB)* and *urge syndrome*, or underactive, as in *underactive or highly compliant bladder (UAB)*. Some children habitually postpone micturition leading to *voiding postponement*.

10.2.2 **Voiding-phase (emptying) dysfunctions**
In voiding-phase (emptying) dysfunctions, interference with the sphincter and pelvic floor during detrusor contraction is the main dysfunction. The general term for this condition is dysfunctional voiding. Different degrees of dysfunction are described, depending on the strength of interference with the sphincter and pelvic floor. Weak interference results in staccato voiding, while stronger interference results in interrupted voiding and straining, due to an inability to relax during voiding.

Bladder sphincter dysfunction is often associated with bowel dysfunction such as obstipation and soiling. Sometimes, secondary anatomical changes are observed, such as trabeculation, diverticulae and vesicoureteral reflux.

10.3 **Diagnosis**
A non-invasive screening, consisting of history-taking, clinical examination, uroflow, ultrasound and voiding diary, is essential to reach a diagnosis. The ICCS published a standardisation document for the diagnosis of LUTS (9).

In the paediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. A voiding diary is mandatory to determine the child’s voiding frequency and voided volumes as well as the child’s drinking habits. History-taking should also include assessment of bowel function. Some dysfunctional voiding scores have recently been developed and validated (10,11). For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool (12).

Upon clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities is necessary to exclude obvious uropathy and neuropathy. Uroflow with post-void residual evaluates the emptying ability, while an upper urinary tract ultrasound screens for secondary anatomical changes. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss.

In the case of resistance to initial treatment, or in the case of former failed treatment, re-evaluation is warranted and further video-urodynamic studies may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using video-urodynamics.

In the case of anatomical problems, such as urethral valve problems, syringocele, congenital obstructive posterior urethral membrane (COPUM) or Moormann’s ring, it may be necessary to perform further cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

Psychological screening may be useful for children or families with major psychological problems associated with the voiding dysfunction.

10.4 **Treatment**
Treatment of voiding dysfunction consists of lower urinary tract rehabilitation, mostly referred to as urotherapy. Urotherapy means non-surgical, non-pharmacological, treatment of lower urinary tract (LUT) function. It is a very broad therapy field, incorporating many treatments used by urotherapists and other healthcare professionals (13). In case of comorbidity due to bowel problems it is advised to treat the bowel first since bowel problems may sustain any bladder problems (12). Urotherapy can be divided into standard therapy and specific interventions.

10.4.1 **Standard therapy**
Standard urotherapy is defined as non-surgical, non-pharmacological, treatment for LUT malfunction. It includes the following components:

- Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
- Instruction about what to do about the problem, i.e. regular voiding habits, sound voiding posture, avoiding holding manoeuvres, etc.
- Lifestyle advice, regarding fluid intake, prevention of constipation, etc.
- Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts.
• Support and encouragement via regular follow-up by the caregiver.

A success rate of 80% has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled.

10.4.2 Specific interventions

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neurostimulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only one RCT was published (13-19).

In some cases, pharmacotherapy may be added. Antispasmodics and anticholinergics have been shown to be effective, though the level of evidence was low. More recently, a few RCTs have been published. One trial on tolterodine showed safety but not efficacy (20), while another RCT on propiverine showed both safety and efficacy (21) (LE: 1). The difference in results is probably due to study design.

Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended (GR: B) because of the large number of studies reporting a positive effect on OAB symptoms.

Although alpha-blocking agents are used occasionally, an RCT showed no benefit (22). Botulinum toxin injection seems promising, but can only be used off-label (23). Other new treatment modalities such as sacral nerve stimulation are described in case series only and there is no evidence to whether they prove useful. These new treatment modalities can only be recommended for standard therapy resistant cases (24).

### Recommendations for the treatment of daytime lower urinary tract conditions

<table>
<thead>
<tr>
<th>Treatment Approach</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime LUTS in children are common and a stepwise treatment approach is recommended, starting with the least invasive approach.</td>
<td>4</td>
<td>B</td>
</tr>
<tr>
<td>Initial management consists of urotherapy. Urotherapy includes non-invasive training and reeducation, as well as non-invasive neurostimulation.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Pharmacotherapy (mainly antispasmodics and anticholinergics) would be the next step.</td>
<td>1</td>
<td>C</td>
</tr>
<tr>
<td>In case of therapy resistance, re-evaluation will be required which may consist of videourodynamic and MRI of LS spine which can guide to off-label treatment like some of the non-licensed drugs in children, botulinum toxin injection and sacral nerve stimulation. Such treatment should only be offered in highly experienced centres.</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

10.5 References


11. **MONOSYMPTOMATIC ENURESIS**

11.1 **Background**

Enuresis is synonymous to intermittent nocturnal incontinence. It is a frequent symptom in children. With a prevalence of 5-10% at 7 years of age, it is one of the most prevalent conditions in childhood. With a
spontaneous yearly cure rate of 15%, it is considered relatively benign (1,2). Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry. The term “secondary nocturnal enuresis” is used when a child or adult begins wetting again after having stayed dry. In most cases of secondary nocturnal enuresis the causes are either organic or stem from a psychologic problem.

However, 7 out of 100 children wetting the bed at age 7 will take this condition into adulthood. As it is a stressful condition, which puts a high psychological burden on children resulting in low self-esteem, treatment is advised from the age of 6-7 years onwards. Treatment is unnecessary in younger children in whom spontaneous cure is likely. The child’s mental status, family expectations, social issues and cultural background need to be considered before treatment can be started.

11.2 Definition
Enuresis is the condition describing the symptom of incontinence during night. Any wetting during sleep above the age of 5 years is enuresis. However, most importantly, there is a single symptom only. Children with other LUT symptoms and enuresis are said to have non-monosymptomatic enuresis. Thorough history-taking, excluding any other daytime symptoms, is mandatory before diagnosing monosymptomatic enuresis. Any associated urinary tract symptoms make the condition a ‘daytime LUT condition’ (3).

The condition is described as ‘primary’ when the symptom has always existed and the patient has not been dry for a period longer than 6 months. The condition is described as ‘secondary’, when there has been a symptom-free interval of 6 months. Genetically, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 (3).

Three factors play an important pathophysiological role:
• high night-time urine output;
• night-time low bladder capacity or increased detrusor activity;
• arousal disorder.

Due to an imbalance between night-time urine output and night-time bladder capacity, the bladder can become easily full at night and the child will either wake up to empty the bladder or will void during sleep if there is a lack of arousal from sleep (1-3).

11.3 Diagnosis
The diagnosis is obtained by history-taking. In a patient with monosymptomatic enuresis, no further investigations are needed. A voiding diary, which records daytime bladder function and night-time urine output, will help to guide the treatment. An estimate of night-time urine production can be obtained by weighing diapers (nappies) in the morning and adding the volume of the morning void. Measuring the daytime bladder capacity gives an estimate of bladder capacity compared to normal values for age (4).

Ultrasound of the urinary tract is not recommended but, when available, it can be used to exclude underlying pathology.

In most children, bedwetting is a familial problem, with most affected children found to have a history of bedwetting within the family. A urinary dipstick may help differentiate between true enuresis resulting from polyuria due to insipidus diabetes.

11.4 Treatment
Before using alarm treatment or medication, simple therapeutic interventions should be considered.

11.4.1 Supportive treatment measures
Explaining the condition to the child and his parents helps to demystify the problem. Eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights has been shown to be successful.

Counselling, provision of information, positive reinforcement, and increasing (and supporting) motivation of the child should be introduced first. There is a high level of evidence to show that supportive treatment is more successful than doing nothing, although the cure rate is not significantly high. However, supportive therapy as an initial management carries a high grade of recommendation (4).

Supportive measures have limited success when used alone, they should be used in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.

11.4.2 Alarm treatment
Alarm treatment is the best form for arousal disorder (LE: 1; GR: A). Initial success rates of 80% are realistic, with low relapse rates, especially when night-time diuresis is not too high and bladder capacity is not too low (5).
11.4.3 Medication

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets, 200–400 μg, or as sublingual desmopressin oral lyophilisate, 120–240 μg. A nasal spray is no longer recommended due to an increased risk of overdose (6,7) (LE: 1; GR: A). However, relapse rates are high after desmopressin discontinuation (4).

In the case of small bladder capacity, treatment with antispasmodics or anticholinergics is possible (4). However, when these medications are necessary, the condition is no longer considered to be monosymptomatic.

Imipramine, which has been popular for treatment of enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death with overdose are described. Its use should therefore be discouraged (8) (LE: 1; GR: C).

Figure 2: Assessment and treatment of nocturnal enuresis

Guidelines for the treatment of monosymptomatic enuresis

<table>
<thead>
<tr>
<th>Treatment is unnecessary in younger children (&lt; 5 years of age) in whom spontaneous cure is likely.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voiding diaries or questionnaires should be used to exclude daytime symptoms.</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>A urine test is indicated to exclude the presence of infection or potential causes such as diabetes insipidus.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Supportive measures have limited success when used alone; they should be used in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Alarm treatment is the best treatment for arousal disorder with low relapse rates. There may be family compliance problems.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>For the treatment of night time diuresis, Desmopressin treatment has shown to be effective. The response rate is high around 70%, relapse rates are high.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>The choice of the treatment modality can be made during parental counselling. The parents should be well informed about the problem and advantages and disadvantages of each one of the two treatment modalities should be explained.</td>
<td>4</td>
<td>B</td>
</tr>
</tbody>
</table>
11.5 References


12. MANAGEMENT OF NEUROGENIC BLADDER IN CHILDREN

12.1 Background
Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of lower urinary tract dysfunction, which may lead to incontinence, UTIs, VUR, and renal scarring. Surgery may be required to establish adequate bladder drainage. If not managed properly, NDSD can potentially cause renal failure, requiring dialysis or transplantation.

The management of neurogenic bladder sphincter dysfunction in children has undergone major changes over the years. Although nappies (diapers), permanent catheters, external appliances, Crede’s manoeuvre and various forms of urinary diversion have been acceptable treatment methods, these are now reserved for only a small number of resistant patients. The introduction of clean intermittent catheterisation (IC) has revolutionised the management of children with neurogenic bladder. Not only has it made conservative management a very successful treatment option, but it has also made surgical creation of continent reservoirs a very effective treatment alternative, with a good outcome for quality of life and kidney protection (1-3).

Neurogenic bladder in children with myelodysplasia presents with various patterns of detrusor-sphincter dysfunction within a wide range of severity. About 15% of neonates with myelodysplasia have no signs of neurourological dysfunction at birth. However, there is a high chance of progressive changes in the dynamics of neurological lesions with time. Even babies with normal neurourological function at birth have a one in three risk of developing either detrusor sphincter dyssynergia or denervation by the time they reach puberty. At birth, the majority of patients have normal upper urinary tracts, but nearly 60% of them develop upper tract deterioration due to infections, bladder changes and reflux (4-7).

As our understanding of urodynamics studies has evolved, it has allowed us to understand the nature and severity of problems and manage these patients in a more rational and individualised manner. Despite the remarkable changes of the last quarter of the 20th century, the main goals of treatment have remained the same, i.e. prevention of urinary tract deterioration and achievement of continence at an appropriate age.
12.2 Definition
The most common presentation is at birth with myelodysplasia. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions may include spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion. Scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth.

In occult myelodysplasia, the lesions are not overt and often occur with no obvious signs of neurological lesion. In nearly 90% of patients, however, a cutaneous abnormality overlies the lower spine, and this condition can easily be detected by simple inspection of the lower back (8).

Total or partial sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. This anomaly can be part of the caudal regression syndrome, and must be considered in any child presenting with anorectal malformation (ARM). Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting.

Bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion.

12.3 Classification
The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurological disease or injury. Such systems are based on the localisation of the neurological lesion and the findings of the neurourological examination. These classifications have been of more value in adults, in whom neurogenic lesions are usually due to trauma and are more readily identifiable.

In children, the spinal level and extent of congenital lesion are poorly correlated with the clinical outcome. Urodynamic and functional classifications have therefore been more practical for defining the extent of the pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction. According to the nature of the neurological deficit, the bladder and sphincter may be in either an overactive or inactive state:

• the bladder may be overactive with increased contractions, and low capacity and compliance, or inactive with no effective contractions;
• the outlet (urethra and sphincter) may be independently overactive causing functional obstruction, or paralysed with no resistance to urinary flow;
• these conditions may present in different combinations.

This is mainly a classification based on urodynamic findings. The understanding of the pathophysiology of disorders is essential to plan a rational treatment plan for each individual patient. In meningomyelocele, most patients will present with hyper-reflexive detrusor and dyssynergic sphincter, which is a dangerous combination as pressure is built up and the upper tract is threatened.

12.4 Urodynamic studies
Urodynamic studies enable the clinician to observe lower urinary tract function and its deviations from normal. Since the treatment plan mainly depends upon a good understanding of the underlying problem in the lower urinary tract, a well-performed urodynamic study is mandatory in the evaluation of each child with neurogenic bladder.

As the bony level often does not correspond with the neurological defect present, and as the effect of the lesion on bladder function cannot be entirely determined by radiographic studies or physical examination, the information gained from a urodynamic study is priceless. A urodynamic study also provides the clinician with information about the response of the vesicourethral unit to therapy, as demonstrated by improvement or deterioration in follow-up.

It is important to determine several urodynamic parameters, including:

• the bladder capacity;
• the intravesical filling pressure;
• the intravesical pressure at the moment of urethral leakage;
• the presence or absence of reflex detrusor activity;
• the competence of the internal and external sphincteric mechanisms;
• the degree of coordination of the detrusor and sphincteric mechanisms;
• the voiding pattern;
• the post-voiding residual urine volume.

12.4.1 Method of urodynamic study
There is very little comparative data evaluating the complexity and invasiveness of urodynamic testing for neurogenic bladders in children.

12.4.2 Uroflowmetry
As uroflowmetry is the least invasive of all urodynamic tests, it can be used as an initial screening tool. It provides an objective way of assessing the efficiency of voiding, and, together with an ultrasonographic examination, the residual urine volume can also be determined. Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry will rarely be used as a single investigational tool in children with neurogenic bladders, as it does not provide information for bladder storage, yet it may be very practical to monitor emptying in the follow-up. The main limitation of a urodynamic study is the need for the child to be old enough to follow instructions and void on request.

The recording of pelvic floor or abdominal skeletal muscle activity by electromyography (EMG) during uroflowmetry can be used to evaluate coordination between detrusor and the sphincter. As it is a non-invasive test, combined uroflowmetry and EMG may be very useful in evaluating sphincter activity during voiding (9-12) (LE: 3; GR: C).

12.4.3 Cystometry
Although moderately invasive and dependent on a cooperative child, cystometry in children provides valuable information regarding detrusor contractility and compliance. The amount of information obtained from each study is related to the degree of interest and care given to the test.

It is important to be aware of the alterations in filling and emptying detrusor pressures as the infusion rates change during cystometry. Slow fill cystometry (filling rate < 10 mL/min) is recommended by the ICCS for use in children (13). However, it has been suggested that the infusion rate should be set according to the child's predicted capacity, based on age and divided by 10 (14).

Several clinical studies using conventional artificial fill cystometry to evaluate neurogenic bladder in children have reported that conventional cystometry provides useful information for diagnosis and follow-up of children with neurogenenic bladder (15-20). All the studies were retrospective clinical series and lacked comparison with natural fill cystometry, so that the grade of recommendation for an artificial cystometry in children with neurogenic bladder is not high (LE: 4). Additionally, there is evidence suggesting that natural bladder behaviour is altered during regular artificial filling cystometry (21,22).

However, conventional cystometry in infants is useful for predicting future deterioration. Urodynamic parameters, such as low capacity and compliance and high leak-point pressures, are poor prognostic factors for future deterioration. Resolution of reflux is less likely to happen in such bladders (15,20,22) (LE: 4).

During natural fill cystometry, the bladder is allowed to fill naturally and the bladder and abdominal pressures are recorded using microtransducer catheters. Theoretically, this allows investigation of bladder function in near-physiological conditions. Studies on natural fill cystometry in children report similar results to those of studies done in adults. Natural fill cystometry gives a lower detrusor pressure rise during filling, and lower voided volumes with higher voiding pressures. The incidence of bladder overactivity is higher with natural filling cystometry when compared with conventional artificial filling cystometry (21,23,24).

Although there are only a few studies on natural fill cystometry in children with neurogenic bladder, the results suggest that natural fill cystometry detects new findings compared with diagnoses delivered by conventional cystometry (21) (LE: 3). However, the comparison between natural fill and artificial fill cystometry has not been performed against a gold standard, making it difficult to conclude which study is a true reflection of natural bladder behaviour. Findings in the non-neurogenic adult population have questioned the reliability of natural fill cystometry, as natural fill cystometry has shown a high incidence of bladder overactivity in totally normal asymptomatic volunteers (25).

The main disadvantage of natural fill cystometry is that it is labour-intensive and time-consuming. Moreover, because of the transurethral catheter used during this study, false-positive findings caused by the catheter are possible. Especially in children, the recording of events is difficult and there is an increased risk of artefacts, which makes interpretation of the huge amount of data even more difficult.

Natural fill cystometry remains a new technique in the paediatric population. More data need to be gathered in a standard way before it can be widely accepted (11).
12.5 Management
The medical care of children with myelodysplasia with a neurogenic bladder requires constant observation and adaptation to new problems. In the first years of life, the kidneys are highly susceptible to back-pressure and infection. During this period, the emphasis is on documenting the pattern of NDSD, and assessing the potential for functional obstruction and VUR.

12.5.1 Investigations
An abdominal ultrasound obtained as soon as possible after birth will detect hydronephrosis or other upper genitourinary tract pathology. Following ultrasound, a voiding cystourethrogram should be obtained to evaluate the lower urinary tract. Measurement of residual urine during both ultrasound and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or VUR, and can help identify children at risk for upper genitourinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks, and needs to be repeated at regular intervals, in combination with evaluation of the upper tracts (26-28) (LE: 3; GR: B).

12.5.2 Early management with intermittent catheterisation
Overwhelming experience gained over the years with early management of neurogenic bladder in infants has led to a consensus that children do not have upper tract deterioration when managed early with IC and anticholinergic medication. IC should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction (26,29-37) (LE: 2; GR: B).

The early initiation of IC in the newborn period makes it easier for parents to master the procedure and for children to accept it as they grow older (38,39).

Early management results in fewer upper tract changes, but also better bladder protection and lower incontinence rates. It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia cause secondary changes of the bladder wall. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance, resulting in a small non-compliant bladder with progressively elevated pressures.

Early institution of IC and anticholinergic drugs may prevent this in some patients (2,37,40) (LE: 3). The retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with an early start of IC (33,34) (LE: 4).

12.5.3 Medical therapy
At present, oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs, with oxybutynin being the most studied.

Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended release formulation of tolterodine has been found to be as efficient as the instant release form, with the advantages of being single dosage and less expensive. Although the clinical outcome is encouraging, the level of evidence is low for anticholinergic medication because there are no controlled studies (40,41-47) (LE: 3; GR: B).

The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied in the literature. A few studies investigating the use of α-adrenergic blockade in children with neurogenic bladder have reported a good response rate, but the studies lacked controls, and long-term follow-up is warranted (48) (LE: 4; GR: C).

12.5.3.1 Botulinum toxin injections
In neurogenic bladders that are refractory to anticholinergics, injection of botulinum toxin into the detrusor muscle is a novel treatment alternative. Initial promising results in adults have initiated its use in children. It has been shown that this treatment has beneficial effects on clinical and urodynamic variables. Complete continence was achieved in 65-87% of patients; in most studies mean maximum detrusor pressure was reduced to at least 40 cmH2O and bladder compliance was increased to at least 20 cmH2O/mL. However these findings are limited by the lack of controlled trials and the fact that most studies involved small numbers of patients (49-54).

Botulinum toxin seems to be more effective in bladders with obvious detrusor muscle overactivity, whereas non-compliant bladders without obvious contractions are unlikely to respond (55-60).

The most commonly used dose of botulinum toxin is 10 U/kg with a maximum dose of 200 units. No dose study has been performed in children and there is no evidence regarding the optimal dose. Currently, it is unclear how many times this treatment can be repeated, although repetitive treatment has been found to be safe in adults (61-64).
Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative (LE: 3; GR: C). Urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases (65-67).

12.5.4 Management of bowel incontinence
Children with neurogenic bladder have disturbances of bowel function as well as urinary function. Bowel incontinence in these children is frequently unpredictable. It is related to the turnover rate of faecal material in the anal area after evacuation, the degree of intactness of sacral cord sensation and motor function, and reflex reactivity of the external anal sphincter (68).

Bowel incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel emptying regimen is often necessary to maintain faecal continence, and may have to be started at a very young age. With antegrade or retrograde enemas, most of these children will have decreased constipation problems and may attain some degree of faecal continence (69-73) (LE: 3).

Biofeedback training programmes to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management programme in achieving faecal continence (74). Electrostimulation of the bowel may also offer a variable improvement in some patients (75) (LE: 3; GR: C).

12.5.5 Urinary tract infection
Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, UTIs should be treated symptomatically. There is strong evidence for not prescribing antibiotics to patients who have bacteriuria but no clinical symptoms. Although bacteriuria is seen in more than half of children on clean IC, patients who are asymptomatic do not need treatment (76-78) (LE: 3). Patients with VUR should usually be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage (79,80).

12.5.6 Sexuality
Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

12.5.7 Bladder augmentation
Children with a good response to anticholinergic treatment and an overactive sphincter may be continent between catheterisations. Bladder pressure and development of the upper urinary tract will determine whether additional treatment is necessary.

Therapy-resistant overactivity of the detrusor, or small capacity and poor compliance, will usually need to be treated by bladder augmentation. A simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a urethra that can be catheterised.

Stomach is rarely used as an augmenting patch because of the associated complications (81). Ileal or colonic patches are frequently used for augmenting the bladder, with either intestinal segment appearing to be equally useful. Despite some advantages (e.g. avoiding mucus, decreased malignancy rate and fewer complications), alternative urothelium-preserving techniques, such as autoaugmentation and seromuscular cystoplasty, have not proven to be as successful as standard augmentation with intestine (82,83).

A range of applications of engineered bladder tissues are at different stages of development. There have been a few in pre-clinical trials; recent progress suggests that engineered bladder tissues may have an expanded clinical application in the future (84).

12.5.8 Bladder outlet procedures
Children with detrusor overactivity, but with underactive sphincters, will be better for protecting their upper tracts, although they will be severely incontinent. Initial treatment is IC (as it might reduce the degree of incontinence and offers much better control over UTIs) with anticholinergic drugs. At a later age, the outlet resistance will be increased in order to render them continent. No medical treatment available has been validated to increase bladder outlet resistance. Alpha-adrenergic receptor stimulation of the bladder neck has not been very effective (85-90).

When conservative measures fail, surgical procedures need to be considered for maintaining
continent. Although a simple augmentation is sufficient for most low-capacity, high-pressure bladders, augmentation with additional bladder outlet procedures is required when both the bladder and outlet are deficient. Bladder outlet procedures include bladder neck reconstruction or other forms of urethral reconstruction.

Various procedures can be used on the bladder neck to increase resistance, but all of them may complicate transurethral catheterisation. Augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation, a continent stoma will be required. However, most surgeons prefer to leave the bladder neck and urethra patent as a safety precaution.

### 12.5.9 Continent stoma

Augmentation with an additional continent stoma is utilised primarily after failure of previous bladder outlet surgery. It is also advisable when an inability to catheterise transurethrally is likely. An abdominal wall continent stoma may be particularly beneficial to wheelchair-bound spina bifida patients, who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. For continence with augmentation and an abdominal wall stoma, an adequate bladder outlet mechanism is essential to maintain continence.

### 12.5.10 Total bladder replacement

Total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urological reconstruction. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience of the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up (91-93).

### 12.5.11 Lifelong follow-up of neurogenic bladder patients

Neurogenic bladder patients require lifelong supervision, and the monitoring of renal function is extremely important. Periodic investigation of upper tract changes, renal function and bladder status is mandatory. Repeat urodynamic tests are therefore needed more frequently (every year) in younger children and less frequently in older children. From the urological viewpoint, a repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In the case of any apparent changes in the upper and lower urinary tract, or changes in neurological symptoms, a more detailed examination including urodynamics and spinal magnetic resonance imaging is indicated. Renal failure can progress slowly or occur with startling speed in these children. Patients who have undergone reconstructive procedures using intestine should be regularly followed up for complications such as infection, stone formation, reservoir rupture, metabolic changes, and malignancy (93).

The risk of malignancy in enteric augmentations has been reported to be higher than expected, and the risk increases with length of follow-up. Malignancy has been found to occur in 0.6-2.8% of patients during median follow-up of 13-21 years (94-99). In a study including 153 patients with a median follow-up time of 28 years (95), malignancy was found in 4.5%. The malignancy seemed to be associated with coexisting carcinogenic stimuli or with the inherent risk present with bladder exstrophy. Although there is poor data on follow-up schemes; after a reasonable time of follow up (t.i: 10 years), an annual diagnostic work-up including cystoscopy should be considered.

### 12.6 References


13. DILATATION OF THE UPPER URINARY TRACT (URETEROPELVIC JUNCTION AND URETEROVESICAL JUNCTION OBSTRUCTION)

13.1 Background
Dilatation of the upper urinary tract remains a significant clinical challenge in deciding which patient will benefit from treatment.

Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common cause of neonatal hydronephrosis (1). It has an overall incidence of 1:1500 and a ratio of males to females of 2:1 in newborns.

Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side (2).

It can be very difficult to define ‘obstruction’ as there is no clear division between ‘obstructed’ and ‘non-obstructed’ urinary tracts. Currently, the most popular definition is that an obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration (3).

13.2 Diagnosis
The widespread use of ultrasonography during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis (4). The challenge in the management of dilated upper urinary tracts is to decide which child should be observed, which child should be managed medically, and which child requires surgical intervention. Despite the wide range of diagnostic tests, there is no single test that can accurately distinguish obstructive from non-obstructive cases (Figure 1).

13.2.1 Antenatal ultrasound
Usually between the 16th and 18th weeks of pregnancy, the kidneys are visualised routinely, when almost all amniotic fluid consists of urine. The most sensitive time for foetal urinary tract evaluation is the 28th week. If dilatation is detected, ultrasound should focus on:
- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydro-ureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child;
- amniotic fluid volume (5).

13.2.2 Postnatal ultrasound
Since transitory neonatal dehydration lasts about 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended (6).

Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

13.2.3 Voiding cystourethrogram (VCUG)
In newborns with identified upper urinary tract dilatation, the primary or important associated factors that must be detected include:
- vesicoureteral reflux (found in up to 25% of affected children) (7);
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures (8).

13.2.4 Diuretic renography
Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. 99mTc-MAG3 is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) between the fourth and sixth weeks of life (9).

Oral fluid intake is encouraged prior to the examination. At 15 minutes before the injection of the
radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the whole time of the investigation (10). The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged 1 to 16 years, up to a maximum dose of 40 mg.

**Figure 3: Diagnostic algorithm for dilatation of the upper urinary tract**

- **Postnatal US**
  - Dilatation (uni- or bilateral)
  - Voiding cystourethrogram (VCUG)*
  - Diuretic renography
  - No dilatation
  - Repeat US after 4 weeks

*A diagnostic work-up including VCUG must be discussed with the parents, as it is possible that, even if a reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis (7).

### 13.3 Treatment

#### 13.3.1 Prenatal management

Counselling the parents of an affected child is one of the most important aspects of care. The prognosis is hopeful for a hydronephrotic kidney, even if it is severely affected, as it may still be capable of meaningful renal function. In contrast, a severely hypoplastic and dysplastic kidney has a much more hopeless outlook.

It is important to be able to tell the parents exactly when they will have a definitive diagnosis for their child and what this diagnosis will mean. In some cases, however, it will be immediately obvious that the child is severely affected: there will be evidence of massive bilateral dilatation, bilateral hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres (11).

#### 13.3.2 UPJ obstruction

It is most important that management decisions are made on the basis of serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances.

Symptomatic obstruction (recurrent flank pain, urinary tract infection) requires surgical correction using a pyeloplasty, according to the standardized open technique of Hynes and Anderson (12). In experienced hands, laparoscopic or retroperitoneoscopic techniques and robot-assisted techniques have the same success rates as standard open procedures. In asymptomatic cases, conservative follow-up is the treatment of choice.

Indications for surgical intervention comprise impaired split renal function (less than 40%), a decrease of split renal function of more than 10% in subsequent studies, increased anteroposterior diameter on the ultrasound, and grade III and IV dilatation as defined by the Society for Fetal Urology (13).

#### 13.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in the Chapter on ‘Reflux & Valves’, Section 14.4).

##### 13.3.3.1 Conservative management

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of urinary tract infections, although there are no existing prospective randomised trials evaluating the benefit of this regimen (14).

With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent urinary tract infections, deterioration of split renal function and significant obstruction (15).
13.3.3.2 Surgical management

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an antireflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering (16). Some institutions perform endoscopic stenting, but there is still no long-term data and no prospective randomised trials to confirm their outcome.

13.4 Conclusion

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are quite standardised and have a good clinical outcome.

13.5 Conclusions and recommendations for UPJ-, UVJ-obstruction

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal ultrasound investigation.</td>
<td>2</td>
</tr>
<tr>
<td>Ureteropelvic junction obstruction is the leading cause of (40%) of hydronephrotic kidneys 40%).</td>
<td>1</td>
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<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
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<tr>
<td>Postnatal investigations include serial ultrasound and subsequent diuretic renogram and sometimes VCUG.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>A decision about surgical intervention should be based on the time course of the hydronephrosis and the impairment of renal function.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Indications for surgical intervention are an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the ultrasound, and grade IV dilatation as defined by the Society for Fetal Urology.</td>
<td>2</td>
<td>B</td>
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<tr>
<td>For ureteropelvic junction obstructions, the gold standard of treatment is pyeloplasty.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Most primary megaureters require no surgical intervention.</td>
<td>2</td>
<td>B</td>
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13.6 References


14. VESICOURETERIC REFUX IN CHILDREN

14.1 Methodology
The scientific literature for reflux disease is still limited and the level of evidence is generally low. Most of the studies are retrospective, include different patient groups, and have poor stratification of quality. Also, there is a high risk of presenting misleading results by combining different types of studies when systematically extracting data. Therefore, for reflux disease, it is unfortunately not possible to produce recommendations based on high-quality studies. The authors have assessed the current literature, but in the absence of conclusive findings, have provided recommendations based on panel consensus. These guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis.

14.2 Background
Vesicoureteric reflux, or the retrograde flow of urine from the bladder into the ureter, is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension, and renal failure. Fortunately, patients with VUR present within a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention (1). VUR is a very common urological anomaly in children, with an incidence of nearly 1%. Its management is one of the most controversial issues in paediatric urology.

The main goal in management is the preservation of kidney function, by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient [i.e. age, sex, reflux grade, lower urinary tract dysfunction (LUTD), anatomical abnormalities, and kidney status], it is possible to identify those patients with a potential risk of UTIs and renal scarring. Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic or open surgical), and the timing of treatment.

Many children present without symptoms of UTI and because invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of VUR is unknown. However, the prevalence of VUR in non-symptomatic children has been estimated at 0.4-1.8% (2). Among infants prenatally identified with hydronephrosis on ultrasonography (US), who were screened for VUR, the prevalence was 16.2% (7-35%) (3). Siblings of children with VUR had a 27.4% (3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2-61.4%) (3).

However, reflux detected by sibling screening is associated with lower grades (3) and significantly earlier resolution (4). When VUR is discovered in siblings after UTI, it is usually high grade and associated with a high incidence of reflux nephropathy, particularly if the sibling is male and the grade of reflux was high in the index patient. Even when asymptomatic, siblings and offspring of those with VUR may be diagnosed with high-grade reflux and scarring (5,6).
The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). UTIs are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve (7-10).

There is a clear co-prevalence between LUTD and VUR (11). LUTD refers to the presence of lower urinary tract symptoms (LUTSs), including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction that may be accompanied with bowel problems (11). Some studies have described a prevalence of 40-60% for VUR in children with LUTD (12). It is possible that VUR is secondary to LUTD, and that treatment of LUTD therefore results in correction of VUR. In contrast, high-grade VUR may affect bladder dynamics, which subsequently leads to LUTD. A recently published Swedish reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction. There was a significant negative correlation between dysfunction at 2 years and improved dilating reflux. Renal damage at study entry and follow-up was associated with LUTD at 2 years. Recurrent UTIs were seen in 33% of children with LUTD, and in 20% of those without (13).

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy (4). Faster resolution of VUR is more likely with age < 1 year at presentation, lower grade of reflux (grade 1-3), and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%, which is higher than the resolution rate for VUR detected after infancy (14,15).

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution (16-18).

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Ten to forty percent of children with symptomatic VUR have evidence of renal scarring, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general wellbeing (19-21).

Higher grades of VUR present with higher rates of renal scars. Scar rates vary in different patient groups. In those with prenatal hydronephrosis, renal scarring occurs in ~10% of patients (22-27), whereas in patients with LUTD, this may increase up to 30% (28-30). Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies have shown that 10-20% of children with RN develop hypertension or end-stage renal disease (31).

### 14.3 Diagnostic work-up

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR, and lower urinary tract function. A basic diagnostic work-up comprises a detailed medical history (including family history, and screening for LUTD), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture, and serum creatinine in patients with bilateral renal parenchymal abnormalities.

Imaging is the basis of diagnosis and management of VUR. The standard imaging tests include renal and bladder ultrasonography (US), VCUG and nuclear renal scans. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR (32). In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR (33,34) (Table 9). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, renal pelvis and calyces on VCUG (35).

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior (36). Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding urosonography and magnetic resonance VCUG (37-39). However, despite the concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard because it allows better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration.
Table 9: Grading system for VUR on VCUG, according to the International Reflux Study Committee (33)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation</td>
</tr>
<tr>
<td>II</td>
<td>Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices</td>
</tr>
<tr>
<td>III</td>
<td>Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible</td>
</tr>
<tr>
<td>V</td>
<td>Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux</td>
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Dimercaptosuccinic acid (DMSA) is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. DMSA is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. DMSA scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up (35,40). DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis (41). Children with a normal DMSA scan during acute UTI have a low risk of renal damage (42).

Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, such as those with spina bifida or boys in whom VCUG is suggestive of posterior urethral valves. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) (11).

Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

The choice of imaging modalities varies depending on the mode of presentation.

14.3.1 Infants presenting because of prenatally diagnosed hydronephrosis

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation (43,44).

Ultrasound should be delayed until after the first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty, may provide significant information about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal ultrasound excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two US scans within the first 1-2 months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is a rare entity, and if present it is likely to be low grade (23,45). The degree of hydronephrosis is not a reliable indicator for the presence of VUR, even though cortical abnormalities are more common in high-grade hydronephrosis (3). The presence of cortical abnormalities on US (defined as cortical thinning and irregularity, as well as increased echogenicity) warrants the use of VCUG for detecting VUR (3). DMSA provides more reliable and quantitative measurement of the degree of cortical abnormalities when first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional (3,46-48). When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered (48). Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive need further evaluation to exclude obstruction (see Chapter 14).

14.3.2 Siblings and offspring of reflux patients

The screening of asymptomatic siblings and offspring is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, whereas others think that screening asymptomatic individuals is likely to result in significant over-treatment of clinically insignificant VUR.

The overall estimate for renal cortical abnormalities is 19.3% (11-54%), with 27.8% having renal
damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only, the rate of renal damage is 14.4% (0-100%). Early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage. (3,5,49,50).

The lack of randomised clinical trials for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

<table>
<thead>
<tr>
<th>Recommendations for paediatric screening for VUR</th>
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<tr>
<td>The parents of children with VUR should be informed that siblings and offspring have a high prevalence of VUR.</td>
</tr>
<tr>
<td>If screening is performed, siblings should be screened by renal US. VCUG is recommended if there is evidence of renal scarring on US or a history of UTI.</td>
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<tr>
<td>In older children who are toilet-trained, there is no added value in screening for VUR.</td>
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14.3.3 **Children with febrile urinary tract infections**

VCUG is recommended at 0-2 years of age after the first proven febrile UTI. If reflux is diagnosed, further evaluation has traditionally consisted of a DMSA scan. However, it can be reserved for high-grade VUR or VUR associated with a suggestion of abnormal renal parenchyma on ultrasound, or it can be used as a baseline test to compare the consequences of potential pyelonephritic complications in the future.

An alternative “top-down” approach is also an option, as suggested by several studies in the literature. This approach carries out an initial DMSA scan close to the time of a febrile UTI, to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to spot VUR in 5-27% of cases, with the missed VUR presumably being less significant. In contrast, a normal DMSA scan with no VCUG avoids unnecessary VCUG in > 50% of those screened (51-54).

14.3.4 **Children with lower urinary tract symptoms and vesicoureteric reflux**

Detection of LUTD is essential in treating children with VUR. There are several hypotheses. For example, it is suggested that reflux with LUTD resolves faster after LUTD correction, and that patients with LUTD are at higher risk for developing UTI and renal scarring (55). Alternatively, it is possible that LUTD is secondary to VUR and that treatment of VUR therefore results in correction of LUTD. Or, it may be that there is a high co-prevalence of LUTD and VUR, but the treatment of one condition does not correct the other. In recent literature, there are no data to support any of the above hypotheses. Most studies are descriptive, uncontrolled and retrospective, and the evidence quality is low.

A recent Swedish reflux study, however, has indicated that patients who have both VUR and LUTD may have a worse final outcome after treatment, including an elevated risk for kidney damage (13). The results from the Swedish study indicate that the coexistence of both conditions should be explored in any patient who has VUR. If there are symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

In LUTD, VUR is often low grade and US findings are normal, and there is no indication for performing VCUG in all children with LUTD. Instead, it would be more rational to ask any patient with LUTD if he or she has a history of febrile UTI, because there is a greater possibility of finding VUR in such patients. However, because of the coexistence of LUTD and VUR, it would be better to do a test covering both conditions, such as a videourodynamic study (VUDS). Any patient with LUTD and a history of febrile UTI should be investigated with a VUDS, if available. Furthermore, any child who fails standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with VCUG is highly recommended.

14.4 **Treatment**

There are two main treatment approaches: conservative (non-surgical) and surgical.

14.4.1 **Conservative therapy**

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- VUR resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within 4-5 years of follow-up. Spontaneous resolution is low for bilateral high-grade reflux (56).
- VUR does not damage the kidney when patients are free of infection and have normal lower urinary tract function.
- There is no evidence that small scars can cause hypertension, renal insufficiency or problems during
pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.

- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD (55-57-60).
- Circumcision during early infancy may be considered as part of the conservative approach, because it is effective in reducing the risk of infection in normal children (61).

14.4.1.1 Follow-up
Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography, or DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

14.4.1.2 Continuous antibiotic prophylaxis (CAP)
The use of CAP and duration of follow-up during prophylaxis in reflux patients is another area of major controversy. Although it is difficult to make definitive recommendations based on recent literature, it is clear that antibiotic prophylaxis may not be needed in every reflux patient (58,62-64). Although there are trials showing no benefit of CAP, especially in low-grade reflux, there are also trials showing that CAP prevents further renal damage, particularly in patients with grade III and V reflux (65-69).

It is difficult and risky to select patients who do not need CAP. A safe approach would be to use CAP in most cases. Decision making may be influenced by the presence of risk factors for UTI, such as young age, high-grade VUR, status of toilet-training/LUTS, female sex, and circumcision status. However, recent literature does not provide any reliable information about the duration of CAP in reflux patients.

A practical approach would be to use CAP until after children have been toilet-trained and ensuring that there is no LUTD. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an antireflux procedure or discontinuation of CAP may also depend on personal preferences and the attitude of patients and parents. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

14.4.2 Surgical treatment
Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation.

14.4.2.1 Subureteric injection of bulking materials
With the availability of biocompatible substances, subureteric injection of bulking materials has become increasingly popular because it is minimally invasive and performed on an outpatient basis. Using cystoscopy, bulking materials are injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow. With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and surgical intervention in the treatment of VUR in children.

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, and more recently, a solution of dextranomer/hyaluronic acid (Deflux).

Although the best results have been obtained with PTFE (70), due to concerns about particle migration, PTFE has not been approved for use in children (71). Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Deflux was approved by the US FDA in 2001 for the treatment of VUR in children. Initial clinical trials have demonstrated that this method is effective in treating reflux (72). Studies with long term follow-up have shown that there is a high recurrence rate which may go up to 20% in 2 years (62).

In a meta-analysis (73) including 5527 patients and 8101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) versus single (73%) systems, and neuropathic (62%) versus normal (74%) bladders.

Clinical validation of the effectiveness of antireflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent prospective, randomised trials comparing three treatment arms (I, endoscopic injection; II, antibiotic prophylaxis; III, surveillance without antibiotic prophylaxis) in 203 children aged 1-2 years with grade III/IV reflux, endoscopic treatment gave the highest resolution rate of 71% compared to 39% and 47% for treatment arms II and III, respectively, after 2 years’ follow-up. The
recurrence rate at 2 years after endoscopic treatment was 20%. The occurrence of febrile UTIs and scar formation was highest in the surveillance group at 57% and 11%, respectively. New scar formation rate was higher with endoscopic injection (7%) compared with antibiotic prophylaxis (0%) (74). Longer follow-up studies are needed to validate these findings.

14.4.2.2 Open surgical techniques
Various intra- and extravesical techniques have been described for the surgical correction of reflux. Although different methods have specific advantages and complications, they all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) (75).

The most popular and reliable open procedure is cross trigonal reimplantation described by Cohen. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed when the child is older. Alternatives are supravesical reimplantation (Politano-Leadbetter technique) and infravesical reimplantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed preoperatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical antireflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary postoperative urine retention (76). Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

14.4.2.3 Laparoscopy
There have been a considerable number of case series of transperitoneal extravesical and pneumovesicoscopic intravesical ureteral reimplantation, which have shown the feasibility of the techniques. Today, both conventional and robot-assisted laparoscopic approaches present comparable outcomes to their open surgical counterparts in terms of successful resolution of reflux. Further studies are needed to define the costs and benefits of both approaches.

The major shortcoming of the new techniques seems to be the longer operative times, which hinders their wider acceptance. Also, laparoscopic approaches are more invasive than endoscopic correction and their advantages over open surgery are still debated. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure. It can be offered as an alternative to the parents in centres where there is enough experience (61,77-83).

14.5 Recommendations for the management of vesicoureteric reflux in childhood

Regardless of the grade of reflux or presence of renal scars, all patients diagnosed within the first year of life should be treated initially with CAP. During early childhood, the kidneys are at higher risk of developing new scars. Immediate, parenteral antibiotic treatment should be initiated for febrile breakthrough infections. Definitive surgical or endoscopic correction is the preferred treatment in patients with frequent breakthrough infections (78).

Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.

There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit. These patients may be candidates for endoscopic treatment.

In all children presenting at age 1-5 years, CAP is the preferred option for initial therapy. For those with high-grade reflux or abnormal renal parenchyma, surgical repair is a reasonable alternative. In patients with lower grades of reflux and without symptoms, close surveillance without antibiotic prophylaxis may be an option.

A detailed investigation for the presence of LUTD should be performed in all children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.

If parents prefer definitive therapy to conservative management, surgical correction may be considered. Endoscopic treatment is an option for all children with low grades of reflux.

The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, because the treatment should be tailored to different risk groups.
The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference (79). Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars.

In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.

**Table 10: Management and follow-up according to different risk groups**

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Presentation</th>
<th>Initial treatment</th>
<th>Comment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD</td>
<td>Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux</td>
<td>Greater possibility of earlier intervention</td>
<td>More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months</td>
</tr>
<tr>
<td>High</td>
<td>Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD</td>
<td>Intervention should be considered</td>
<td></td>
<td>Post-operative VCUG on indication only; follow-up of kidney status until after puberty</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys</td>
<td>CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux</td>
<td>Spontaneous resolution is higher in males</td>
<td>Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months</td>
</tr>
<tr>
<td>Moderate</td>
<td>Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys</td>
<td>CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux</td>
<td></td>
<td>Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD</td>
<td>Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT, infections or persistent reflux</td>
<td>In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial</td>
<td>Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD</td>
<td>Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed.</td>
<td></td>
<td>Follow-up for UTI, LUTD, and kidney status until after puberty</td>
</tr>
<tr>
<td>Moderate</td>
<td>All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD</td>
<td>Initial treatment is always for LUTD with or without CAP</td>
<td></td>
<td>Follow-up for UTI and LUTD</td>
</tr>
<tr>
<td>Low</td>
<td>All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD</td>
<td>No treatment or CAP</td>
<td>If no treatment is given, parents should be informed about risk of infection</td>
<td>Follow-up for UTI</td>
</tr>
<tr>
<td>Low</td>
<td>All asymptomatic patients with normal kidneys with low-grade reflux</td>
<td>No treatment or CAP in infants</td>
<td>If no treatment is given, parents should be informed about risk of infection</td>
<td>Follow-up for UTI</td>
</tr>
</tbody>
</table>

PNH = prenatal diagnosed hydronephrosis.
14.6 References


15. URINARY STONE DISEASE

15.1 Background
Paediatric stone disease is an important clinical problem in paediatric urology practice. Because of its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with interventional management and close follow-up are of the utmost importance.

Paediatric stone disease has its own unique features, which are different in both presentation and treatment compared to stone disease in adults. In contrast to adults with stone disease who are more likely to be male, boys and girls are affected almost equally. Most paediatric stones are located in the upper urinary tract. However, bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors (1).

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American states. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world (2,3) especially in girls, Caucasian ethnicity, and older children (4). In the UK and other European countries, 75% of calculi in children are composed of organic matrix and struvite, with many stone formations associated with Proteus infection and urinary tract anomalies (5).

15.2 Stone formation mechanisms, diagnosis of causative factors and medical treatment for specific stone types
Urinary stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection.

Calcium, oxalate, uric acid or cystine molecules may develop into stones when they are supersaturated in urine. In the presence of a supersaturated solution, a decreased concentration of
crystallisation inhibitors (citrate, magnesium, pyrophosphate, macromolecules and glycosaminoglycans) may be all that is needed for a urinary stone to form. Urinary pH changes also affect stone formation. In addition, an impaired flow of urine due to an abnormal morphology may facilitate stasis and increase the concentration of stone-forming substances.

15.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Supersaturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia), play a major role in the formation of calcium oxalate stones.

Hypercalciuria. This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day in a child weighing less than 60 kg. In infants younger than 3 months, 5 mg/kg/day is considered to be the upper limit of normal for calcium excretion (6).

Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause. Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary (hypercalcaemic) hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilization, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) (7).

A good screening test for hypercalciuria compares the ratio of urinary calcium to creatinine. The normal calcium-to-creatinine ratio in children is less than 0.2. If the calculated ratio is higher than 0.2, repeat testing is indicated. Neonates and infants have a higher calcium excretion and lower creatinine excretion than older children (6,74). If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed. However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated.

The 24-hour calcium excretion test is the criterion standard for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted. Further evaluation includes levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH (6-9).

A 24-hour urine collection should also be collected for measurement of calcium, phosphorus, sodium, magnesium, citrate and oxalate. Meanwhile dietary manipulations should be tried to normalise urine calcium (9).

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child (10).

A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake is contributing to high urinary calcium. However, great caution should be used when trying to restrict calcium intake for long periods (LE: 3; GR: B).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat hypercalciuria at a dosage of 1-2 mg/kg/day (5,11) (LE: 3; GR: C). Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies (5,12) (LE: 4; GR: C).

Hyperoxaluria. Oxalic acid is a metabolite excreted by the kidneys. Only 10-15% of oxalate comes from diet. Normal school children excrete less than 50 mg (0.57 mmol)/1.73m2/day (5,13), while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. In primary hyperoxaluria there is increased deposition of calcium oxalate in the kidney and in urine. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues. The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children who have high levels of oxalate excretion in urine may not have any documented metabolic problem or any dietary cause. This is known as idiopathic 'mild' hyperoxaluria, with urine oxalate levels elevated only mildly in these cases.

The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria (5,13) (LE: 4; GR: C).
Hypocitraturia. Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus, low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size (14,15).

Hypocitraturia usually occurs in the absence of any concurrent symptoms or any known metabolic derangements. It may also occur in association with any metabolic acidosis, distal tubular acidosis or diarrhoeal syndromes.

Environmental factors that lower urinary citrate include a high protein intake and excessive salt intake. Many reports emphasise the significance of hypocitraturia in paediatric calcium stone disease. The presence of hypocitraturia ranges from 30% to 60% in children with calcium stone disease.

Due to the increased stone risk in hypocitraturia, the restoration of normal citrate levels is advocated to reduce stone formation. Although some studies have shown that citrate replacement therapy reduces the risk of stone formation in an adult population, there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses (15) (LE: 3; GR: B).

15.2.2 Uric acid stones

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day is considered to be hyperuricosuria (5).

The formation of uric acid stones is mainly dependent on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at pH of less than 5.8. As the pH becomes more alkaline, uric acid crystals become more soluble and the risk of uric acid stone formation is reduced.

In the familial or idiopathic form of hyperuricosuria, children usually have normal serum uric acid levels. In other children, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children.

Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis.

Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones (5).

15.2.3 Cystine stones

Cystinuria is the cause of cystine stone formation and accounts for 2-6% of all urinary stones in children. Cystinuria is an incompletely recessive autosomal disorder characterised by failure of renal tubules to reabsorb four basic amino acids: cystine, ornithine, lysine and arginine.

Of these four amino acids, only cystine has poor solubility in urine, so that only cystine stones may form in the case of excessive excretion in urine. Cystine solubility is pH-dependent, with cystine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones.

Cystine stones are faintly radiolucent and may be difficult to show on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shock wave lithotripsy (SWL).

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0. If this treatment fails, the use of \(-\)mercaptopropionil glycine may reduce cystine levels in urine and prevent stone formation. Use of these drugs can be associated with severe side effects, such as bone marrow depression and nephrotic syndrome (16) (LE: 4; GR: C).

15.2.4 Infection stones (struvite stones)

Infection-related stones constitute nearly 5% of urinary stones in children. Bacteria capable of producing urease enzyme (Proteus, Klebsiella, Pseudomonas) are responsible for the formation of such stones.

Urease converts urea into ammonia and bicarbonate, so alkalinizing the urine and further converting bicarbonate into carbonate. In the alkaline environment, triple phosphates form, eventually resulting in a supersaturated environment of magnesium ammonium phosphate and carbonate apatite, which in turn leads to stone formation.

In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.
15.3 Clinical presentation
Presentation tends to be age-dependent, with symptoms such as flank pain and haematuria being more common in older children. Non-specific symptoms (e.g. irritability, vomiting) are common in very young children. Haematuria, usually gross, occurring with or without pain, is less common in children. However, microscopic haematuria may be the sole indicator and is more common in children. In some cases, urinary infection may be the only finding leading to radiological imaging in which a stone is identified (174,18).

15.4 Diagnosis
15.4.1 Imaging
Generally, ultrasonography should be used as a first study. Renal ultrasonography is very effective for identifying stones in the kidney. Many radiopaque stones can be identified with a simple abdominal flat-plate examination.

If no stone is found but symptoms persist, spiral CT scanning is indicated. The most sensitive test for identifying stones in the urinary system is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity (19-21) (LE: 2; GR: B).

Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

15.4.2 Metabolic evaluation
Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with urinary stone should be given a complete metabolic evaluation (1,22,23).

Metabolic evaluation includes:

- Family and patient history of metabolic problems.
- Analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type).
- Electrolytes, BUN, creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia).
- Spot urinalysis and culture, including ratio of calcium to creatinine.
- Urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, cystine, protein, and creatinine clearance.

Figure 4 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and to plan medical treatment accordingly.
K-citrate diet (normal calcium, low sodium intake; HCTZ (diuretic))

Diet low in ox. K-citrate, pyridoxine

alkal replacement - K-citrate
Allopurinol (10 mg/kg)
low purine diet

Mg Ammonium phosphate (struvite)

urine culture
possibly urease producing bacteria
total elimination of stone (surgery/SWL) antibiotics

Uric acid stone

urine pH
urine and serum uric acid levels

acidic urine
hyperuricosuria
hyperuricemia

Cystine

urine pH
urine cystine level
cystinuria

Calcium stones CaOx-CaPO

high fluid intake
potassium citrate
3-4 mEq/kg/d
mercaptopropionylglycine
10-15 mg/kg/d

Further investigation for RTA

hyperparathyroidism
hypercalciuria
hyperoxaluria
hyperuricosuria
hypocitraturia

serum PTH
hypercalcaemia
urine pH < 5.5

urine - blood pH
urine - blood Ca - uric acid levels, Mg, Phosphate
urine Ca-Oxalate-Citrate-Mg-Uric A -Phosphate
urine pH > 5.5

Elimination of stones by spontaneous passage
or active removal (SWL, surgery)
15.5 Management

With the advance of technology stone management has changed from open surgical approach to endoscopic techniques that are less invasive. Deciding the form of treatment depends on the number, size, location, composition and anatomy of the urinary tract (22,24,25).

Currently, most paediatric stones can easily be managed by SWL. Endoscopic treatment can be applied easily for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in children. Only a small portion of children will need an open surgical approach.

15.5.1 Extracorporeal shock wave lithotripsy (SWL)

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney (26-31).

The mean number of shock waves for each treatment is about 1800 and 2000 (up to 4000 if needed) and the mean power set varies between 14 kV and 21 kV. The use of ultrasonography and digital fluoroscopy has significantly decreased the radiation exposure and it has been shown that children are exposed to significantly lower doses of radiation compared to adults (24,32,33). Concerns about anaesthesia do not seem to be a problem anymore because of advances in technique and medication, even in the infant period. The type of anaesthesia should be general or dissociative for children under 10 years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to co-operate (34) (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and re-treatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases (24,32,33,35-39).

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in renal pelvis and upper ureter seem to respond better to SWL. In these mentioned sites, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% (40-43).

Shockwave lithotripsy can also be used to treat ureteral calculi. However, this is a more specific issue and with controversies. The success rates with SWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children (40,42-45).

The type of machine used has a strong effect on success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma. However, additional treatments may be needed with later-generation machines. The success rate is higher in younger children (38).

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient (37,38). Stenting is essential in solitary kidneys undergoing SWL treatment. Children with a large stone burden have a high risk of developing Steinstrasse and urinary obstruction and should be followed more closely for the risk of prolonged urinary tract obstruction after SWL.

Post-SWL stent or nephrostomy tube placement may be needed in prolonged obstruction (23,39).

Complications arising from SWL in children are usually self-limiting and transient. The most common complications are:

- renal colic;
- transient hydronephrosis;
- dermal ecchymosis;
- urinary tract infection;
- formation of Steinstrasse;
- sepsis;
- rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended (46). However, every effort should be made to sterilize the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

15.5.2 Percutaneous nephrolithotomy

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery can be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique
are similar in children compared to adults. Percutaneous nephrolithotomy is used as monotherapy in most cases, but is also used as an adjunctive procedure to other therapies.

The use of adult-sized instruments, in association with an increased number of tracts and sheath size, seems to increase blood loss. However, the development of small-calibre instruments means that PCNL can be used in children. Percutaneous nephrolithotomy has some advantages for children (particularly smaller children), such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost (46,47).

As monotherapy, PCNL is considerably effective and safe. The reported stone-free rates in the recent literature are between 86.9% and 98.5% after a single session. These rates increase with adjunctive measures, such as second-look PCNL, SWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session (48-51,53,54).

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion in the modern series is reported in less than 10% (55-60) and is closely associated with stone burden, operative time, sheath size and the number of tracts (60,61). In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% (55,56,58-60,62) and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturized PCNL (‘mini-perc’) through a 13F or 14F sheath has become possible (63-65), with decreased transfusion rates (65). This miniaturization has been further developed into the technique of ‘micro-perc’ using a 4.85F ‘all-seeing needle’. This technique is still experimental and enables the stone to fragmented by a laser in situ and left for spontaneous passage (66).

As experience has accumulated in adult cases, new approaches have also started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones smaller than 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter (67,68) or totally tubeless (69).

The mean post-operative hospital stay is similar to adults. It is reported as 3-4 days in all published literature and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2; GR: B).

15.5.3 Ureterorenoscopy

The increasing availability of smaller size endourological equipment has made it possible to manage paediatric ureteral stones using endoscopic techniques.

The technique used in children is similar to the one used in adults. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed much less and only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective (46,70-73,74-76) (LE: 3; GR: B).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases (53,71,73,77-83).

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1; GR: A). A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children has revealed that the procedure is effective with a 90% stone-free rate and efficacy quotient. The study also focused on the factors affecting the complication rates. The authors found that although operating time, age, institutional experience, orifice dilation, stenting and stone burden were significant on univariate analysis, multivariate analysis revealed that operating time was the only significant parameter affecting the complication rate (84).

A recent literature review contains a growing number of case series on the use of flexible ureterorenoscopic interventions in children. Both intrarenal and ureteric stones can be treated using this approach (85-89). In these series, the authors generally did not use active orifice dilation, but attempted to use a ureteral sheath where possible. However, an important problem was the inability to obtain retrograde access to the ureter in approximately half of the cases (87,88). This problem can be overcome by stenting and leaving the stent indwelling for passive dilation of the orifice, and performing the procedure in a second session. The success rates varied between 60 and 100%, with a negligible number of complications (85-87,89). The need for additional procedures was related to stone size (85). Although the use of flexible instruments seems feasible for the present time, more data are needed for comparison with other endourological modalities in children.

15.5.4 Open stone surgery

Most stones in children can be managed by SWL and endoscopic techniques. However, in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system, which also requires surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.
In centres with a well-established experience, a laparoscopic approach may be a good alternative for some cases as a last resort before open surgery. Suitable candidates include patients who have a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant ureteropelvic junction obstruction or caliceal diverticula, megaureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is very limited experience with these techniques and they are not routine therapeutic modalities (90,91).

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

Recommendations for interventional management are given in Table 11.

<table>
<thead>
<tr>
<th>Stone size and localisation*</th>
<th>Primary treatment option</th>
<th>LE GR</th>
<th>Secondary treatment options</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staghorn stones</td>
<td>PCNL</td>
<td>2B</td>
<td>Open/SWL</td>
<td>Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.</td>
</tr>
<tr>
<td>Pelvis &lt; 10 mm</td>
<td>SWL</td>
<td>1A</td>
<td>RIRS/PCNL</td>
<td></td>
</tr>
<tr>
<td>Pelvis 10-20 mm</td>
<td>SWL</td>
<td>2B</td>
<td>PCNL/Open</td>
<td>Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.</td>
</tr>
<tr>
<td>Pelvis &gt; 20 mm</td>
<td>PCNL</td>
<td>2B</td>
<td>SWL/Open</td>
<td>Multiple sessions with SWL may be needed.</td>
</tr>
<tr>
<td>Lower pole calyx &lt; 10 mm</td>
<td>SWL</td>
<td>2B</td>
<td>RIRS/PCNL</td>
<td>Anatomical variations are important for complete clearance after SWL.</td>
</tr>
<tr>
<td>Lower pole calyx &gt; 10 mm</td>
<td>PCNL</td>
<td>2B</td>
<td>SWL</td>
<td>Anatomical variations are important for complete clearance after SWL.</td>
</tr>
<tr>
<td>Upper ureteric stones</td>
<td>SWL</td>
<td>2B</td>
<td>PCNL/URS/Open</td>
<td></td>
</tr>
<tr>
<td>Lower ureteric stones</td>
<td>URS</td>
<td>1A</td>
<td>SWL/Open</td>
<td>Additional intervention need is high with SWL.</td>
</tr>
<tr>
<td>Bladder stones</td>
<td>Endoscopic</td>
<td>2B</td>
<td></td>
<td>Open is easier and with less operative time with large stones.</td>
</tr>
</tbody>
</table>

* Cystine and uric acid stones excluded.

PCNL = percutaneous nephrolithostomy; SWL = shock-wave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

15.6 Conclusions and recommendations

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The incidence of stone disease in children is increasing.</td>
<td>2</td>
</tr>
<tr>
<td>Any child with urinary stone disease deserves metabolic and anatomical evaluation.</td>
<td>2</td>
</tr>
<tr>
<td>Treatment should be supported with medical treatment for the underlying metabolic abnormality if detected.</td>
<td>1</td>
</tr>
<tr>
<td>Open surgery for stone disease in children is an exceedingly rare requirement.</td>
<td>1</td>
</tr>
<tr>
<td>Surgical treatment is based on minimally invasive modalities.</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In most cases, plain abdominal X-ray and ultrasonography is sufficient for diagnosis and follow-up.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Non-contrast CT may be required in cases with a doubtful diagnosis or complex cases requiring surgery.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>The use of appropriate-size instruments will decrease the number of complications in surgical treatment.</td>
<td>1</td>
<td>A</td>
</tr>
</tbody>
</table>
15.7 References


16. OBSTRUCTIVE PATHOLOGY OF RENAL DUPLICATION: URETEROCELE AND ECTOPIC URETER

16.1 Background

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication, but they also occur in a single system. At present, antenatal ultrasonography detects both conditions in the
majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further examination. Later in life, these anomalies are revealed by clinical symptoms: UTI, pain, calculus formation, disturbances of micturition, and urinary incontinence. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and upper tract dilatation after birth).

16.1.1 Ureterocele
Ureterocele is 4-7 times more frequent in female than in male patients; the overall incidence in autopsies is around 1 in 4,000 children. Around 80% is associated with the upper pole ureter in duplicated systems and 20% in single systems. About 10% of ureteroceles are bilateral (1).

16.1.2 Ectopic ureter
Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies), but is also more common in female patients (male to female ratio, 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine (2). Eighty per cent of ectopic ureters are associated with complete renal duplication, however, in male patients, most ectopic ureters are associated with a single system (3,4).

16.2 Definition and classification
16.2.1 Ureterocele
Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear (5-7). A single-system ureterocele is associated with a kidney with one ureter, and in duplex systems, the ureterocele belongs to the upper pole. Ureteroceles usually cause obstruction of the upper pole, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the orthotopic form, there is often no or only mild obstruction, and frequently the function of the moiety is normal or slightly impaired, and the corresponding ureter may be dilated. Cystic renal dysplasia is also associated with a single system ureterocele (8,9). Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon (10).

In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional (11,12). The corresponding ureter is a megaureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional.

16.2.1.1 Ectopic (extravesical) ureterocele
If any portion of the ureterocele extends into the bladder neck or urethra, it is called an ectopic ureterocele. Ectopic ureterocele is the most common form of ureterocele (> 80%). It can be voluminous, dissociating the trigone and slipping into the urethra, and may prolapse through the urethral meatus (caeco-ureterocele). The ureterocele orifice is tight, and located in the bladder itself or below the neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive megaureter. A contralateral renal duplication is associated in 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

16.2.1.2 Orthotopic (intravesical) ureterocele
The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is seen more in older children or adults.

16.2.2 Ectopic ureter
The term ectopic ureter describes a ureter with the orifice located at the bladder neck, in the urethra, or outside the urinary tract. The ureter can drain the upper pole of a duplex or single system. There is a fundamental difference between the sexes. In boys, the ectopic orifice is never below the external sphincter.

In girls, the ureteral orifice may be located (13):
- in the urethra, from the bladder neck to the meatus (35%)
- in the vaginal vestibule (34%)
- in the vagina (25%)
- in the uterus and Fallopian tube (6%).

In boys, the ureteral orifice may be located (13):
- in the posterior urethra (47%)
- in the prostatic utricle (10%)
- in the seminal vesicles (33%)
- in the vas deferens or ejaculatory ducts (10%).

16.3 Definition and classification
16.3.1 Ectopic ureter
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- in the posterior urethra (47%)
- in the prostatic utricle (10%)
- in the seminal vesicles (33%)
- in the vas deferens or ejaculatory ducts (10%).
16.3  Diagnosis

16.3.1  Ureterocele
Prenatal ultrasound easily reveals voluminous obstructive ureteroceles (14,15). In cases with a small upper pole or a slightly obstructive ureterocele, prenatal diagnosis is difficult. If prenatal diagnosis is impossible, the following clinical symptoms, besides incidental findings, can reveal the congenital anomaly at birth or later:

- At birth, a prolapsed and sometimes strangulated ureterocele may be observed in front of the urethral orifice. In a newborn boy, it might cause acute urinary retention, simulating urethral valves.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later symptoms can include dysuria, recurrent cystitis and urgency.

In cases of prenatal diagnosis at birth, ultrasonography confirms the ureteral dilatation that ends at the upper pole of a renal duplication. It also demonstrates the presence of a ureterocele in the bladder, with a dilated ureter behind the bladder.

At this point, it is important to assess the function of the upper pole using nuclear renography of the region of interest. This is best assessed with DMSA (16-18). Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux, and assessing the degree of intraurethral prolapse of the ureterocele (19).

Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic megaureter.

16.3.2  Ectopic ureter
Most of the ectopic megaureters are diagnosed primarily by ultrasonography. In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region (20).
- In pre-adolescent boys: epididymitis is the usual clinical presentation and the seminal vesicle may be palpable.

Ultrasonography, radionuclide studies (DMSA), VCUG, magnetic resonance urography, high-resolution MR imaging, and cystoscopy are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction (21). In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele (22,23).

Girls who present with lifelong minimal urinary incontinence, never being dry, normal bladder function, complete emptying, and normal ultrasound are very suspicious for ectopic ureter. This needs to be excluded or confirmed by further imaging (e.g. MR imaging). Filling the bladder with methylene blue and checking for clear urine output from the vagina can give clear evidence of extrasphincteric ureteral ectopia. This test is also helpful in confirming a vesicovaginal fistula (in this case blue fluid is drained from the vagina).

16.4  Treatment

16.4.1  Ureterocele
The management is controversial with a choice between a conservative approach, endoscopic decompression, ureteral reimplantation, partial nephroureterectomy, or complete primary reconstruction (24-29). The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis); patient age; function of the upper pole; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and parents’ and surgeon’s preferences (30).

When the diagnosis is made by ultrasound, prophylactic antibiotic treatment is indicated until a VCUG can be performed.

16.4.1.1 Early treatment
In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non- or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated.

16.4.1.2 Re-evaluation
Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction,
without severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux (30,31).

If decompression is effective and there is no reflux (~25% of cases and more often in intravesical ureterocele), the patient is followed-up conservatively. After an endoscopic incision, most of the children with an extravesical ureterocele (50-80%) need a secondary procedure, compared with only 18% of those with an intravesical ureterocele (32). Secondary surgery is necessary if decompression is not effective, significant reflux is present, or there is obstruction of the ipsi- or contralateral ureters, and/or bladder neck obstruction. Surgery may vary from upper pole nephrectomy to complete unilateral bladder reconstruction (10,26,33-40). In an ectopic ureterocele with severe hydroureteronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/uretero-pyelo/ureterostomy and upper-pole ureterectomy) gives up to an 80% chance of being the definitive treatment (30,41).

Figure 5: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life (30)

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**DSU** = duplex system ureterocele; **ED** = endoscopic decompression; **HUN** = hydroureteronephrosis; **MCUG** = micturating cystourethrography; **UPPN** = upper pole partial nephrectomy; **VUR** = vesicoureteric reflux.

Obstruction is considered to be the presence of non-refluxing dilatation of non-ureterocele-bearing moieties (especially of the lower pole) or of an obstructive drainage pattern on diuretic renography.

16.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and heminephro-ureterectomy should be considered. Ureteral reconstruction (ureteral reimplantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) is a therapeutic option in cases in which the upper pole has function worth preserving. Both procedures can be performed through an open or laparoscopic approach (42-44). In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex and renal and bladder function is necessary. Usually the bladder neck is insufficient in these patients (45-48).
### 16.5 Conclusions and recommendations for obstructive pathology of renal duplication: ureterocele and ectopic ureter

#### Conclusions
Ureterocele and ectopic ureter are associated with complete renal duplication, but they also occur in a single system.

In most cases, in young children (first years of life) diagnosis is done by ultrasonography.

In older children clinical symptoms will prompt assessment.

Management includes a conservative approach, endoscopic decompression, partial nephroureterectomy, or complete primary reconstruction. Choice of treatment will depend on:
- clinical status of the patient (e.g., urosepsis);
- patient age;
- function of the upper pole;
- presence of reflux or obstruction of the ipsilateral or contralateral ureter;
- presence of bladder neck obstruction caused by ureterocele;
- intravesical or ectopic ureterocele;
- and parents’ and surgeon’s preferences.

#### Recommendations

<table>
<thead>
<tr>
<th>Ureterocele</th>
<th>Diagnosis</th>
<th>Ultrasoundography, radionuclide studies (MAG III / DMSA), VCUG, magnetic resonance urography, high-resolution MRI, and cystoscopy are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Choice of treatment will depend on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral reimplantation, partial nephroureterectomy, complete primary reconstruction.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- In patients (single/duplex systems) with no hydronephrosis and no symptoms, the risk for renal injury is low and conservative treatment is a good option.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- In those with reflux, endoscopic treatment is an option; open reimplantation especially in dilating reflux provides better results.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- In patients with an obstructing ureterocele, early endoscopic decompression is indicated. In half, to two-thirds of children with an extravesical ureterocele a secondary procedure is needed (compared to 20-25% of those with an intravesical ureterocele).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- In patients with a non-functioning moiety and symptoms, heminephrectomy is indicated.</td>
<td></td>
</tr>
</tbody>
</table>

| Ectopic ureter | Diagnosis                          | Ultrasound, DMSA scan, VCUG, MRI should be used for a definitive diagnosis |
|               | Treatment                           | Choice of treatment option will depend on the function of the upper urinary tract: |
|               |                                     | - in poorly or non-functioning moieties, (hemi-) nephroureterectomy is an definite solution. |
|               |                                     | - in patients with a functioning renal moiety, ureteral reimplantation, ureteroureterostomy and ureteropyelostomy are reliable options, especially in cases in which the upper pole has function worth preserving. |

#### References


17. DISORDERS OF SEX DEVELOPMENT

17.1 Background

The formerly called ‘intersex disorders’ were recently the subject of a consensus document in which it was decided that the term ‘intersex’ should be changed to ‘disorders of sex development’ (DSD) (1,2).

The new classification has arisen because of advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues. Controversial and pejorative terminology, e.g. ‘pseudohermaphroditism’ and ‘hermaphroditism’, have been renamed according to the new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis, cloacal extrophy, which could not be categorised, have also been included. The term ‘disorders of sex development’ is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex. This will also include the idiopathic micropenis which is added here as a separate heading in this chapter on DSD.

We refer to the consensus document as a general guideline, while this chapter will focus on what is relevant for the practising paediatric urologist. As the urologist is likely to be involved in both surgical and nonsurgical neonatal work, this chapter will discuss the neonatal emergency and the diagnostic and therapeutic role of the paediatric urologist.

Overall, there is a low evidence base for the published literature on DSD. There are no randomised controlled trials and most studies are based on retrospective clinical descriptive studies (grade 4 level of evidence) or are expert opinion. An exception is the risk of gonadal cancer, for which the level of evidence is higher.

Disorders of sex development require a multidisciplinary approach to diagnosis and treatment, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD and a team should have enough new patients to ensure experience.

17.2 Micropenis

17.2.1 Background

Micropenis is a small but otherwise normally formed penis with a stretched length of less than 2.5 SD below the mean (1-3).

Besides an idiopathic micropenis, two major causes of abnormal hormonal stimulation have been identified:

- Hypogonadotrophic hypogonadism (due to an inadequate secretion of GnRH);
- Hypergonadotrophic hypogonadism (due to failure of the testes to produce testosterone).
17.2.2 **Diagnosis**

The penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans (1). The corpora cavernosa are palpated, the scrotum is often small, and the testes may be small and descended. Micropenis should be distinguished from buried and webbed penis, which is usually of normal size.

The initial evaluation has to define whether the aetiology of the micropenis is central (hypothalamic/pituitary) or testicular. A paediatric endocrinology work-up has to be carried out immediately. Karyotyping is mandatory in all patients with a micropenis.

Endocrine testicular function is assessed (baseline and stimulated testosterone, LH and FSH serum levels). Stimulated hormone levels may also give an idea of the growth potential of the penis. In patients with non-palpable testes and hypogonadotropic hypogonadism, laparoscopy should be carried out to confirm vanishing testes syndrome or intra-abdominal undescended hypoplastic testes. This investigation can be delayed until the age of 1 year (2).

17.2.3 **Treatment**

Pituitary or testicular insufficiency are treated by the paediatric endocrinologist. In patients with testicular failure and proven androgen sensitivity, androgen therapy is recommended during childhood and at puberty to stimulate the growth of the penis (4-7) (LE: 2; GR: B). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered (8-10).

17.3 **The neonatal emergency**

The first step is to recognise the possibility of DSD (Table 12) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatric centre, the situation should be explained to the parents fully and kindly. Registering and naming the newborn should be delayed as long as necessary.

17.3.1 **Family history and clinical examination**

A careful family history must be taken followed by a thorough clinical examination (Table 13).

**Table 12: Findings in a newborn suggesting the possibility of DSD (adapted from the American Academy of Pediatrics)**

<table>
<thead>
<tr>
<th>Apparent male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypospadias associated with bifid scrotum</td>
</tr>
<tr>
<td>Undescended testes/testes with hypospadias</td>
</tr>
<tr>
<td>Bilateral non-palpable testes in a full-term apparently male infant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clitoral hypertrophy of any degree, non-palpable gonads</td>
</tr>
<tr>
<td>Vulva with single opening</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambiguous genitalia</td>
</tr>
</tbody>
</table>

**Table 13: Diagnostic work-up of neonates with ambiguous genitalia**

<table>
<thead>
<tr>
<th>History (family, maternal, neonatal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental consanguinity</td>
</tr>
<tr>
<td>Previous DSD or genital anomalies</td>
</tr>
<tr>
<td>Previous neonatal deaths</td>
</tr>
<tr>
<td>Primary amenorrhoea or infertility in other family members</td>
</tr>
<tr>
<td>Maternal exposure to androgens</td>
</tr>
<tr>
<td>Failure to thrive, vomiting, diarrhoea of the neonate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmentation of genital and areolar area</td>
</tr>
<tr>
<td>Hypospadias or urogenital sinus</td>
</tr>
<tr>
<td>Size of phallus</td>
</tr>
<tr>
<td>Palpable and/or symmetrical gonads</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
</tbody>
</table>

**Investigations**

| Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH |
| Urine: adrenal steroids             |
| Karyotype                          |
| Ultrasound                         |
| Genitogram                         |
| hCG stimulation test               |
| Androgen-binding studies           |
| Endoscopy                          |

*LH = luteinizing hormone; FSH = follicle stimulating hormone; TST = testosterone; ACTH = adrenocorticotropic hormone; hCG = human chorionic gonadotrophin.*

### 17.3.2 Choice of laboratory investigations

The following laboratory investigations are mandatory:
- Karyotype;
- Plasma 17-hydroxyprogesterone assay;
- Plasma electrolytes;
- Ultrasonography to evaluate the presence of Müllerian duct structures.

These investigations will provide evidence of congenital adrenal hyperplasia (CAH), which is the most frequently occurring DSD. If this evidence is found, no further investigation is needed. If not, then the laboratory work-up should proceed further.

The hCG stimulation test is particularly helpful in differentiating the main syndromes of 46XYDSD by evaluating Leydig cell potential. When testosterone metabolism is evaluated, the presence or absence of metabolites will help to define the problem. An extended stimulation can help to define phallic growth potential and to induce testicular descent in some cases of associated cryptorchidism.

### 17.4 Gender assignment

This is a very complicated task. It should take place after a definitive diagnosis has been made. The idea that an individual is sex-neutral at birth and that rearing determines gender development is no longer the standard approach. Instead, gender assignment decisions should be based upon:
- age at presentation;
- fertility potential;
- size of the penis;
- presence of a functional vagina;
- endocrine function;
- malignancy potential;
- antenatal testosterone exposure;
- general appearance;
- psychosocial well-being and a stable gender identity.
- sociocultural aspect
- parental opinions.

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits. Minimal time needed is 48 hrs. During this period any referral to gender should be avoided, better to address the patient as “the child”, “your child”.

### 17.5 Role of the paediatric urologist

The role of the paediatric urologist can be divided into a diagnostic role and a therapeutic role (Table 14). Each of these roles will be discussed briefly.
Table 14: Role of the paediatric urologist

<table>
<thead>
<tr>
<th>Diagnostic role</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical examination</td>
</tr>
<tr>
<td>• Ultrasound</td>
</tr>
<tr>
<td>• Genitography</td>
</tr>
<tr>
<td>• Cystoscopy</td>
</tr>
<tr>
<td>• Diagnostic laparoscopy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic role</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Masculinising surgery</td>
</tr>
<tr>
<td>• Feminising surgery</td>
</tr>
<tr>
<td>• Gonadectomy</td>
</tr>
</tbody>
</table>

17.5.1 Diagnosis

17.5.1.1 Clinical examination

A good clinical examination in a neonate presenting with ambiguous genitalia is important. As well as a good description of the ambiguous genitalia, some detailed information should be given on palpability and localisation of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis.

Palpable gonad. It must be remembered that if it is possible to feel a gonad, it is almost certainly a testis; this clinical finding therefore virtually excludes 46XXDSD.

Medical photography can be useful but requires sensitivity and consent (13).

Phallus. The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening. The opening of the urogenital sinus must be well evaluated. Is there only one opening visible? Can a hymenal ring be seen? What does the fusion of the labioscrotal folds look like; do the folds show rugae or some discolouration?

17.5.1.2 Investigations

Ultrasound can help to describe the palpated gonads or to detect non-palpated gonads. However, the sensitivity and specificity are not high. On ultrasound, the Müllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utriculur structure visible? (14,15).

Genitography can provide some more information on the urogenital sinus. How low or how high is the confluence? Is there any duplication of the vagina? How does the urethra relate to the vagina?

General anaesthesia. In some cases, further examinations under general anaesthesia can be helpful. On cystoscopy, the urogenital sinus can be evaluated and the level of confluence between the bladder neck and the bladder. Cystoscopy can also be used to evaluate the vagina or utriculus, e.g. the presence of a cervix at the top of the vagina can be important information.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed (16,17).

17.6 Management

Referring to the consensus document (1,2), it is clear that the timing of surgery is much more controversial than it used to be.

The rationale for early surgery includes:

- beneficial effects of oestrogen on infant tissue;
- avoiding complications from anatomical anomalies;
- minimising family distress;
- mitigating the risks of stigmatisation and gender-identity confusion (18).

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinised genitalia and boys with undervirilised genitals. Vaginoplasty should be delayed until puberty and milder forms of
masculinisation should not be treated surgically.

17.6.1 Feminising surgery

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and clitoral surgery should therefore be limited to severely enlarged clitorises (19,20). Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown (21).

Separation of the vagina and the urethra is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively (22,23).

Vaginoplasty should be performed during the teenage years. Every technique (self dilatation, skin or bowel substitution) has its specific advantages and disadvantages (24). All carry a potential for scarring that would require further surgery before sexual function was possible.

Aesthetic refinements. The goals of genital surgery are to maximise anatomy to allow sexual function and romantic partnering. Aesthetics are important in this perspective. The reconstruction of minor labiae from an enlarged clitoral hood is an example of aesthetic refinement.

17.6.2 Masculinising surgery

Hormone therapy early in life is advocated by many doctors. The level of evidence is low for restoration of normal penile size.

Hypospadias surgery. See section on hypospadias (Chapter 6).

Excision of Mullerian structures. In the DSD patient assigned a male gender, Müllerian structures should be excised. There is no evidence about whether utricular cysts need to be excised.

Orchiopexy. See section on orchidopexy (Chapter 3).

Phalloplasty. The increasing experience of phalloplasty in the treatment of female to male transsexual patients has led to reports about the reliability and feasibility of this technique. It has therefore become available to treat severe penile inadequacy in DSD patients.

Aesthetic refinements. These include correction of penoscrotal transposition, scrotoplasty and insertion of testicular prostheses.

Gonadectomy. Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material. The highest risk is seen in patients with gonadal dysgenesis and in patients with partial androgen insensitivity with intra-abdominal gonads (LE: 2). Intra-abdominal gonads of high-risk patients should be removed at the time of diagnosis (25) (GR: A).

17.7 Guidelines for the treatment of disorders of sex development

Disorders of sex development (DSD) are the example of conditions for which a multidisciplinary approach is mandatory and gold standard. These children should be referred to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.

Any neonate presenting with ambiguous genitalia is an emergency since salt-losing in a 46XX CAH girl can be fatal.

Gender assignment is imminent and should be based on multidisciplinary consensus taking into account the latest knowledge.

Timing of surgery will be dependent on the severity of the condition and on the assigned sex.
- In severe anomalies in girls early surgical treatment is indicated.
- In less severe cases, in consultation with the parents, a more conservative approach might be followed.
- In boys the surgical correction will mainly consist of hypospadias repair and orchiopexy, so the timing will follow the recommendations for hypospadias repair and orchiopexy (from 6 months onwards and before 2 years of age).
17.8 References


18. POSTERIOR URETHRAL VALVES

18.1 Background
Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. Despite optimal treatment, PUV in children may result in renal insufficiency in nearly one-third of cases (1-3). PUV are found in 1 in 1,250 in a population undergoing foetal ultrasound screening (4). An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated (5,6). In one report, up to 46% of foetuses with a PUV diagnosis were terminated, indicating a possible decrease in incidence(7).

18.2 Classification

18.2.1 Urethral valve
Despite recent attempts to introduce new classification terms, such as ‘congenital obstructive posterior urethral membrane (COPUM)’ (8), the original classification by Hugh Hampton Young remains the most commonly used (9).

Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young’s descriptions of type I and III are as follows:

Type I (90-95%). ‘In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbo-membranous junction. These processes are continued as thin membranous sheets, direct upward and forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet the fusion of the valves anteriorly may not be complete in all cases, and at this point a slight separation of the folds exists (9).

Type III. ‘There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the uretha, with a small opening in the centre (9).

The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane (10). The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca (11).

18.3 Diagnosis
An obstruction above the level of the urethra affects the whole urinary tract in varying degrees.

• The prostatic urethra is distended and the ejaculatory ducts may be dilated due to urinary reflux. The
The hypertrophied bladder occasionally has multiple diverticula. Nearly all valve patients have dilatation of both upper urinary tracts. This may be due to the valve itself and the high pressure in the bladder, or due to obstruction of the ureterovesical junction by the hypertrophied bladder. If there is secondary reflux, the affected kidney functions poorly in most cases.

During prenatal ultrasonography screening, bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. If a dilated posterior urethra and a thick-walled bladder ('keyhole' sign) are seen, a PUV is likely. In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

VCUG confirms a PUV diagnosis. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV (12). Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a ‘pressure pop-off valve’, which would protect the other kidney, leading to a better prognosis (13). Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites (14). However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV (15,16).

Nuclear renography with split renal function is important to assess kidney function. Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. A nadir creatinine of 80 μmol/L is correlated with a better prognosis (3).

18.4 Treatment

18.4.1 Antenatal treatment

About 40-60% of PUV are discovered before birth (17). The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amniotic fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem. Intrauterine attempts have been made to treat a foetus with PUV.

As renal dysplasia is not reversible, it is important to identify those foetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of < 90mmol/L and an osmolarity below 200 mOsm/L found in three foetal urine samples gained on three different days are associated with a better prognosis (18).

The placing of a vesicoamniotic shunt has a complication rate of 21-59%, dislocation of the shunt occurs in up to 44%, mortality lies between 33% and 43%, and renal insufficiency is above 50% (18-20). Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and long-term results of patients with PUV (19,20).

18.4.2 Postnatal treatment

Bladder drainage. If a boy is born with suspected PUV, drainage of the bladder and, if possible, an immediate VCUG is necessary. A neonate can be catheterised with a 3.5-5 F catheter. Balloon catheters are not available in this size. A VCUG is performed to see if the diagnosis is correct and whether the catheter is within the bladder and not in the posterior urethra. An alternative option is to place a suprapubic catheter, perform a VCUG and leave the tube until the neonate is stable enough to perform an endoscopic incision or resection of the valve.

Valve ablation. When the medical situation of the neonate has stabilised and the creatinine level decreased, the next step is to remove the intravesical obstruction. Small paediatric cystoscopes and resectoscopes are now available either to incise or to resect the valve at the 4-5, 7-8 or 12 o’clock position, or at all three positions, depending on the surgeon’s preference. It is important to avoid extensive electrocoagulation, as the most common complication of this procedure is stricture formation. One recently published studied demonstrated a significant lower urethral stricture rate using the cold knife compared to diathermy (21).

Vesicostomy. If the child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is used to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for 6-12 weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of upper urinary tracts in over 90% of cases (22). Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations (23,24).

High diversion. If bladder drainage is insufficient to drain the upper urinary tract, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice...
of urinary diversion depends on the surgeon’s preference for high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages (25-27). Reconstructive surgery should be delayed until the upper urinary tract has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% (28). During the first months of life, antibiotic prophylaxis may be given especially in those with high grade reflux (29) and in those with a phimosis, circumcision can be discussed in order to reduce the risk of urinary tract infections (30). However, there are no randomized studies to support this for patients with PUV. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor (1,31). However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. It may be necessary to augment the bladder and in this case the ureter may be used (32).

Life-long monitoring of these patients is mandatory, as bladder dysfunction is not uncommon and the delay in day- and night-time continence is a major problem (12,3). Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder instability, anticholinergic therapy can improve bladder function. However, with a low risk of reversible myogenic failure (3 out of 37 patients in one study) (33,34). Between 10% and 47% of patients may develop end-stage renal failure (1-3). Renal transplantation in these patients can be performed safely and effectively (35,36). Deterioration of the graft function is mainly related to lower urinary tract dysfunction (37,38).
Figure 6. An algorithm providing information on assessment, treatment and follow up of newborns with possible PUV

Newborn with possible PUV, UUT dilatation and renal insufficiency

- USG and VCUG
- Assessment of renal function and electrolyte disorders

Confirm diagnosis

Bladder drainage

Nephrological care if needed

No stabilisation

Valve ablation when baby is stable

Improvement in UT dilation and RF

- Close follow-up
- Monitor urinary infection
- Monitor renal function
- Monitor bladder function and emptying

No improvement but stable

No improvement and ill

Consider diversion

Short term

- Check residual PUV
- CIC if not emptying
- Consider overnight drainage
- Consider alpha-blockers
- Anticholinergics if OAB

Long term

Consider augmentation and Mitrofanoff

PUV = posterior urethral valve; UUT = upper urinary tract; USG = urinary specific gravity; VCUG = voiding cystourethrogram; UT = urinary tract; RF = renal function; CIC = clean intermittent catheterization; OAB = overactive bladder.
18.5 Summary
Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period and despite optimal treatment result in renal insufficiency in nearly one-third of cases. Bilateral hydronephrosis and a distended bladder are suspicious signs of a PUV in the neonates. A voiding cystourethrogram (VCUG) confirms a PUV diagnosis. Nuclear renography with split renal function assess kidney function and serum creatinine nadir above 80 μmol/L is correlated with a poor prognosis.

Postnatal treatment includes bladder drainage either transurethral or suprapubic and if the child is stable enough, endoscopic incision of the valve is performed. If a child too small and/or too ill to undergo endoscopic surgery, a vesicostomy is an option for bladder drainage. If bladder drainage is insufficient to drain the upper urinary tract, high urinary diversion should be considered.

In all patients life-long monitoring is mandatory, as bladder dysfunction is quite common and may cause progressive upper tract deterioration, if not managed properly. In the long run between 10% and 47% of patients may develop end-stage renal failure. Renal transplantation in these patients can be performed safely and effectively.

18.6 Conclusions and recommendations posterior urethral valves

<table>
<thead>
<tr>
<th>PUV</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>An ultrasound can indicate an anomaly, but a VCUG is required to confirm the diagnosis. - Split renal function is to be assessed by DMSA scan. - Serum creatinine is the prognostic marker.</td>
<td>3</td>
</tr>
<tr>
<td>Treatment antenatal</td>
<td>A vesico-amniotic shunt is effective in reversing oligohydramnios, but it has a relatively high complication rate. There is no difference in the renal outcome and long-term results.</td>
<td>3</td>
</tr>
<tr>
<td>Treatment postnatal</td>
<td>After bladder drainage and stabilization of the child, endoscopic valve ablation should be performed. - In case the child is too small, a vesicostomy is an option for bladder drainage. - If bladder drainage is insufficient to drain the upper urinary tract, high urinary diversion should be considered (see Fig. 6).</td>
<td>3</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Life-long monitoring is mandatory (bladder dysfunction; end-stage renal failure) in all patients. - Those with serum creatinine nadir above 80μmol/L have a poor prognosis. Despite optimal treatment 10-47% of cases develop end-stage renal failure. - Renal transplantation can safely be performed if bladder function is stable.</td>
<td>3</td>
</tr>
</tbody>
</table>

DMSA = dimercaptosuccinic acid scan; VCUG = voiding cystourethrogram.

18.7 References
19. **PAEDIATRIC UROLOGICAL TRAUMA**

19.1 **Background**

Trauma is the leading cause of morbidity and mortality in children and is responsible for more childhood deaths than the total of all other causes (1). In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract (2). This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, and sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

19.2 **Paediatric renal trauma**

In blunt abdominal trauma, the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries (1). Children are more likely than adults to sustain renal injuries after blunt trauma because of their anatomy. Compared to an adult kidney, a child’s kidney is larger in relation to the rest of the body and often retains foetal lobulations, so that blunt trauma is more likely to lead to a local parenchymal disruption. The
paediatric kidney is also less well protected than the adult kidney. Children have less perirenal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage (3).

Blunt renal trauma is usually a result of sudden deceleration of the child’s body, particularly due to sport accidents, falls, and contact with blunt objects. Deceleration or crush injuries result in contusion, laceration or avulsion of the less well-protected paediatric renal parenchyma.

19.2.1 Diagnosis
In a child who has sustained blunt abdominal trauma, renal involvement can often be predicted from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures or vertebral pedicles, trunk contusions and abrasions, and haematuria.

19.2.1.1 Haematuria
Haematuria may be a reliable finding. In severe renal injuries, 65% suffer gross haematuria and 33% micro-haematuria, while only 2% have no haematuria at all (4).

The radiographic evaluation of children with suspected renal trauma remains controversial. Some centres rely on the presence of haematuria to diagnose renal trauma, with a threshold for renal involvement of 50 RBCs/HPF. Although this may be a reliable threshold for significant micro-haematuria in trauma, there have been many reports of significant renal injuries that manifest with little or even no blood in the urine (5). It is therefore compulsory to consider all the clinical aspects involved, including the history, physical examination, consciousness of the child, overall clinical status and laboratory findings to decide on the diagnostic algorithm and whether or not a child needs further imaging studies.

19.2.1.2 Blood pressure
It is important to consider that children, unlike adults, are able to maintain their blood pressure, even in the presence of hypovolaemia, due to compliance of the vascular tree and mechanisms for cardiac compensation (6).

Because blood pressure is an unreliable predictor of renal involvement in children, some centres recommend imaging of the urinary tract in children with any degree of haematuria following significant abdominal trauma.

19.2.1.2 Choice of imaging method
Nowadays, computed tomography (CT) is the best imaging method for renal involvement in children. CT scanning is the cornerstone of modern staging of blunt renal injuries especially when it comes to grading the severity of renal trauma. Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 15) (7).

CT scanning is quite rapid and usually performed with the injection of contrast media. To detect extravasation, a second series of images is necessary since the initial series usually finishes 60 seconds after injection of the contrast material and may therefore fail to detect urinary extravasation (8).

In acute trauma ultrasound may be used as a screening tool and for reliably following the course of renal injury. However, ultrasound is of limited value in the initial and acute evaluation of trauma. The standard IVP is a good alternative imaging method if a CT scan is not available. It is superior to ultrasound but not as good as CT scanning for diagnostic purposes.

Table 15: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma (7).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of injury</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Contusion</td>
<td>Microscopic or gross haematuria</td>
</tr>
<tr>
<td></td>
<td>Haematoma</td>
<td>Normal urological studies</td>
</tr>
<tr>
<td>II</td>
<td>Haematoma</td>
<td>Non-expanding subcapsular haematoma</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>Laceration of the cortex of less than 1.0 cm</td>
</tr>
<tr>
<td>III</td>
<td>Laceration</td>
<td>Laceration &gt; 1.0 cm without rupture of collecting system</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Through the cortex, medulla and collecting system</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Vascular injury</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Completely shattered kidney</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Avulsion of the renal hilum</td>
</tr>
</tbody>
</table>
19.2.2 Treatment
The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists, and other specialties as required.

Non-surgical conservative management with bed rest, fluids and monitoring has become the standard approach for treating blunt renal trauma. Even in high-grade renal injuries, a conservative approach is effective and recommended for stable children. However, this approach requires close clinical observation, serial CT scans, and frequent re-assessment of the patient’s overall condition.

Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue (9).

19.2.3 Guidelines for the diagnosis and treatment of paediatric renal trauma

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging is recommended in all children who have sustained a blunt or penetrating trauma with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.</td>
<td>B</td>
</tr>
<tr>
<td>Rapid spiral CT scanning is the cornerstone in the diagnostic work-up and allows accurate staging.</td>
<td>B</td>
</tr>
<tr>
<td>Most injured kidneys can be managed conservatively.</td>
<td>B</td>
</tr>
<tr>
<td>Haemodynamic instability and a Grade V renal injury are absolute indications for surgical intervention.</td>
<td>A</td>
</tr>
</tbody>
</table>

19.3 Paediatric ureteral trauma
Injuries to the ureter are rare. The ureter is well protected; the upper part is protected by its close approximation to the vertebral column and paraspinal muscles and the lower part by its route through the bony pelvis. In addition, the ureter is a small target, and both flexible and mobile. This also means that ureteral injuries are caused more often by penetrating trauma than blunt trauma (10). Since the ureter is the sole conduit for urinary transport between the kidney and the bladder, any ureteral injury can threaten the function of the ipsilateral kidney.

19.3.1 Diagnosis
Since there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic work-up using different imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable; a study of 11 disruptions of the ureteropelvic junction found that 72% had a normal or non-diagnostic IVP on initial studies (10). Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to 10 minutes after injection of the contrast material (11). The most sensitive diagnostic test is a retrograde pyelogram.

Quite a few patients present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever.

Because the symptoms may often be quite vague, it is important to remain suspicious for a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

19.3.2 Treatment
Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries (12).

If endoscopic management is not possible, primary repair of partial lacerations should be followed by internal stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and its location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary re-anastomosis is not achievable, distal ureteral injuries can be managed using a psoas bladder hitch, Boari flap or even nephropexy. Proximal injuries can be managed using transureteroureterostomy, autotransplantation or ureteral replacement with bowel of appendix (13).
19.3.3  **Guidelines for the diagnosis and treatment of paediatric ureteral trauma**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde pyelogram is the most sensitive diagnostic method and is the method of choice. However, in the initial phase of an injury, it is very likely that ureteral injuries will not be detected by routine imaging methods, including contrast-enhanced spiral CT.</td>
<td>A</td>
</tr>
<tr>
<td>Endoscopic treatment is the method of choice, such as internal stenting or drainage of a urinoma, either percutaneously or via a nephrostomy tube.</td>
<td>B</td>
</tr>
<tr>
<td>For distal and proximal ureteral injuries, open procedures are the methods of choice.</td>
<td>B</td>
</tr>
<tr>
<td>For distal injuries, they include direct re-anastomosis and ureteroneocystostomy.</td>
<td>B</td>
</tr>
<tr>
<td>For proximal injuries, they include transureteroureterostomy, ureteral replacement with bowel or appendix, or even autotransplantation.</td>
<td>B</td>
</tr>
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</table>

19.4  **Paediatric bladder injuries**

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries than the adult bladder, especially when it is full, due to:
- The paediatric bladder has a higher position in the abdomen and is exposed above the bony pelvis.
- The abdominal wall provides less muscular protection.
- There is less pelvic and abdominal fat surrounding the bladder to cushion it in trauma.

Blunt trauma is the most common cause of significant bladder injury. In adults, bladder injury is often associated with pelvic fractures. This is less common in children because the paediatric bladder sits above the pelvic ring. Thus, only 57% of children with pelvic fractures also had a bladder injury compared to 89% of adults (14).

19.4.1  **Diagnosis**

The characteristic signs of bladder injury are suprapubic pain and tenderness, an inability to urinate, and gross haematuria (95% of injuries). Patients with a pelvic fracture and gross haematuria present with a bladder rupture in up to 45% of cases (15).

The diagnosis of bladder rupture can be difficult in some cases. The bladder should be imaged both when fully distended and after drainage using standard radiography or a CT scan. The best results can be achieved by retrograde filling of the bladder using a catheter. Despite advances in CT imaging, the bladder must still be filled to capacity to accurately diagnose a possible bladder injury (16).

Blunt injuries to the bladder are categorized as:
- contusions with damage to the bladder mucosa or muscle, without loss of bladder wall continuity or extravasation, or,
- ruptures, which are either intraperitoneal or extraperitoneal.

Intraperitoneal bladder ruptures are more common in children because of the bladder’s exposed position and the acute increase in pressure during trauma. These cause the bladder to burst at its weakest point, i.e. the dome.

Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram will show extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

19.4.2  **Treatment**

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

19.4.2.1  **Intraperitoneal injuries**

The accepted management of intraperitoneal bladder ruptures is open surgical exploration and primary repair. Post-operative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be as effective, with fewer complications, resulting in shorter periods of diversion (17). Usually, after about 7-10 days, a repeat cystogram is performed to ensure healing is taking place properly.

19.4.2.2  **Extraperitoneal injuries**

Non-operative management with catheter drainage for 7-10 days alone is the method of choice for extraperitoneal bladder rupture. However, if there are bone fragments within the bladder, these must be removed and the bladder must then be repaired and drained, according to the principles for treating intraperitoneal ruptures (18).
19.4.3 Guidelines for the diagnosis and treatment of paediatric bladder injuries

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde cystography will allow for an accurate diagnosis, provided that the bladder has been filled full to its capacity and an additional film is taken after drainage.</td>
<td>A</td>
</tr>
<tr>
<td>Extraperitoneal bladder ruptures are usually managed conservatively with a transurethral catheter left in place for 7-10 days.</td>
<td>A</td>
</tr>
<tr>
<td>Intraperitoneal bladder ruptures require immediate surgical exploration and repair as well as post-operative drainage for 7-10 days.</td>
<td>A</td>
</tr>
</tbody>
</table>

19.5 Paediatric urethral injuries

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity mean the urethra is seldom injured by trauma. However, a urethral injury should be suspected in any patient with a pelvic fracture or significant trauma to the perineum until confirmed otherwise by a diagnostic work-up.

19.5.1 Diagnosis

Patients with suspected urethral trauma and pelvic fractures usually present with a history of severe trauma, often involving other organ systems.

Signs of urethral injury are blood at the meatus, gross haematuria, and pain during voiding or an inability to void. There may also be perineal swelling and haematoma involving the scrotum.

A rectal examination to determine the position and fixation of the prostate is important in any male with a suspected urethral injury. The prostate, as well as the bladder, may be displaced up out of the pelvis, especially in membranous urethral trauma.

Radiographic evaluation of the urethra requires a retrograde urethrogram. It is important to expose the entire urethral length, including the bladder neck. If a catheter has already been placed by someone else and there is suspected urethral trauma, the catheter should be left in place and should not be removed. Instead, a small infant feeding tube can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan (19).

19.5.2 Treatment

Since many of these patients are unstable, the urologist’s initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed.

A suprapubic tube may be placed in the emergency department percutaneously, or even in the operating room, if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbous urethral or straddle injury and management is therefore usually straightforward. In these cases, a transurethral catheter is the best option for preventing urethral bleeding and/or painful voiding (20).

The initial management of posterior urethral injuries remains controversial, mainly regarding the long-term results with primary realignment compared to simple suprapubic drainage with later reconstruction.

The main goals in the surgical repair of posterior urethral injuries are:

• providing a stricture-free urethra
• avoiding the complications of urinary incontinence and impotence.

Suprapubic drainage and late urethral reconstruction was first attempted because immediate surgical repair had a poor outcome, with significant bleeding and high rates of incontinence (21%) and impotence in up to 56% of cases (21). In adults, a study of the success rates of delayed repair reported re-structure rates of 11-30%, continence rates of 90-95% and impotence rates of 62-68% (22). However, in children, there is much less experience with delayed repair. The largest paediatric series of delayed repair in 68 boys reported a success rate of 90% (23). Another study reported strictures and impotence in 67% of boys, although all the boys were continent (22).

An alternative to providing initial suprapubic drainage and delayed repair is primary realignment of the urethra via a catheter. The catheter is usually put in place during open cystostomy by passing it from either the bladder neck or meatus and through the injured segment. In a series of 14 children undergoing this procedure,
this resulted in a stricture rate of 29% and incontinence in 7% (24).

19.5.3 **Guidelines for the diagnosis and treatment of paediatric trauma**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging of the urethra with a retrograde urethrogram is mandatory in suspected urethral trauma.</td>
<td>A</td>
</tr>
<tr>
<td>Rectal examination is recommended to determine the position of the prostate.</td>
<td>B</td>
</tr>
<tr>
<td>Bulbous urethral injuries can usually be managed conservatively with a transurethral catheter.</td>
<td>B</td>
</tr>
<tr>
<td>There is still controversy about the optimal management for posterior urethral disruption. The options include primary reconstruction; primary drainage with a suprapubic catheter alone and delayed repair; primary re-alignment with a transurethral catheter.</td>
<td>C</td>
</tr>
</tbody>
</table>

19.6 **References**

20. POST-OPERATIVE FLUID MANAGEMENT

20.1 Background
It is often stated that children are not simply small adults. Children are growing and developing organisms, with specific metabolic features. Compared to adults, children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms (1). Because they are developing organisms, children have a high metabolic rate and low body stores of fat and other nutrients, which means they are more susceptible to metabolic disturbances caused by surgical stress (2). The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation (3).

20.2 Pre-operative fasting
Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. Table 16 gives the current guidelines for pre-operative fasting for elective surgery (4,5).

Table 16: Pre-operative fasting times for elective surgery

<table>
<thead>
<tr>
<th>Ingested material</th>
<th>Minimum fasting period (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear liquids</td>
<td>2</td>
</tr>
<tr>
<td>Breast milk</td>
<td>4</td>
</tr>
<tr>
<td>Infant formula</td>
<td>4 (&lt; 3 months old) to 6 (&gt; 3 months old)</td>
</tr>
<tr>
<td>Non-human milk</td>
<td>6</td>
</tr>
<tr>
<td>Light meal</td>
<td>6</td>
</tr>
</tbody>
</table>

Although hypoglycaemia is an important issue in children, research has shown that hypoglycaemia is uncommon if children are still fed up to 4 h before the induction of anaesthesia (6). Newborns often have low glycogen stores and impaired gluconeogenesis, both of which can be helped by limiting the period of pre-operative starvation and feeding with glucose-containing solutions. It is important to monitor blood glucose...
and to adjust the glucose supply continuously in neonates and those children who are small for their age, as this helps to prevent excessive fluctuation in blood glucose levels (7).

20.3 Maintenance therapy and intra-operative fluid therapy

Generally, the anaesthetist is responsible for intra-operative management and the surgeon is responsible for post-operative instructions. The goal of intra-operative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid; this maintains adequate intravascular volume, cardiac output and oxygen delivery to tissues at a time when normal physiological functions have been altered by surgical stress and anaesthetic agents (7).

The fluids for maintenance therapy replace losses from two sources: insensible (evaporation) and urinary loss. They do not take replace blood loss or third-space fluid loss into the interstitial space or gut. The main formulae for calculating the daily maintenance requirement for water requirement have not changed in the past 50 years (Table 17) (8). Calculations have shown that anaesthetised and non-anaesthetised children have similar fluid requirements (9).

The combination of maintenance fluid and electrolyte requirements results in a hypotonic electrolyte solution. The usual intravenous maintenance fluid given to children by paediatricians is one-quarter to one-third strength saline (4,10).

Table 17: Hourly and daily fluid requirements according to body weight

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Hourly</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 kg</td>
<td>4 mL/kg</td>
<td>100 mL/kg</td>
</tr>
<tr>
<td>10-20 kg</td>
<td>40 mL + 2 mL/kg; &gt; 10 kg</td>
<td>1000 mL + 50 mL/kg; &gt; 10 kg</td>
</tr>
<tr>
<td>&gt; 20 kg</td>
<td>60 mL + 1 mL/kg; &gt; 20 kg</td>
<td>1500 mL+ 20 mL/kg; &gt; 20 kg</td>
</tr>
</tbody>
</table>

The fasting deficit is calculated by multiplying the hourly maintenance fluid requirement by the number of hours of fluid restriction. It is recommended that 50% of the fasting deficit is replaced in the first hour and 25% in the second and third hours (11). Berry (1986) proposed simplified guidelines for fluid administration according to the child’s age and severity of surgical trauma (12) (Table 18).

Table 18: Intra-operative fluid management adapted for children fasted for 6-8 h, following the classical recommendation ‘nil per oral after midnight’

<table>
<thead>
<tr>
<th>Hour of fluid replacement</th>
<th>Maintenance fluid</th>
<th>Fasting deficit replacement</th>
<th>Persistent losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hour</td>
<td>As Table 16</td>
<td>50%</td>
<td>Third space + blood loss replacement</td>
</tr>
<tr>
<td>Second hour</td>
<td>As Table 16</td>
<td>25%</td>
<td>Third space + blood loss replacement</td>
</tr>
<tr>
<td>Third hour</td>
<td>As Table 16</td>
<td>25%</td>
<td>Third space + blood loss replacement</td>
</tr>
<tr>
<td>Berry (12)</td>
<td></td>
<td></td>
<td>Blood replacement</td>
</tr>
<tr>
<td>First hour</td>
<td>≤ 3 years: 25 mL/kg</td>
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<tr>
<td></td>
<td>≥ 4 years: 15 mL/kg</td>
<td>Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids</td>
<td></td>
</tr>
<tr>
<td>All other hours</td>
<td>Maintenance volume = 4 mL/kg/h</td>
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<tr>
<td></td>
<td>Maintenance + mild trauma = 6 mL/kg/h</td>
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<tr>
<td></td>
<td>Maintenance + moderate trauma = 8 mL/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance + severe trauma = 10 mL/kg/h</td>
<td>Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids</td>
<td></td>
</tr>
</tbody>
</table>

* Reduce the amount of fluid given during the first hour if children are fasting for a shorter period of time, or if the child was already being given intravenous fluid prior to surgery.

Five percent dextrose with one-quarter- to half-normal saline is often used as a maintenance fluid, while balanced salt solution or normal saline is used as replacement fluid. Blood losses are replaced with a 1:1 ratio of blood or colloid or a 3:1 ratio of crystalloid. However, the administration of a large volume of normal saline can cause dilutional acidosis or hyperchloremic acidosis, while a large volume of balanced salt solution, such as lactated Ringer’s solution, can decrease serum osmolality, which is not beneficial in patients with decreased
intracranial compliance. If appropriate, albumin, plasma, synthetic colloids, and blood should be administered (7).

Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to 15-20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotising enterocolitis in premature infants. Third-space losses should be replaced with crystalloids (normal saline or Ringer’s lactate) (4).

Most of the fluids required during surgery are needed to replace fasting deficit or third-space losses, which are mainly extracellular fluids. Hydrating solutions should contain high concentrations of sodium and chloride and low concentrations of bicarbonate, calcium and potassium.

Intra-operative hypoglycaemia is rare in children. In contrast, hyperglycaemia is commonly encountered during anaesthesia and surgery. The replacement fluid should be free of dextrose or should not have > 1% dextrose. Current recommendations include the use of low-dextrose-containing solutions for maintenance fluid therapy, except in patients who are at high risk of hypoglycaemia (1,10). Intra-operative administration of glucose-free isotonic hydrating solutions should be the routine practice for most procedures in children over 4-5 years of age. In infants and young children, 5% dextrose solutions should be avoided, but it is appropriate to use 1% or 2% dextrose in lactated Ringer’s solution (4).

20.4 Post-operative fluid management

During the post-operative period, the fundamental principle is to monitor gastrointestinal function and to continue oral or enteral nutrition as much as possible (2), while remembering that withholding oral fluids post-operatively from children undergoing day surgery helps prevent vomiting (13). In minor surgical procedures, intra-operative administration of large volumes of crystalloids is associated with a reduced incidence of post-operative nausea and vomiting after anaesthesia in both paediatric and adult patients (14). Berry’s fluid replacement guidelines can be followed, provided the child is given lactated Ringer’s solution or polyionique B66, which has an osmolarity similar to plasma (15).

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative renal and hepatic function. However, if oral intake has been postponed for > 24 h (e.g. as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent management, particularly with potassium. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalemia, which may be corrected with a solution of 20 mmol/L potassium and an infusion rate of not more than 3 mmol/kg/day. The potassium should be given via peripheral venous access if the duration of infusion is not expected to exceed 5 days, or via central venous access when long-term parenteral nutrition is necessary.

The goals of fluid therapy are to provide basic metabolic requirements and to compensate for gastrointestinal and additional losses. If hypovolemia is present, it should be treated rapidly. Hyponatremia is the most frequent electrolyte disorder in the post-operative period (15,16). This means that hypotonic fluid should not be routinely administered to hospitalised children because they have several stimuli for producing arginine vasopressin and are therefore at high risk for developing hyponatremia (4,15,17-20). The preferred fluids for maintenance therapy are 0.45% saline with dextrose or isotonic fluids, in the absence of a specific indication for 0.25% saline. It is also advisable to administer isotonic fluids intra-operatively and also immediately post-operatively, albeit at two-thirds of the calculated maintenance rate in the recovery room. Fluid composition should balance high sodium requirements, energy requirements and solution osmolarity. The extra losses from gastric or chest tubes should be replaced with lactated Ringer’s solution. Fluid that has been given to dilute medications must also be taken into account (4).

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially the risk of polyuria due to post-obstructive diuresis. In children who develop polyuria, it is important to monitor fluid intake and urine output, as well as renal function and serum electrolytes.

If necessary, clinicians should not feel any hesitation about consulting with a paediatric nephrologist.

20.5 Post-operative fasting

It has been reported that fasting reduces the risk of vomiting by up to 50% (13,21,22). However, a recent study has found that, if children were freely allowed to drink and eat when they felt ready or requested it, the incidence of vomiting did not increase and the children felt happier and were significantly less bothered by pain than children who were fasting (23). The mean times until first drink and first eating in the children who were free to eat or drink were 108 and 270 min, respectively, which were 4 h and 3 h earlier than in the fasting group. Previous studies have suggested that gastric motility returns to normal 1 h after emergence from anaesthesia in children who have undergone non-abdominal surgery (24). The first oral intake in children at 1 h after emergence from anaesthesia for minor surgery did not cause an increase in the incidence of vomiting, provided that the fluid ingested was at body temperature (25). The EAU Panel members therefore recommend encouraging an early intake of fluid in children who have undergone minor or non-abdominal urological surgery.
## 20.6 Summary conclusions and recommendations

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children are not simply smaller physiological versions of adults. They have their own unique metabolic features, which must be considered during surgery.</td>
<td>2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative fasting periods for elective surgeries (up to 4 h) can be shorter than normally used.</td>
<td>B</td>
</tr>
<tr>
<td>Care should be taken for hyperglycaemia, which is common in children, compared to intra-operative hypoglycaemia, which is very rare. Fluids with lower dextrose concentrations should therefore be considered.</td>
<td>B</td>
</tr>
<tr>
<td>Avoid the routine use of hypotonic fluid in hospitalised children because they are at high risk of developing hyponatremia.</td>
<td>A</td>
</tr>
<tr>
<td>There is an increased risk of electrolyte abnormalities in children undergoing surgery. It is therefore essential to measure the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen.</td>
<td>B</td>
</tr>
<tr>
<td>In patients treated with minor surgical procedures, early oral fluid intake should be encouraged.</td>
<td>A</td>
</tr>
</tbody>
</table>

## 20.7 References


21. POST-OPERATIVE PAIN MANAGEMENT IN CHILDREN: GENERAL INFORMATION

21.1 Introduction
The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia (1). However, there is still no standardised algorithm for management of post-operative pain in children (2). There is an urgent need for a post-operative pain management protocol in children, particularly for guidance on the frequency of pain assessment, use of parenteral opioids, introduction of regional anaesthesia, and the application of rescue analgesics (3).

Traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned following recent and better understanding of how the pain system matures in humans, better pain assessment methods and a knowledge of the clinical consequences of pain in neonates (4-8). Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and somatic...

21.2 Assessment of pain
Assessment of pain is the first step of pain management. Validated pain assessment tools are needed for this purpose and it is important to select the appropriate pain assessment technique. Several pain assessment tools have been developed according to the child’s age, cultural background, mental status, communication skills and physiological reactions (14,15).

One of the most important topics in paediatric pain management is informing and involving the child and parents during this process. Parents and patients can manage post-operative pain at home or in hospital if provided with the correct information. Parents and patients, if they are old enough, can actively take part in pain management in patient-family-controlled analgesia applications (16-21).

21.3 Drugs and route of administration
Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitization occurs (22). Local anaesthetics or non-steroidal analgesics are given intra-operatively to delay post-operative pain and to decrease post-operative analgesic consumption. Analgesics must be titrated until an appropriate response is achieved. Opioids can be administered to children by the oral, mucosal, transdermal, subcutaneous, intramuscular or intravenous routes (18). The combination of opioids with non-steroidal anti-inflammatory drugs (NSAIDs) or local anaesthetics (balanced or multimodal analgesia) can be used to increase the quality of analgesia and decrease undesired effects related to opioids (23). The same combination of local anaesthetics, opioids, and non-opioid drugs used in adults can also be used in children taking into account their age, body weight and individual medical status.

The World Health Organization’s ‘pain ladder’ is a useful tool for the pain management strategy (24). A three-level strategy seems practical for clinical use. Post-operative management should be based on sufficient intra-operative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia.

Paracetamol and NSAIDs are the drugs of choice at the first level. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. Every institute must build their own strategy for post-operative analgesia. A proposed strategy for post-operative analgesia may be as follows:

1. Intra-operative regional or caudal block
2. Paracetamol + NSAID
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine)
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine)

21.4 Circumcision
Circumcision without anaesthesia, irrespective of age, is not recommended. Circumcision requires proper pain management (28). Despite this, adequate pain management is still below expectation (29). Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (e.g. lidocaine-prilocaine cream, or 4% liposomal lidocaine cream), a less painful clamp (e.g. Mogen clamp), a pacifier, sucrose, and swaddling, preferably in combination (30-35).

Although DPNB and topical anaesthetics seem to have a similar post-operative analgesic effect, DPNB is still the most preferred method (33) (LE: 1a). Ultrasonographic guidance may improve the results, with an increase in procedural time (36,37). Caudal blockade methods have similar efficacy compared to DPNB. However, parents should be informed about the more frequent incidence of post-operative motor weakness and micturition problems (38-43).

21.5 Penile, inguinal and scrotal surgery
Caudal block is the most studied method for analgesia following surgery for hypospadias. Several agents with different doses, concentrations and administration techniques have been used with similar outcomes (44-58). Both single and combined use of these agents is effective (46,48,53,54,56,57).

Penile blocks can be used for post-operative analgesia and have similar post-operative analgesic properties as caudal blocks (59). Two penile blocks at the beginning and end of surgery seems to provide better pain relief (60). Severe bladder spasms caused by the presence of the bladder catheter may sometimes cause more problems than pain and is managed with antimuscarinic medications.

For inguinoscrotal surgery, all anaesthetic methods, such as caudal blocks (61-65), nerve block (66,67), wound infiltration or instillation, and irrigation with local anaesthetics (68-70), have been shown to have adequate post-operative analgesic properties. Combinations may improve the results (71).
Table 19: List of several drugs used in post-operative pain management in children (5,13,19,25-27)

<table>
<thead>
<tr>
<th>Name</th>
<th>Route of administration</th>
<th>Dose</th>
<th>Side effects</th>
<th>General remarks</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-narcotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acetaminophen</td>
<td>Rectal, Oral, Intravenous</td>
<td>40 mg/kg loading, 20 mg/kg/dose 4 times/day 15-40 mg/kg, followed by 30 mg/kg/8 h Propacetamol (prodrug)</td>
<td>Nephrotoxicity, hepatotoxicity (neonates)</td>
<td>Most common used analgesic Antipyretic effect Opioid-sparing effect Wide safety range</td>
<td>Slow onset time and variable absorption via the rectal route; dividing the vehicle is not recommended. Total dose should not exceed: 100 mg/kg for children; 75 mg/kg for infants; 60 mg/kg for term and preterm neonates &gt; 32 weeks post-conceptual age; and 40 mg/kg for preterm neonates &lt; 32 weeks post-conceptual age</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Oral, rectal</td>
<td>4-10 mg/kg/dose 3-4 times/day</td>
<td></td>
<td>Better analgesic than paracetamol</td>
<td>Safety not established for infants &lt; 6 months old</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Tablet, syrup, suppository</td>
<td>1-1.5 mg/kg 2-3 times/day</td>
<td>Nephrotoxicity, gastrointestinal disturbances</td>
<td>Better than ibuprofen</td>
<td>&gt; 6 years old</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Oral, IV, IM</td>
<td>0.2-0.5 mg/kg every 6 h (48 h) Total dose &lt; 2 mg/kg/day, maximum 5 days</td>
<td></td>
<td>Opioid-sparing effect</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>Oral, rectal, IM, SC, IV, intraspinal</td>
<td>&lt; 2 mg/kg (IM) &lt; 1 mg/kg (IV, epidural)</td>
<td></td>
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<tr>
<td>Metamizole, dipyrene</td>
<td>Oral, IM, Oral drop</td>
<td>10-15 mg/kg/dose (max 40 mg/kg total) 10-15 mg/kg 1 drop/kg/dose, up to 4 times/day</td>
<td>Risk of agranulocytosis, not clarified definitely</td>
<td>Very effective antipyretic</td>
<td>Not approved in some countries including USA, Sweden, Japan and Australia</td>
</tr>
<tr>
<td><strong>Narcotics</strong></td>
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<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td>Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol (weak opioid)</td>
<td>Oral, rectal, IV, IM (dose can be repeated 4-6 times/day)</td>
<td>2-3 mg/kg/dose (oral, drop) 1-2 mg/kg/dose (oral, tablet) 1.5-3 mg/kg/dose (rectal) 0.75-2 mg/kg/dose (IM) 2-2.5 mg/kg/dose (IV) 0.1-0.25 mg/kg/h (continuous)</td>
<td>Nausea, vomiting, pruritus and rash</td>
<td>Does not inhibit prostaglandin synthesis</td>
<td>An IM injection is not recommended. Slow IV infusion. Be careful in patients taking psychoactive medications and with seizures</td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Dose and Administration</td>
<td>Side Effects</td>
<td>Caution</td>
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<tr>
<td><strong>Non-narcotics</strong></td>
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<tr>
<td>Acetaminophen</td>
<td>Rectal</td>
<td>40 mg/kg loading, 20 mg/kg/dose 4 times/day</td>
<td>Nephrotoxicity, hepatotoxicity (neonates)</td>
<td>Most common used analgesic Antipyretic effect</td>
<td>Opioid-sparing effect Wide safety range</td>
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<td></td>
<td>Oral</td>
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<td></td>
<td>IV</td>
<td>15-40 mg/kg, followed by 30 mg/kg/8 h</td>
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<tr>
<td>Propacetamol</td>
<td></td>
<td>Oral, rectal</td>
<td>40 mg/kg loading, 8 mg/kg/4 h</td>
<td>Most common used analgesic Antipyretic effect</td>
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<td>IX</td>
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<tr>
<td>Diclofenac</td>
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<tr>
<td>Ketorolac</td>
<td>Oral, IV</td>
<td>0.2-0.5 mg/kg every 6 h (48 h)</td>
<td>Total dose &lt; 2 mg/kg/day, maximum 5 days</td>
<td>Opioid-sparing effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM, SC</td>
<td></td>
<td></td>
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<tr>
<td>Metamizole, dipyrone</td>
<td>Oral, IM</td>
<td>10-15 mg/kg/dose (max 40 mg/kg total)</td>
<td>Risk of agranulocytosis, not clarified definitely</td>
<td>Very effective antipyretic Not approved in some countries including USA, Sweden, Japan and Australia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral drop</td>
<td>1 drop/kg/dose, up to 4 times/day</td>
<td></td>
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<tr>
<td><strong>Narcotics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Codeine</td>
<td>Oral</td>
<td>1 mg/kg, single dose</td>
<td>Respiratory depression not seen after single dose</td>
<td>Both antitussive and analgesic effect</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>IM, IV</td>
<td>6-12 months: 0.1 mg/kg, IM 0.05 mg/kg, IV</td>
<td>Most commonly used opioid, but not the most suitable opioid for pain relief in children</td>
<td>IM injection not recommended &lt; 2 months old: be careful</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Nalbuphine</td>
<td>IV</td>
<td>&lt; 3 months old: 0.05 mg/kg/dose &gt; 3 months old: 0.05-0.10 mg/kg/dose (4-6 times/day)</td>
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<tr>
<td>Piritramide</td>
<td>IV</td>
<td>0.05-0.10 mg/kg/dose (4-6 times/day)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td>Oral, syrup</td>
<td>1 mg/kg</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pethidine/ meperidine</td>
<td>IM, IV</td>
<td>1.5-2 mg/kg IM as premedicant 1 mg/kg IV as analgesic</td>
<td>No advantage over morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV</td>
<td>1-2 µg/kg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Buprenorphine</td>
<td>IV</td>
<td>3-5 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>IV, IM</td>
<td>1 mg/kg IM 0.5-0.75 mg/kg IV</td>
<td>In small infants, observe respiration after IV administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regional (local) anaesthetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td></td>
<td>Maximum single bolus dose: 2.5-3.0 mg/kg Maximum infusion: 0.4-0.5 mg/kg/h (10-20 mg/kg/day) in older infants and children; 0.2-0.25 mg/kg/h (5-6 mg/kg/day) in neonates</td>
<td>Cardiotoxicity, convulsion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>IV, IM</td>
<td>0.2-0.25% 1-2.5 mg/kg for single-shot epidural 0.2-0.4 mg/kg/h for IV continuous administration</td>
<td>Less toxic than bupivacaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>IV, IM</td>
<td>0.2-0.25% 1-2.5 mg/kg for single-shot epidural 0.2-0.4 mg/kg/h for IV continuous administration</td>
<td>Less toxic than levobupivacaine</td>
<td></td>
<td></td>
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</table>
21.6  Bladder and kidney surgery
Continuous epidural infusion of local anaesthetics (72-74), as well as systemic (intravenous) application of analgesics (75), has been shown to be effective. Ketorolac is an effective agent that is underused. It decreases the frequency and severity of bladder spasms and the length of post-operative hospital stay and costs (76-81).

Open kidney surgery is particularly painful because all three muscle layers are cut during conventional loin incision. A dorsal lumbotomy incision may be a good alternative because of the shorter post-operative hospital stay and earlier return to oral intake and unrestricted daily activity (82).

Caudal blocks plus systemic analgesics (83), and continuous epidural analgesia, are effective in terms of decreased post-operative morphine requirement after renal surgery (84,85). However, when there is a relative contraindication to line insertion, a less experienced anaesthetist is available, or parents prefer it (86), non-invasive regimens composed of intra-operative and post-operative analgesics may be the choice. Particularly in this group of patients, stepwise analgesia protocols can be developed (87). For laparoscopic approaches, intraperitoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial (88).

Table 20: A simple pain management strategy for paediatric urological surgery

<table>
<thead>
<tr>
<th>Intensity of surgery</th>
<th>First step</th>
<th>Second step</th>
<th>Third step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (inguinal, scrotal,</td>
<td>Paracetamol and wound infiltration with</td>
<td>Regional block/weak</td>
<td>Epidural local/major peripheral nerve/plexus block/opioid injection (IV</td>
</tr>
<tr>
<td>penile)</td>
<td>local anaesthetics</td>
<td>opioid or intravenous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>strong opioid with</td>
<td>PCA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>small increments as</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rescue analgesia (nalbuphine, fentanyl,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>meperidine, morphine</td>
<td></td>
</tr>
<tr>
<td>Moderate (lower</td>
<td>Peripheral nerve block (single shot or</td>
<td>Peripheral nerve</td>
<td></td>
</tr>
<tr>
<td>abdominal)</td>
<td>continuous infusion)/opioid injection (IV</td>
<td>block/plexus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCA)</td>
<td>opioid injection (IV</td>
<td></td>
</tr>
<tr>
<td>Severe (upper abdominal or</td>
<td></td>
<td>PCA)</td>
<td></td>
</tr>
<tr>
<td>lombotomy)</td>
<td></td>
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</table>

*IV PCA = intravenous patient-controlled analgesia.*

21.7  Conclusions and recommendations

Conclusions LE

- Neonates experience pain. 3
- Pain may cause behavioural and somatic sequelae. 3
- Every institute must develop their own well-structured strategy for post-operative analgesia. 4

Recommendations GR

- Pain must be prevented/treated in children of all ages. B
- Pain must be evaluated by age-compatible assessment tools. B
- Patients and parents must be informed accurately. B
- Pre-emptive analgesia is important and balanced analgesia should be used in order to decrease the side effects of opioids. B

21.8  References


   http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=459
34. Lehr VT, Cepeda E, Frattarelli DA, et al. Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision. Am J Perinatol 2005 Jul;22(5):231-7.


22. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<td>AGS</td>
<td>adrenogenital syndrome</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AMH</td>
<td>anti-Müllerian hormone</td>
</tr>
<tr>
<td>ARM</td>
<td>anorectal malformation</td>
</tr>
<tr>
<td>CAH</td>
<td>congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>CIC</td>
<td>clean self-intermittent catheterisation</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COPUM</td>
<td>congenital obstructive posterior urethral membrane</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DDAVP</td>
<td>desmopressin</td>
</tr>
<tr>
<td>DHTST</td>
<td>dihydrotestosterone</td>
</tr>
<tr>
<td>DMSA</td>
<td>dimercaptosuccinic acid</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>GnRH</td>
<td>gonadotrophin-releasing hormone</td>
</tr>
<tr>
<td>hCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>IC</td>
<td>intermittent catheterisation</td>
</tr>
<tr>
<td>ICCS</td>
<td>International Children’s Continence Society</td>
</tr>
<tr>
<td>IVU</td>
<td>intravenous urogram</td>
</tr>
<tr>
<td>LH</td>
<td>luteinizing hormone</td>
</tr>
<tr>
<td>LHRH</td>
<td>luteinizing hormone releasing hormone</td>
</tr>
<tr>
<td>LUTD</td>
<td>lower urinary tract dysfunction</td>
</tr>
<tr>
<td>LUT(S)</td>
<td>lower urinary tract (symptoms)</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NDSD</td>
<td>neurogenic detrusor-sphincter dysfunction</td>
</tr>
<tr>
<td>OAB</td>
<td>overactive bladder</td>
</tr>
<tr>
<td>PNL</td>
<td>percutaneous litholapaxy</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>RN</td>
<td>reflux nephropathy</td>
</tr>
<tr>
<td>RNC</td>
<td>radionuclide cystography</td>
</tr>
<tr>
<td>RTA</td>
<td>renal tubular acidosis</td>
</tr>
<tr>
<td>SWL</td>
<td>(extracorporeal) shockwave lithotripsy</td>
</tr>
<tr>
<td>Tc-MAG3 (99m)</td>
<td>technetium-99m mercaptoacetyltriglycine (MAG3)</td>
</tr>
<tr>
<td>TIP</td>
<td>tubularised incised plate urethroplasty</td>
</tr>
<tr>
<td>TST</td>
<td>testosterone</td>
</tr>
<tr>
<td>UPJ</td>
<td>ureteropelvic junction</td>
</tr>
<tr>
<td>URS</td>
<td>ureterorenoscopy</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>UTIs</td>
<td>urinary tract infections</td>
</tr>
<tr>
<td>VCUUG</td>
<td>voiding cystourethrography</td>
</tr>
<tr>
<td>VR</td>
<td>vesicorenal reflux</td>
</tr>
<tr>
<td>VUR</td>
<td>vesicoureteral reflux</td>
</tr>
<tr>
<td>VUS</td>
<td>voiding urosonography</td>
</tr>
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Conflict of interest

All members of the Paediatric Urology Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. BACKGROUND

The European Association of Urology (EAU) Guidelines Group for Urological Trauma prepared these guidelines in order to assist medical professionals in the management of urological trauma.

1.1 Methodology

1.1.1 Evidence sources

The Urological Trauma guidelines are based on a review of the relevant literature, using on-line searches of the following databases: Medline, Embase, Cochrane, and other source documents published between 2002 and 2012. A critical assessment of the findings was made. The majority of publications on the subject are comprised of case reports and retrospective case series. The paucity of high-powered randomized controlled trials makes it difficult to draw meaningful conclusions. The panel recognizes this critical limitation.

A level of evidence (LE) and/or grade of recommendation (GR) have been assigned where possible. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Levels of evidence and grade of guideline recommendations*

Table 1: Level of evidence (1)*

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<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

Table 2: Grade of recommendation (1)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

* Modified from Oxford Centre for Evidence-based Medicine (1).

1.1.2 Publication history

The Urological Trauma Guidelines were first published in 2003; partial or full updates were available in 2006 and 2009. In 2012, the panel published comprehensive guidelines for the evaluation and treatment of iatrogenic urologic trauma (iatrogenic trauma Euro Urology paper). The entire Urological Trauma Guidelines have now been updated, with the exception of the “Mass casualty events, triage, and damage control” which has not been revised in this current version of the trauma guidelines. This will be extensively reworked for the next edition of the Guidelines. Paediatric trauma is addressed in the paediatric urology guidelines, and not in this urological trauma document.

A quick reference document presenting the main findings of the Trauma guidelines is also available alongside several scientific publications in the EAU scientific journal European Urology (2,3).

All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

1.1.3 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.
1.2 Definition and Epidemiology
Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent. Trauma is the sixth leading cause of death worldwide, accounting for 10% of all mortalities. It accounts for approximately 5 million deaths each year worldwide and causes disability to millions more (4,5). About half of all deaths due to trauma are in people aged 15–45 years and in this age it is the leading cause of death. Death from injury is twice as common in males as females, especially from motor vehicle accidents (MVA) and interpersonal violence. Trauma is therefore a serious public health problem with significant social and economic costs.

Significant differences exist in the causes and the effects of traumatic injuries between geographical areas, and between low, middle, and high-income countries. It should be noted that alcohol and drug abuse increase the rate of traumatic injuries by precipitating interpersonal violence, child and sexual abuse, and motor vehicle accidents.

1.2.1 Genito-Urinary Trauma
Genito-urinary trauma is seen in both sexes and in all age groups, but is more common in males.

The kidney is the most commonly injured organ in the genito-urinary system and renal trauma is seen in up to 5% of all trauma cases (6,7), and in 10% of all abdominal trauma cases (8). In MVAs, renal trauma is seen after direct impact into the seatbelt or steering wheel (frontal crashes) or from body panel intrusion in side-impact crashes (9).

Ureteral trauma is relatively rare but due mainly to iatrogenic injuries, and in penetrating gunshot wounds – both in military and civilian settings (10).

Traumatic bladder injuries are usually due to blunt (MVA) causes and associated with pelvic fracture (11), although may also be a result of iatrogenic trauma.

The anterior urethra is most commonly injured by blunt or “fall-astride” trauma, whereas the posterior urethra is usually injured in pelvic fracture cases – the majority of which are seen in MVAs (12).

Genital trauma is much more common in males due to anatomical considerations and more frequent participation in physical sports, violence and war-fighting. Of all genitor-urinary injuries, 1/3-2/3rds involve the external genitalia (13).

1.2.2 Classification of trauma
Traumatic injuries are classified by the world health organization (WHO) into intentional (either interpersonal violence related, war-related or self-inflicted injury), and unintentional injury - mainly motor vehicle collisions, falls, and other domestic accidents. Intentional trauma accounts for approximately half of the trauma-related deaths worldwide (5). A specific type of unintentional injury consists of iatrogenic injury which is created during treatment or diagnostic procedures by healthcare personnel.

Traumatic injuries are classified according to the basic mechanism into penetrating when an object pierces the skin, and blunt.

Penetrating trauma is further classified according to the velocity of the projectile:
1. High-velocity projectiles (e.g. rifle bullets – 800-1000m/sec)
2. Medium-velocity (e.g handgun bullets – 200-300 m/sec)
3. Low-velocity items (e.g. knife stab)

High-velocity weapons inflict greater damage because the bullets transmit large amounts of energy to the tissues. They form temporary expansive cavitation that immediately collapses and creates shear forces and destruction in a much larger area then the projectile tract itself. Cavity formation disrupts tissue, ruptures blood vessels and nerves, and may fracture bones away from the missile path. In lower velocity injuries, the damage is usually confined to the track of the projectile.

Blast injury is a complex cause of trauma because it commonly includes both blunt and penetrating trauma, and may also be accompanied by a burn injury.

Several classifications are used to describe the severity and the features of a traumatic injury. The most common is the AAST (American Association for the Surgery of Trauma) injury scoring scale, which is widely used in renal trauma (see the relevant section) (14). For the other urological organs, general practice is that injuries are described by their anatomical site and severity (partial/complete), therefore the elaborated AAST tables were omitted from these guidelines.
1.2.3 Initial evaluation and treatment

The initial emergency assessment of the trauma patient is beyond the focus of these guidelines, and is usually carried out by emergency medicine and trauma specialised personnel. The first priority is stabilisation of the patient and treatment of associated life-threatening injuries. The initial treatment should include securing the airway, controlling external bleeding and resuscitation of shock. In many cases, physical examination is carried out during the stabilisation of the patient.

A direct history is obtained from conscious patients. Witnesses and emergency personnel can provide valuable information about unconscious or seriously injured patients. In penetrating injuries, important information includes the size of the weapon in stabbings, and the type and calibre of the weapon used in gunshot wounds. The medical history should be as detailed as possible, as pre-existing organ dysfunction can have a negative effect on trauma patient outcome (15,16).

It is essential that all persons treating trauma patients are aware of the risk of hepatitis B and C infection. An infection rate of 38% was reported among males with penetrating wounds to the external genitalia (17). In any penetrating trauma, tetanus vaccination should be considered according to the patient’s vaccination history and the features of the wound itself (CDC tetanus wound management) (18).

1.3 References


2. RENAL TRAUMA

2.1 Introduction
The incidence of urological tract injury following abdominal trauma is approximately 10%. Renal trauma occurs in approximately 1-5% of all trauma cases (1,2). The kidney is the most commonly injured genitourinary organ in all ages, with the male to female ratio being 3:1 (3-5). Although renal trauma can be acutely life-threatening, most injuries can be managed conservatively (6). During the past 20 years, advances in imaging and treatment strategies have decreased the need for surgical intervention and increased renal preservation (7-9).

2.2 Mode of injury
Renal injuries are classified by their mechanism as blunt or penetrating. In rural settings, blunt trauma can account for the largest percentage (90-95%), while in urban settings, the percentage of penetrating injuries can increase to 20% or higher (10,11)

2.2.1 Blunt renal injuries
Blunt mechanisms, include motor vehicle collision, falls, vehicle-associated pedestrian accidents, sports and assault. Traffic accidents are the major cause of almost half the blunt injuries (12). Renal injury in frontal and side-impact collisions appears to occur after direct impact from objects in the vehicle compartment. For frontal crashes, the acceleration of the occupant(s) into the seat belt or steering wheel seems to result in renal injuries. Side-impact injuries occur when the vehicle side panel intrudes into the compartment, striking the occupant (13). Passengers in automobiles with frontal and side airbags were associated with a 45.3% and 52.8% reduction in renal injury, respectively, compared with those without airbags (14). A 20-year review of renal injuries following free falls found a rate of 16% (15). A direct blow to the flank or abdomen during sports activities is another cause of blunt trauma injury. Sudden deceleration or a crash injury may result in contusion, laceration or avulsion of the renal parenchyma.

Renal vascular injuries in general occur in less than 5% of blunt abdominal trauma patients. The incidence of blunt renal artery injury is even less, with estimated incidences ranging between 0.05% and 0.08% among blunt trauma patients (16). Renal artery occlusion is associated with rapid deceleration injuries. In theory, the kidney is displaced causing renal artery traction; the resulting tear in the inelastic intima and subsequent haemorrhage into the vessel wall leads to thrombosis. Compression of the renal artery between the anterior abdominal wall and the vertebral bodies may result in thrombosis of the renal artery.

2.2.2 Penetrating renal injuries
Gunshot and stab wounds represent the most common causes of penetrating injuries. Renal injuries from penetrating trauma tend to be more severe and less predictable than those from blunt trauma. Bullets, because of their higher kinetic energy, have the potential for greater parenchymal destruction and are most often associated with multiple-organ injuries (17). Penetrating injury produces direct tissue disruption of the renal parenchyma, vascular pedicles, or collecting system.

In wartime, the kidney is the most commonly injured urogenital organ. Most are associated with major abdominal injuries, and the rate of nephrectomies is high (25-65%) (18-20).
2.2.3 Injury classification

Twenty six classifications for renal injuries have been presented in the literature in the past 60 years (21), but the committee on organ injury scaling of the AAST has developed a renal-injury scaling system that is now widely used (22). Renal injuries are classified as grade 1 to 5 (Table 3). Abdominal computed tomography (CT) or direct renal exploration is used to classify injuries. All recent publications have adopted this classification. The AAST scaling system is the most important variable predicting the need for kidney repair or removal (23,24) and it also predicts for morbidity after blunt or penetrating injury and for mortality after blunt injury (25).

Table 3: AAST renal injury grading scale (22)

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Description of injury</th>
</tr>
</thead>
</table>
| 1      | Contusion or non-expanding subcapsular haematoma  
No laceration |
| 2      | Non-expanding peri-renal haematoma  
Cortical laceration < 1 cm deep without extravasation |
| 3      | Cortical laceration > 1 cm without urinary extravasation |
| 4      | Laceration: through corticomedullary junction into collecting system  
Or  
Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis |
| 5      | Laceration: shattered kidney  
Or  
Vascular: renal pedicle or avulsion |

*Advance one grade for bilateral injuries up to grade III.

Proposals for changes include a substratification of the intermediate grade renal injury into grade 4a (low risk-cases likely to be managed non-operatively) and grade 4b (high risk-cases likely to benefit from angiographic embolisation, renal repair or nephrectomy), based on the presence or absence of a series of important radiographic risk factors, including peri-renal haematoma, intravascular contrast extravasation and renal laceration complexity (26), and a suggestion that grade 4 injuries comprise all collecting system injuries, including ureteropelvic junction (UPJ) injury of any severity and segmental arterial and venous injuries. According to the last proposal, grade 5 injuries should include only renal hilar injuries, including thrombotic events (27).

2.3 Diagnosis

When renal injury is suspected during clinical examination, further evaluation (CT scan, laparotomy) is required for a prompt diagnosis.

2.3.1 History and physical examination

Possible indicators of major renal injury include a rapid deceleration event (fall, high-speed MVAs) or a direct blow to the flank. In assessing trauma patients after MVAs, the history should include the vehicle’s speed and whether the patient was a passenger or pedestrian.

In the early resuscitation phase, special consideration should be given to pre-existing renal disease (28). Patients with solitary kidney present a special group and in case of renal injury, the whole functioning renal mass might be endangered (29).

Pre-existing renal abnormality makes renal injury more likely following trauma. Pre-existing renal pathology should be noted. Hydronephrosis due to UPJ abnormality, renal calculi, cysts and tumours are the most commonly reported entities that may complicate a minor renal injury (30). The overall percentage of these cases varies from 4% to 22% (31,32).

Haemodynamic stability is the primary criterion for the management of all renal injuries. Vital signs should be recorded throughout diagnostic evaluation. Physical examination may reveal an obvious penetrating trauma from a stab wound to the lower thoracic back, flanks and upper abdomen, or bullet entry or exit wounds in this area. In stab wounds, the extent of the entrance wound may not accurately reflect the depth of penetration.

Blunt trauma to the back, flank, lower thorax or upper abdomen may result in renal injury. The following findings on physical examination raise the suspicion of renal involvement:

- haematuria;
- flank pain;
- flank ecchymoses;
- flank abrasions;
- fractured ribs;
- abdominal distension;
- abdominal mass;
- abdominal tenderness.

2.3.1.1 Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodynamic stability should be assessed upon admission:</td>
<td></td>
</tr>
<tr>
<td>- History should be taken from conscious patients, witnesses and rescue team</td>
<td>A</td>
</tr>
<tr>
<td>personnel with regard to the time and setting of the incident.</td>
<td></td>
</tr>
<tr>
<td>- Past renal surgery, and known pre-existing renal abnormalities (ureteropelvic</td>
<td>A</td>
</tr>
<tr>
<td>junction obstruction, large cysts, lithiasis) should be recorded.</td>
<td></td>
</tr>
<tr>
<td>A thorough examination should be made of the thorax, abdomen, flanks and</td>
<td>B</td>
</tr>
<tr>
<td>back for penetrating wounds. Findings on physical examination such as</td>
<td></td>
</tr>
<tr>
<td>haematuria, flank pain, flank abrasions and bruising ecchymoses, fractured</td>
<td></td>
</tr>
<tr>
<td>ribs, abdominal tenderness, distension or mass, could indicate possible</td>
<td></td>
</tr>
<tr>
<td>renal involvement.</td>
<td></td>
</tr>
</tbody>
</table>

GR = grade of recommendation.

2.3.2 Laboratory evaluation

Urinalysis, haematocrit and baseline creatinine are the most important tests for evaluating renal trauma. Haematuria, either microscopic or gross is often seen in renal injury, but is neither sensitive nor specific enough for differentiating minor and major injuries. It does not necessarily correlate with the degree of injury (33).

Major renal injury, such as disruption of the ureteropelvic junction, renal pedicle injuries or segmental arterial thrombosis may occur without haematuria (34). In a study by Eastham et al., 9% of patients with stab wounds and resultant proven renal injury did not manifest haematuria (35).

Haematuria that is out of proportion to the history of trauma may suggest pre-existing renal pathology (36). A urine dipstick is an acceptably reliable and rapid test to evaluate haematuria. However, some studies have shown false-negative result rates ranging from 3-10% using the dipstick test for haematuria (37).

Serial haematocrit determination in combination with vital signs are used for continuous evaluation of the trauma patient. The decrease in haematocrit and the requirement for blood transfusions is an indirect sign of the rate of blood loss and, along with the patient’s response to resuscitation, is valuable in the decision-making process. However, until evaluation is complete, it will not be clear whether it is due to renal trauma and/or associated injuries.

As most trauma patients are evaluated within 1 hour of injury, creatinine measurement reflects renal function prior to the injury. An increased creatinine level usually reflects pre-existing renal pathology.

2.3.2.1 Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine from a patient with suspected renal injury should be inspected for</td>
<td>B</td>
</tr>
<tr>
<td>haematuria (visually or by dipstick analysis).</td>
<td></td>
</tr>
<tr>
<td>A decrease in serial haematocrit measurement indicates blood loss.</td>
<td>B</td>
</tr>
<tr>
<td>Creatinine levels should be measured to identify patients with impaired renal</td>
<td>C</td>
</tr>
<tr>
<td>function prior to injury.</td>
<td></td>
</tr>
</tbody>
</table>

GR = grade of recommendation.

2.3.3 Imaging: criteria for radiographic assessment

Decisions about radiographic imaging in cases of suspected renal trauma are based on the clinical findings and the mechanism of injury. Since the majority of renal injuries are not significant and resolve without any intervention, many attempts have been made to identify which patients could be spared the discomfort, radiation exposure, possible allergic reaction, time and expense of a radiographic evaluation (38).

Some patients do not require radiographic evaluation following blunt renal trauma. Patients with microscopic haematuria and no shock after blunt trauma have a low likelihood of concealing significant renal injury. The indications for radiographic evaluation are gross haematuria, microscopic haematuria and shock, or the presence of major associated injuries. However, patients with a history of rapid deceleration injury with clinical indicators of renal trauma or associated injuries also need immediate imaging to rule out ureteral avulsion or...
renal pedicle injury (39).

Patients with penetrating trauma to the torso have a high incidence of significant renal injuries. If renal injury is clinically suspected on the basis of an entry or exit wound, renal imaging should be performed, regardless of the degree of haematuria (40).

2.3.3.1 Ultrasonography
Ultrasonography provides a quick, non-invasive, low-cost means of detecting peritoneal fluid collections without exposure to radiation (41). Focused assessment with sonography for Trauma (FAST) rapidly assesses for haemoperitoneum and haemopericardium. The major disadvantage of using FAST is that the results are highly dependent on the operator and the patient.

Ultrasound scans can detect renal lacerations but cannot accurately assess their depth and extent. They do not provide functional information about renal excretion or urine leakage. Ultrasound is useful for the routine follow-up of parenchymal lesions or haematomas in the intensive care unit and for serially evaluating stable injuries for the resolution of urinomas and retroperitoneal haematomas (33).

Since ultrasound scans are used in the triage of patients with blunt abdominal trauma in many centres, they can be helpful in identifying which patients require a more aggressive radiological exploration to obtain a certain diagnosis, as well as following up injuries and hematomas (42).

Contrast-enhanced sonography is described as more sensitive than conventional ultrasound in the detection of renal injuries but it is not commonly used. In haemodynamically stable patients, it is a useful tool in the assessment of blunt injuries (43).

2.3.3.2 Intravenous pyelography
Although intravenous pyelography (IVP) is a sensitive modality for renal trauma, it is not the study of choice and has largely been replaced by CT scanning (44). Use of IVP is recommended only in centres where it is the only modality available (45). Intravenous pyelography can be used to establish the presence or absence of one or both of the kidneys, clearly define the parenchyma and outline the collecting system. The most significant findings from IVP are non-function and extravasation. Non-function is usually a sign of extensive trauma to the kidney, pedicle injury (vascular avulsion or thrombosis), or a severely shattered kidney. Extravasation of the contrast medium also implies a severe degree of trauma, involving the capsule, parenchyma and collecting system. Other less reliable signs are delayed excretion, incomplete filling, caliceal distortion and obscuring of the renal shadow. Non-visualisation, contour deformity or contrast extravasation should prompt further radiological evaluation. The sensitivity of IVP is high (> 92%) for all degrees of trauma severity.

2.3.3.3 One-shot intraoperative IVP
In unstable patients with signs or symptoms of renal injury selected for immediate operative intervention, one-shot IVP provides important information for decision making in the critical time of urgent laparotomy concerning the injured kidney, as well as the presence of a normal functioning kidney on the contralateral side (46).

The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after 10 minutes. The study is safe, efficient, and of high quality in most cases. It provides important information for decision-making, although in cases of penetrating abdominal trauma 80% of patients with normal oneshot IVP findings had renal injuries not detected by the IVP (47).

2.3.3.4 Computed tomography (CT)
Computed tomography is the gold standard method for the radiographic assessment of stable patients with renal trauma. Computed tomography is more sensitive and specific than IVP, ultrasonography or angiography, and more accurately defines the location of injuries, easily detects contusions and devitalised segments, visualises the entire retroperitoneum and any associated haematomas, and simultaneously provides a view of both the abdomen and pelvis. It demonstrates superior anatomical detail, including the depth and location of renal laceration and presence of associated abdominal injuries, and establishes the presence and location of the contralateral kidney (48).

CT is particularly useful in evaluating traumatic injuries to kidneys with pre-existing abnormalities (49). Intravenous contrast should be administered for renal evaluation. A lack of contrast enhancement of the injured kidney is a hallmark of renal pedicle injury. In cases where this typical finding is not demonstrated, central parahilar haematoma increases the possibility of renal pedicle injury. This sign should be considered even if the renal parenchyma is well enhanced (50). Renal vein injury remains difficult to diagnose with any type of radiographic study. However, the presence on CT of a large haematoma, medial to the kidney and displacing
the renal vasculature, should raise the suspicion of venous injury.

Spiral CT provides shorter scanning time and thus fewer artefacts in the examinations of patients who cannot co-operate adequately (51). Three-dimensional post-processing modalities allow assessment of the renal vascular pedicle by CT angiography and improve the demonstration of complex lacerations of the renal parenchyma (52). However, injury to the renal collecting system may be missed during routine spiral CT. In all cases of suspected renal trauma evaluated with spiral CT, repeat scans of the kidneys should be performed 10-15 minutes after contrast injection (53). Most blunt ureteral and ureteropelvic junction injuries can be identified if delayed excretory CT scans are performed (54).

Computed tomography scanning is also safe as part of the diagnostic procedure for patients with gunshot wounds who are being considered for non-operative management (55). Missed renal injuries are common but minor and do not alter the patients’ clinical course (56).

2.3.3.5 Magnetic resonance imaging (MRI)
Although MRI is not used in the majority of renal trauma patients, it is a sensitive study in the evaluation of blunt renal trauma (57). Magnetic resonance imaging is not the first choice in managing patients with trauma because it requires a longer imaging time and limits access to patients when they are in the magnet during the examination. Magnetic resonance imaging is therefore useful in renal trauma only if CT is not available, in patients with iodine allergy, or in the very few cases where the findings on CT are equivocal (58).

2.3.3.6 Angiography
Angiography is indicated mainly for stable patients who are candidates for radiological control of haemorrhage defined on CT (35). Angiography is less specific, more time-consuming and more invasive than CT but is more specific for defining the exact location and degree of vascular injuries. It is indicated in the management of persistent or delayed management of haemorrhage from branching renal vessels (49).

Angiography can define renal lacerations, extravasation and pedicle injury. Additionally, it is the test of choice for evaluating renal venous injuries. Another indication for the use of angiography is nonenhancement of the renal cortex on CT scan caused by total avulsion of the renal vessels, renal artery thrombosis and severe contusion causing major vascular spasm.

2.3.3.7 Radionuclide scans
Radionuclide scans are generally used or required only in trauma patients with allergy to iodinated contrast material (49).

2.3.3.8 Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt trauma patients with macroscopic haematuria or microscopic haematuria and haemodynamic instability should undergo radiographic evaluation.</td>
<td>B</td>
</tr>
<tr>
<td>Radiographic evaluation is recommended for all patients with a history of rapid deceleration injury and/or significant associated injuries.</td>
<td>B</td>
</tr>
<tr>
<td>All patients with or without haematuria after penetrating abdominal or thoracic injury require urgent renal imaging.</td>
<td>B</td>
</tr>
<tr>
<td>Ultrasonography alone should not be used to set the diagnosis of renal injury since it cannot provide sufficient information. However, it can be informative during the primary evaluation of polytrauma patients and for the follow-up of recuperating patients.</td>
<td>C</td>
</tr>
<tr>
<td>A CT scan with enhancement of intravenous contrast material and delayed images is the gold standard for the diagnosis and staging of renal injuries in haemodynamically stable patients.</td>
<td>A</td>
</tr>
<tr>
<td>In the absence of or contraindication for CT, IVP, MRI and radiographic scintigraphy are reasonable alternatives for imaging renal trauma.</td>
<td>C</td>
</tr>
<tr>
<td>One-shot IVP should be considered in unstable patients who require emergency surgical exploration.</td>
<td>C</td>
</tr>
<tr>
<td>Angiography is a safe and reliable diagnostic examination.</td>
<td>B</td>
</tr>
</tbody>
</table>

GR = grade of recommendation; CT = computed tomography; IVP = intravenous pyelography; MRI = magnetic resonance imaging.

2.4 Treatment

2.4.1 Indications for renal exploration
The need for renal exploration can be predicted considering the type of injury, transfusion requirements, blood urea nitrogen (BUN), creatinine and injury grade (59). However, the management of renal injury may be influenced by the decision to explore or observe associated abdominal injuries (60).
A life-threatening haemodynamic instability due to renal haemorrhage is an absolute indication for renal exploration, irrespective of the mode of injury (61,62). Other indications include an expanding or pulsatile peri-renal haematoma identified at exploratory laparotomy performed for associated injuries. Persistent extravasation or urinoma are usually managed successfully with endourological techniques. Inconclusive renal imaging and a pre-existing renal abnormality or an incidentally diagnosed tumour could require surgery even after relatively minor renal injury (36).

Grade 5 vascular renal injuries are regarded as an absolute indication for exploration. An increasing number of reports suggest that parenchymal grade 5 patients who are haemodynamically stable at presentation might be safely treated conservatively (63-66). In these patients, intervention is predicted by the need for continued fluid and blood resuscitation. Other factors that increase the risk of surgical intervention are peri-renal haematoma size > 3.5 cm, presence of intravascular contrast extravasation and presence of grade 4-5 injuries (26). Injury Severity Score (ISS) 16 and grade 4 renal injury are predictive factors for an operation, while higher injury severity (ISS > 16) and lower consciousness level (GCS < 8) are significantly associated with mortality in patients with renal injuries (67).

### 2.4.2 Interventional radiology

Interventional radiology provided the most important advance in renal trauma management in the last decade. Decisions regarding major renal lacerations must balance the increased incidence of nephrectomy in patients undergoing immediate versus delayed surgical exploration, with the increased morbidity of patients who are managed expectantly. Endovascular treatment is an important and less invasive option for managing renovascular trauma that may allow for maximum tissue/organ preservation.

Angiography with selective renal embolisation is a reasonable alternative to laparotomy provided that no other indication for immediate open surgery exists. Haemodynamically stable patients with grade 3 injuries or higher should be considered for formal angiography followed by embolisation if active bleeding is noticed (68). Positive radiological findings, such as massive extravasation, presence of a large devascularised segment or identification of grade 4 or 5 lesions, arterial laceration, avulsion, global or segmental hypoperfusion of kidney, intimal tear or false aneurysm, segmental of subsegmental arterial bleeding and thrombosis indicate the need for angiography.

Peri-renal haematoma size compressing the kidney and impairing perfusion (peri-nephric compartment syndrome or ‘page kidney’) and intravascular contrast extravasation are also readily detectible radiographic features, associated with the need for angiographic embolisation (69).

Some polytrauma patients will undergo laparotomy and open repair of intra-peritoneal organ injuries but then undergo angio-embolisation of renal injuries identified on CT or suspected by an expanding retroperitoneal haematoma at the time of surgery. Angio-embolisation also has a role in patients with persistent post-traumatic haematuria. Since the success rate is equally high for initial and repeat interventions, re-intervention is justified when the clinical course allows (70).

The most common injury to the main renal artery is dissection, usually with partial or complete occlusion. Complete arterial avulsion is less common. The management of renal artery occlusion remains controversial. Arterial bleeding may spontaneously cease when tamponade develops within Gerota’s fascia. However, when the fascia has been violated, tamponade will not occur and the haematoma will extend to the pararenal space. Without transcatheter embolisation, attempts to stabilise such patients are unlikely to be successful so that the only option is emergency laparotomy (71).

The reported clinical success rate of renal embolisation for trauma is 65% (72) but angiography has a success rate of 94.45% for blunt injuries in stable patients (73). Cure of haematuria after superselective transarterial embolisation is reported as high as 98%, which is similar for both blunt and penetrating injuries (74). The complication rate is minimal and although it has been proven effective for grade 4 injuries initially selected for conservative therapy, it failed when applied to grade 5 injuries (72).

Renal pedicle injuries are normally managed surgically, but there are increasing reports of endovascular treatment options for traumatic arterial dissections and ruptures. In specific clinical circumstances, such as severe polytrauma or a patient with high operative risk, the main renal artery may be embolised, either as a definitive treatment or to be followed by interval nephrectomy after the patient’s clinical condition has improved. The angiographic findings in more peripheral renal artery injuries include contrast extravasation, pseudoaneurysm, arterial transection, arterial wall irregularity, arteriovenous fistulae (AVF) and arterio-caliceal fistula.

Angio-embolisation for grade 4-5 injuries should be done with caution since the initial success rate is low and usually requires additional procedures. However, the procedure itself is safe and not associated
with intermediate-term adverse events (73,75). Such patients, who have no other indications for immediate abdominal surgery, benefit from arteriography and possible embolisation. The additional contrast agent needed for arteriography does not increase the incidence of nephropathy (76).

2.4.3 Operative findings and reconstruction
The overall exploration rate for blunt trauma is less than 10% (61), and may be even lower as more centres adopt a conservative approach to the management of these patients (77). The goal of renal exploration following renal trauma is control of haemorrhage and renal salvage. Most large series suggest the transperitoneal approach for surgery (78,79). Access to the renal vascular pedicle is then obtained through the posterior parietal peritoneum, which is incised over the aorta, just medial to the inferior mesenteric vein. Temporary vascular occlusion before opening Gerota’s fascia is a safe and effective method during exploration and renal reconstruction (80). It tends to lower blood loss and the nephrectomy rate appears not to increase postoperative azotaemia or mortality (81). Stable perirenal hematomas detected during exploration for associated injuries should not be opened.

Renal reconstruction is feasible in most cases. The overall rate of patients who have a nephrectomy during exploration is around 13%, usually in patients with penetrating injury and higher rates of transfusion requirements, haemodynamic instability, and higher injury severity scores (82). Other intra-abdominal injuries also slightly increase the need for nephrectomy (83). Mortality is associated with the overall severity of the injury and is not often a consequence of the renal injury itself (84).

In gunshot injuries caused by a high-velocity bullet, reconstruction can be difficult and nephrectomy is often required (85). Renorrhaphy is the most common reconstructive technique. Partial nephrectomy is required when non-viable tissue is detected. Watertight closure of the collecting system, if open, might be desirable, although some experts merely close the parenchyma over the injured collecting system with good results. If the renal capsule is not preserved, an omental pedicle flap or perirenal fat bolster may be used for coverage (86). The use of haemostatic agents and sealants in traumatic renal reconstruction can be helpful (87). In all cases, drainage of the ipsilateral retroperitoneum is recommended to provide an outlet for any temporary leakage of urine.

Renovascular injuries are associated with extensive associated trauma and increased peri- and postoperative mortality and morbidity. Blunt renal artery injury is rare. Non-operative management should be considered as an acceptable therapeutic option (10). Following blunt trauma, repair of grade 5 vascular injury is seldom, if ever, effective (88). Repair might be attempted in patients with a solitary kidney or bilateral injuries (89). Revascularisation is no longer used in the presence of a functioning contralateral kidney (8,12). Nephrectomy for main renal artery injury has outcomes similar to those of vascular repair. It does not worsen post-treatment renal function in the short term.

2.4.4 Non-operative management of renal injuries
2.4.4.1 Blunt renal injuries
As the indications for renal exploration become clearer, non-operative management has become the treatment of choice for most renal injuries. In stable patients, this means supportive care with bed-rest and observation, though some authors also advocate the use of prophylactic antibiotics (8). Primary conservative management is associated with a lower rate of nephrectomy, without any increase in the immediate or long-term morbidity (90).

Hospitalisation or prolonged observation for evaluation of possible renal injury after a normal abdominal CT scan, when combined with clinical judgment, is unnecessary in most cases (91). All grade 1 and 2 renal injuries can be managed non-operatively, whether due to blunt or penetrating trauma. The treatment of grade 3 injuries has been controversial, but recent studies support expectant treatment (92-94). Patients diagnosed with urinary extravasation in solitary injuries can be managed without major intervention and a resolution rate of > 90% [98]. Persistent bleeding is the main indication for a reconstruction attempt (96).

Most patients with grade 4 and 5 renal injuries present with major associated injuries, and consequently experience high exploration and nephrectomy rates (97), although emerging data indicate that many of these patients can be managed safely with an expectant approach (98). An initially conservative approach is feasible in stable patients with devitalised fragments (99), although these injuries are associated with an increased rate of complications and late surgery (100).

Non-operative management for segmental renal artery injury results in excellent outcomes (101). Unilateral main renal arterial injuries will normally be managed non-operatively in a haemodynamically stable patient with surgical repair reserved for bilateral renal artery injuries or injuries involving a solitary functional kidney.
Conservative management is advised in the treatment of unilateral complete blunt renal artery thrombosis. These patients need close follow-up for the risk of hypertension. Blunt renal artery thrombosis in multiple trauma patients indicates severe injury. Surgeons should critically assess the added risk of mortality against chances of recovering the renal function.

### 2.4.4.2 Penetrating renal injuries

Although almost all grade 4 patients with penetrating injury require renal exploration, only 20% of those with blunt trauma do (103). Isolated grade 4 renal injuries represent a unique situation to treat the patient based solely on the extent of the renal injury. Non-operative management is used more often.

Persistent bleeding represents the main indication for renal exploration and reconstruction. In all cases of severe renal injury, non-operative management should occur only after complete renal staging in haemodynamically stable patients (96).

Penetrating wounds have traditionally been approached surgically. However, stable patients should undergo complete staging to define the full extent of the injury. Renal gunshot injuries should be explored only if they involve the hilum or are accompanied by signs of continued bleeding, ureteral injuries, or renal pelvis lacerations (104).

Low-velocity gunshot and stab wounds of minor degree may be managed conservatively with an acceptably good outcome (105). In contrast, tissue damage from high-velocity gunshot injuries can be more extensive and nephrectomy may be required. Non-operative management of penetrating renal injuries in selected stable patients is associated with a high rate of successful management in approximately 50% of patients with stab wounds and up to approximately 40% of patients with gunshot wounds (106-108).

If the site of penetration by stab wound is posterior to the anterior axillary line, 88% of such renal injuries can be managed non-operatively (109). Injuries to the flank are more likely to be grade 3, while injuries to the abdomen are more likely to be grade 1. A systematic approach based on clinical, laboratory and radiological evaluation might minimise negative exploration without increasing morbidity from a missed injury (62). Renal stab wounds producing major renal injuries (grade 3 or higher) are more unpredictable and are associated with a higher rate of delayed complications if treated expectantly (110). In recent years, selective non-operative management of abdominal stab wounds is generally accepted by an increasing proportion of trauma centres (111).

All patients sustaining a gunshot wound that are evaluable, haemodynamically stable and without diffuse abdominal pain or peritonitis are candidates for non-operative management. A positive FAST is not a contra-indication to non-operative management as this may be a result of an isolated solid organ injury. Computed tomography remains critical in delineating the extent of solid organ damage, the absence of hollow viscus injury, and the presence of any acute complications requiring invasive radiological treatment. With this intensive approach, selected liver, spleen and kidney injuries after gunshot wounding can be managed non-operatively with good functional outcomes (106). The excellent outcomes in patients observed following segmental arterial injury support a role for conservative management in this subgroup (101).

### 2.4.5 Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th>Following blunt renal trauma, stable patients should be managed conservatively with bed rest and close monitoring of vital signs until gross haematuria resolves.</th>
</tr>
</thead>
</table>
| B   | Following grade 1-3 stab and low-velocity gunshot wounds, stable patients, after complete staging, should be selected for expectant management. Indications for renal exploration include:  
– haemodynamic instability;  
– exploration for associated injuries;  
– expanding or pulsatile peri-renal haematoma identified during laparotomy;  
– grade 5 vascular injury. |
|     | Interventional radiology is indicated in patients with active bleeding from renal injury but without other indications for immediate abdominal operation. |
|     | Renal reconstruction should be attempted in cases in which the primary goal of controlling haemorrhage is achieved and a sufficient amount of renal parenchyma is viable. |

GR = grade of recommendation.
2.4.6 Postoperative care and follow-up

The risk of complications in patients who have been treated conservatively increases with grade. Repeat imaging 2-4 days after trauma minimizes the risk of missed complications, especially in grade 3-5 blunt renal injuries (112). However, the usefulness of frequent CT scanning after injury has never been satisfactorily proven and its use should be weighed against the risk of increased radiation exposure. Computed tomography scans should always be performed on patients with fever, unexplained decreasing haematocrit or significant flank pain. Repeat imaging can be safely omitted for patients with grade 1-4 injuries as long as they remain clinically well (113).

Nuclear renal scans are useful for documenting and tracking functional recovery in patients following renal reconstruction (114). Follow-up should involve physical examination, urinalysis, individualized radiological investigation, serial blood pressure measurement and serum determination of renal function (99). A decline in renal function directly correlates with AAST renal injury grade; this is independent of the mechanism of injury (blunt vs. penetrating) and the method of management (nonoperative vs. renal repair) (115,116). Follow-up examinations should continue until healing is documented and laboratory findings have stabilised, although checking for latent renovascular hypertension may need to continue for years (117). The literature is generally inadequate on the subject of the long-term consequences of trauma on renal tissue.

2.4.7 Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th>Repeat imaging is recommended in cases of suspected complications, cases of fever, flank pain, or falling haematocrit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Nuclear scintigraphy is useful for documenting functional recovery.</td>
</tr>
<tr>
<td>C</td>
<td>First follow-up should be at approximately 3 months after major renal injury with hospitalization. Each follow up should include:</td>
</tr>
<tr>
<td></td>
<td>1. Physical examination.</td>
</tr>
<tr>
<td></td>
<td>2. Urinalysis.</td>
</tr>
<tr>
<td></td>
<td>3. Individualized radiological investigation.</td>
</tr>
<tr>
<td></td>
<td>4. Serial blood pressure measurement.</td>
</tr>
<tr>
<td></td>
<td>5. Serum determination of renal function.</td>
</tr>
<tr>
<td>C</td>
<td>Long-term follow-up should be decided on a case-by-case basis.</td>
</tr>
</tbody>
</table>

GR = grade of recommendation.

2.4.8 Complications

Early complications, occurring less than 1 month after injury, can be bleeding, infection, perinephric abscess, sepsis, urinary fistulae, hypertension, urinary extravasation and urinoma. Delayed complications include bleeding, hydroureteronephrosis, calculus formation, chronic pyelonephritis, hypertension, arteriovenous fistulae, hydronephrosis and pseudoaneurysms. Delayed retroperitoneal bleeding may be life-threatening and selective angiographic embolisation is the preferred treatment (118). Perinephric abscess formation is usually best managed by percutaneous drainage, although open drainage may sometimes be required. Percutaneous management of complications may pose less risk of renal loss than re-operation, which may lead to nephrectomy when infected tissues make reconstruction difficult (61).

Renal trauma is a rare cause of hypertension, mostly in young men. The frequency of posttraumatic hypertension is estimated to be less than 5% in all published series (119,120). Hypertension may occur acutely as a result of external compression from perirenal haematoma (Page kidney), or chronically because of compressive scar formation. Hypertension is usually renin-dependent and associated with parenchymal injury. Renin-mediated hypertension may occur as a long-term complication; aetiologies include renal artery thrombosis, segmental arterial thrombosis, renal artery stenosis (Goldblatt kidney), devitalised fragments and AVF. Arteriography is informative in cases of post-traumatic hypertension (121). Treatment is required if the hypertension persists and could include medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or total nephrectomy (121).

Urinary extravasation after renal reconstruction often subsides without intervention as long as ureteral obstruction and infection are not present. Ureteral retrograde stenting may improve drainage and allow healing (122). Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage as necessary (123).

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating
trauma. Percutaneous embolisation is often effective for symptomatic AVF, but larger ones may require surgery (124). Post-procedural complications include infection, sepsis, urinary fistulae, and renal infarction (125). The development of pseudoaneurysm is a rare complication following blunt renal trauma. In numerous case reports, transcatheter embolisation appears to be a reliable minimally invasive solution (126,127). Acute renal colic from a retained missile has been reported, and can be managed endoscopically if possible (128). Other unusual late complications, such as duodenal obstruction, may result from retroperitoneal haematoma following blunt renal trauma (129).

2.4.9  Recommendations

| Complications following renal trauma require a thorough radiographic evaluation. | B |
| Medical management and minimally invasive techniques should be the first choice for the management of complications. | C |

GR = grade of recommendation.

2.4.10  Renal injury in the polytrauma patient

Approximately 8-10% of blunt and penetrating abdominal injuries involve the kidneys. The incidence of associated injury in penetrating renal trauma ranges from 77% to 100%. Gunshot wounds are associated with organ injury more often than are stab wounds. Most patients with penetrating renal trauma have associated adjacent organ injuries that may complicate treatment. In the absence of an expanding haematoma with haemodynamic instability, associated multiorgan injuries do not increase the risk of nephrectomy (11). Blunt and penetrating trauma equally contributed to combined renal and pancreatic injury, as reported by Rosen and McAninch. Renal preservation was achieved in most patients, and the complication rate of the series was 15% (130). A similar rate of complications (16%) was reported in patients with simultaneous colon and renal injury. In a report reviewing this combination of injuries over a period of 17 years, 58% of patients underwent an exploration, with nephrectomies performed in 16% of explorations (131).

Renal injuries seem to be rather rare in patients with blunt chest trauma. In a study of polytrauma patients, conservative management was safely attempted without increasing morbidity (65).

2.4.11  Recommendations

| Polytrauma patients with associated renal injuries should be evaluated on the basis of the most threatening injury. | C |
| In cases where surgical intervention is chosen, all associated abdominal injuries should be managed where appropriate simultaneously. | C |
| The decision for conservative management should consider all injuries independently. | C |

GR = grade of recommendation.

2.5  Iatrogenic renal injuries

2.5.1  Introduction

Iatrogenic renal trauma (IRT) is rare but can lead to significant morbidity.

2.5.2  Incidence and aetiology

The commonest causes of IRT are listed in Table 4 (132).
Table 4: Incidence and aetiology of commonest iatrogenic renal trauma during various procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Haemorrhage</th>
<th>AVF</th>
<th>Pseudo-aneurysm</th>
<th>Renal pelvis injury</th>
<th>Aorto-caliceal fistula</th>
<th>Foreign body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrostomy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>+ (0.5-1.5%)</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Percutaneous nephrolithotomy (PCNL)</td>
<td>+</td>
<td></td>
<td>+</td>
<td>(0.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic surgery (oncology)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open surgery (oncology)</td>
<td>+</td>
<td></td>
<td>+ (0.43%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplantation</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endopyelotomy</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular procedure</td>
<td>+ (1.6%)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

AVF = arteriovenous fistulae; PCNL = percutaneous nephrolithotomy.

Large haematomas after biopsy (0.5-1.5%) are caused by laceration or arterial damage [136]. Renal artery and intraparenchymal pseudoaneurysms (0.9%) may be caused by percutaneous biopsy, nephrostomy, and partial nephrectomy (0.43%) (133). In percutaneous nephrolithotomy (PCNL), haemorrhage is the most dangerous IRT. Vascular injuries are quite common at any stage of the procedure, especially when punctures are too medial or directly of the renal pelvis.

Other injuries include AVFs or a tear in the pelvicaliceal system, causing extravasation and absorption of irrigation fluid. Iatrogenic renal traumas in renal transplantation are more common and include AVFs, intrarenal pseudoaneurysms, arterial dissection and arteriocaliceal fistulae. Pseudoaneurysm is a rare complication of allograft biopsy. Although the overall complication rate with biopsies in transplant kidneys is 9% (including haematoma, AVF, macroscopic haematuria and infection), vascular complications requiring intervention account for 0.2-2.0% (134). Predisposing factors include hypertension, renal medullary disease, central biopsies, and numerous needle passes (135). Arteriovenous fistulae and pseudoaneurysms can occur in 1-18% of allograft biopsies, and may coexist in up to 30% of cases (136).

Extrarenal pseudoaneurysms after transplantation procedures generally occur at the anastomosis, in association with local or haematogenous infection. Arterial dissection related to transplantation is rare and presents in the early postoperative period (137).

Iatrogenic renal traumas associated with endopyelotomy are classified as major (vascular injury), and minor (urinoma) (138). Patients undergoing cryoablation for small masses via the percutaneous or the laparoscopic approach may have minor IRTs, including asymptomatic perinephric haematoma and self-limited urine leakage.

Vascular injury is a rare complication (1.6%) of endovascular interventions in contrast to patients with surgical injuries. The renal vessels are vulnerable mainly during oncological procedures (139). Renal foreign bodies, with retained sponges or wires during open or endourological procedures, are uncommon.

2.5.3 Diagnosis (clinical signs, imaging)

Haematuria is common after nephrostomy, but massive retroperitoneal haemorrhage is rare. If a nephrostomy catheter appears to transfix the renal pelvis, significant arterial injury is possible. The misplaced catheter should be withdrawn over a guide wire and embolisation may arrest the haemorrhage rapidly. Computed tomography can also successfully guide repositioning of the catheter into the collecting system (140). Haemorrhage can be prevented by avoiding puncture in patients receiving anticoagulation treatment or with coagulopathy, by careful targeting the calices and by avoiding medial puncture. Injuries to the renal pelvis are less likely to occur if the dilator is not advanced further than the calix, sheaths are handled with care, especially during advancement around the pelviureteric junction, and kinking of the guide wires is avoided (141). After percutaneous biopsy, arteriovenous fistulae may present with severe hypertension. A pseudoaneurysm should be suspected if the patient presents with flank pain and decreasing haematocrit, even in the absence of haematuria.

During PCNL, acute bleeding may be caused by injury to the anterior or posterior segmental arteries, or late postoperative bleeding may be caused by interlobar and lower-pole arterial lesions, AVF and post-traumatic aneurysms (142). Duplex ultrasound and CT angiography can be used to diagnose vascular injuries. A close watch on irrigation fluid input and output is required to ensure early recognition of extravasation of fluid. Intra-operative evaluation of serum electrolytes, acid-base status, oxygenation, and monitoring of airway pressure are good indicators of this complication, since metabolic acidosis, hyponatraemia, hypokalaemia, peritonitis and ileus may occur.
In arterial dissection related to transplantation, symptoms include anuria and a prolonged dependence on dialysis. Doppler ultrasound can demonstrate compromised arterial flow. Dissection can lead to thrombosis of the renal artery and/or vein.

After angioplasty and stent-graft placement in the renal artery, during which wire or catheters may enter the parenchyma and penetrate through the capsule, possible radiological findings include AVF, pseudoaneurysm, arterial dissection and contrast extravasation. Common symptoms of pseudoaneurysms are flank pain and gross haematuria within 2 or 3 weeks after surgery (143). Transplant AVF and pseudoaneurysms may be asymptomatic or may cause gross haematuria or hypovolemia due to shunting and ‘steal’ phenomenon, renal insufficiency, hypertension, and high-output cardiac failure. Patients with extrarenal pseudoaneurysms may present with infection/bleeding, swelling, pain and intermittent claudication. Doppler ultrasound findings for AVF include high-velocity, low-resistance, spectral waveforms, with focal areas of disorganised colour flow outside the normal vascular borders, and possibly a dilated vein (144). Pseudoaneurysms appear on ultrasound as anechoic cysts, with intracystic flow on colour Doppler.

Potential complications of retained sponges include abscess formation, fistulisation to the skin or intestinal tract, and sepsis. Retained sponges may cause pseudotumours or appear as solid masses. Magnetic resonance imaging clearly shows the characteristic features (145). Absorbable haemostatic agents may also produce a foreign-body giant cell reaction, but the imaging characteristics are not specific. Retained stents, wires, or fractured Acucise cutting wires may also present as foreign bodies and can serve as a nidus for stone formation (146).

2.5.4 Management
Small subcapsular haematomas after nephrostomy resolve spontaneously, while AVFs are best managed by embolisation. Arteriovenous fistulae and pseudoaneurysms after biopsy are also managed by embolisation (147).

During PCNL, bleeding can be venous or arterial. In major venous trauma with haemorrhage, patients with concomitant renal insufficiency can be treated without open exploration or angiographic embolisation using a Council-tip balloon catheter (148). In the case of profuse bleeding at the end of a PCNL, conservative management is usually effective. The patient should be placed in a supine position, clamping the nephrostomy catheter and forcing diuresis. Superselective embolisation is required in less than 1% of cases and has proved effective in more than 90% of cases (149). Short-term deleterious effects are more pronounced in patients with a solitary kidney, but long-term follow-up shows functional and morphological improvements (150). Termination of PCNL if the renal pelvis is torn or ruptured is a safe choice. Management requires close monitoring, placement of an abdominal or retroperitoneal drain and supportive measures (151). Most surgical venous injuries have partial lacerations that can be managed with techniques, such as venorrhaphy, patch angioplasty with autologous vein, or expanded polytetrafluoroethylene (ePTFE) graft (152).

If conservative measures fail in cases of pseudoaneurysm and clinical symptoms or a relevant decrease in haemoglobin occurs, transarterial embolisation should be considered (153). As the success rate is similar for initial and repeat interventions, a repeat intervention is justified when the clinical course allows this (70).

Traditionally, patients with postoperative haemorrhage following intra-abdominal laparoscopic surgery of the kidney require laparotomy. Pseudoaneurysms and AVF are uncommon after minimally invasive partial nephrectomy, but can lead to significant morbidity. Temporary haemostasis occurs with coagulation and/or tamponade, but later degradation of the clot, connection with the extravascular space, and possible fistulisation with the collecting system may develop. Patients typically present with gross haematuria, although they may also experience flank pain, dizziness and fever. Embolisation is the reference standard for both diagnosis and treatment in the acute setting, although CT can be used if the symptoms are not severe and/or the diagnosis is ambiguous. Reports have described good preservation of renal function after embolisation (154).

Endoluminal management after renal transplantation consists of stabilising the intimal flap with stent placement. Embolisation is the treatment of choice for a symptomatic transplant AVF or enlarging pseudoaneurysm (155). Superselective embolisation with a coaxial catheter and metallic coils helps limit the loss of normal functioning graft tissue (156). A success rate of 71-100% has been reported, with alleviation of symptoms in 57-88% of cases. Major infarcts involving more than 30-50% of the allograft and leading to allograft loss have been reported in up to 28.6% of cases in which combined coil embolisation and polyvinyl alcohol or Gelfoam were used. If symptoms persist, a second angiogram with a possible repeat embolisation is warranted (157). Failure of embolisation is associated with a high nephrectomy rate. The long-term outcome depends on the course of the transplant and the amount of contrast medium used during the procedure. Surgical treatment for AVF consists of partial or total nephrectomy or arterial ligation, which results in loss of part of the transplant or the entire transplant.
Surgery has to date been the main approach in the treatment of renal vascular injuries. In patients with retroperitoneal haematoma, AVFs, and haemorrhagic shock, interventional therapy is associated with a lower level of risk than surgery (72). Renal arteriography followed by selective embolisation can confirm the injury. In injuries during angioplasty and stent-graft placement, transcatheter embolisation is the first choice of treatment (158). The treatment for acute iatrogenic rupture of the main renal artery is balloon tamponade. If this fails, immediate availability of a stent graft is vital (159). The true nature of lesions caused by foreign bodies is revealed after exploration.

2.5.5 Statements and recommendations

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic renal injuries are procedure-dependent (1.8-15%).</td>
<td>3</td>
</tr>
<tr>
<td>Significant injury requiring intervention is rare.</td>
<td>3</td>
</tr>
<tr>
<td>Most common injuries are vascular.</td>
<td>3</td>
</tr>
<tr>
<td>Renal allografts are more susceptible.</td>
<td>3</td>
</tr>
<tr>
<td>Injuries occurring during surgery are rectified immediately.</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms suggestive of a significant injury require investigation.</td>
<td>3</td>
</tr>
</tbody>
</table>

GR = grade; LE = level of evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with minor injuries should be treated conservatively.</td>
<td>B</td>
</tr>
<tr>
<td>Severe or persistent injuries require intervention with embolisation.</td>
<td>B</td>
</tr>
<tr>
<td>In stable patients, a second embolisation should be considered in case of failure.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.6 Algorithms

Figures 1 and 2 show the suggested treatment of blunt and penetrating renal injuries in adults.
Figure 1: Evaluation of blunt renal trauma in adults

* Suspected renal trauma results from reported mechanism of injury and physical examination.

† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where the method is not available, the urologist should rely on other imaging modalities (IVP, angiography, radiographic scintigraphy, MRI).

‡ Renal exploration: Although renal salvage is a primary goal for the urologist, decisions concerning the viability of the organ and the type of reconstruction are made during the operation.
Figure 2: Evaluation of penetrating renal trauma in adults

* Suspected renal trauma results from reported mechanism of injury and physical examination.
† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where the method is not available, the urologist should rely on other imaging modalities (IVP, angiography, radiographic scintigraphy, MRI).
‡ Renal exploration: Although renal salvage is a primary goal for the urologist, decisions concerning the viability of the organ and the type of reconstruction are made during the operation.
2.7 References


3. URETERAL TRAUMA

Ureteral trauma is relatively rare because the ureters are protected from injury by their small size, mobility, and the adjacent vertebrae, bony pelvis, and muscles. Iatrogenic ureteral trauma gives rise to the commonest cause of ureteral injury. It is seen in open, laparoscopic or endoscopic surgery and is often missed intraoperatively. Any trauma to the ureter may result in severe sequelae.

3.1 Aetiology

Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma (1-3). This incidence is even higher in modern combat injuries (4). Penetrating external ureteral trauma, mainly caused by gunshot wounds, dominates most of the modern series, both civilian and military (1,2,5). About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly MVAs (3).

Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, because it occurs in 2-3% of cases (1). It should also be suspected in blunt trauma with deceleration mechanism, when the renal pelvis can be torn away from the ureter (1). In external ureteral trauma, the relative frequency of injury site in the ureter varies between series, but it is more common in the upper ureter (2,3).

Gynaecological operations are the commonest cause of iatrogenic trauma to the ureters (Table 5) and usually involve damage to the lower ureter (1,5-7). Ureteral damage may also be caused by colorectal operations, especially abdominoperineal resection and sigmoid colectomy, and urological operations, especially endoscopic surgery. With ureteroscopic procedures, most iatrogenic injuries are minor, though occasionally they can be serious, e.g. complete ureteral avulsion. The incidence of urological iatrogenic trauma has decreased in the last 20 years (5,8) due to improvements in technique, instruments and surgical experience. Iatrogenic ureteral trauma can result from various mechanisms: ligation or kinking with a suture, crushing from a clamp, partial or complete transection, thermal injury, or ischaemia from devascularisation (5,6,9).

Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intraoperatively. In gynaecological surgery, if routine intraoperative cystoscopy is used, the detection rate of ureteral trauma is five times higher than usually reported (10,11). Risk factors for iatrogenic trauma include conditions that alter the normal anatomy, e.g. advanced malignancy, prior surgery or irradiation, diverticulitis, endometriosis, anatomical abnormalities, and major haemorrhage (5,11). Nevertheless, most cases have no identifiable risk factors (5,9,12).
3.2 Diagnosis
The diagnosis of ureteral trauma can be challenging. In penetrating external trauma, it is usually made intraoperatively during laparotomy (16), but it is delayed in most blunt trauma and iatrogenic cases (5,7,17). A high index of suspicion should be maintained.

3.2.1 Clinical diagnosis
External ureteral trauma usually accompanies severe abdominal and pelvic injuries. Penetrating trauma is usually associated with vascular and intestinal injuries, while blunt trauma is associated with damage to the pelvic bones and lumbosacral spine injuries (3). Haematuria is unreliable and a poor indicator of ureteral injury, as it is present in only 50-75% of patients (1,5,18).

Iatrogenic injury may be noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) may be injected to exclude ureteral injury. It may also be noticed later, when it is typically discovered by subsequent evidence of upper tract obstruction, urinary fistula formation or sepsis.

The following clinical signs are characteristic of delayed diagnosis: flank pain, urinary incontinence, vaginal or drain urinary leakage, haematuria, fever, uraemia or urinoma.

When the diagnosis is missed, the complication rate increases (1,4,17). Early recognition facilitates immediate repair and provides better outcome. Delayed diagnosis predisposes the patient to pain, infection and renal damage (14).

3.2.2 Radiological diagnosis
Extravasation of contrast medium in computerised tomography (CT) or in IVP is the hallmark sign of ureteral trauma. However, it is often only hydronephrosis, ascites, urinoma or mild ureteral dilation that are noticed. In unclear cases, a retrograde or antegrade urography is the gold standard for confirmation (5). Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients (1,5).

With the increasing use of CT scanning in polytrauma patients, the diagnosis of external ureteral trauma is increasingly made radiographically before the clinical signs.

3.3 Prevention of iatrogenic trauma
The prevention of iatrogenic trauma to the ureters depends upon the visual identification of the ureters and careful intraoperative dissection in their proximity (5,6,9). The use of prophylactic preoperative ureteral stent insertion assists in visualisation and palpation and is often used in complicated cases. However, it does not decrease the rate of injury (5). Apart from its evident disadvantages (potential complications and cost), a stent may alter the location of the ureter and diminish its flexibility (6,15). Stenting is probably also useful in secondary prevention by making it easier to detect ureteral injury (6). Routine prophylactic stenting is generally not cost-effective (6). In hysterectomy, it was estimated to become cost-effective when the rate of injury exceeded 3.2% (11), and it is therefore advocated only in selected patients with risk factors (15).

Another form of secondary prevention is intraoperative cystoscopy after intravenous dye injection, which can provide confirmation of ureteral patency (7). Routine cystoscopy has minimal risks and markedly increases the rate of ureteral injury detection (10). However, there are significant costs to its universal use. It has been estimated to be cost-saving for benign gynaecological operations with a threshold of injury above the rate of 1.5-2% (7).

3.4 Management
Management of a ureteral trauma depends on many factors concerning the nature, severity and location of

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### Table 5 – Incidence of ureteral injury in various procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynaecological (7,13,14)</td>
<td></td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>0.02 – 0.5</td>
</tr>
<tr>
<td>Abdominal hysterectomy</td>
<td>0.03 – 2.0</td>
</tr>
<tr>
<td>Laparoscopic hysterectomy</td>
<td>0.2 – 6.0</td>
</tr>
<tr>
<td>Urogynaecological (anti-incontinence/prolapse)</td>
<td>1.7 – 3.0</td>
</tr>
<tr>
<td>Colorectal (9,15)</td>
<td>0.3 - 10</td>
</tr>
<tr>
<td>Ureteroscopy (8)</td>
<td></td>
</tr>
<tr>
<td>Mucosal abrasion</td>
<td>0.3 – 4.1</td>
</tr>
<tr>
<td>Ureteral perforation</td>
<td>0.2 – 2.0</td>
</tr>
<tr>
<td>Intussusception / avulsion</td>
<td>0 – 0.3</td>
</tr>
</tbody>
</table>
the injury. Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement. Partial injuries can be repaired immediately with a stent or urine diversion by a nephrostomy tube. Stenting may be helpful because it provides canalisation and may decrease the risk of stricture (5). On the other hand, its insertion has to be weighed against potentially aggravating the ureteral injury. Immediate repair of ureteral injury is usually advisable. However, in cases of unstable trauma patients, a “damage control” approach is preferred with ligation of the ureter, diversion of the urine (e.g. by a nephrostomy), and a delayed definitive repair.

Injuries that are diagnosed late are usually treated first by a nephrostomy tube with or without a stent (5). Retrograde stenting is often unsuccessful in this setting.

The endourological treatment of small ureteral fistulae and strictures is safe and effective in selected cases (19), but an open surgical repair is often necessary. Laparoscopic and robotic repairs of ureteral injuries are increasingly common in the literature (20). The basic principles for any surgical repair of a ureteral injury are outlined in Table 6, while the various options for surgical reconstruction are given in Table 3. Proximal and mid-ureteral injuries can often be managed by primary ureteroureterostomy, while a distal injury is often treated with ureteral reimplantation. Wide debridement is highly recommended for gunshot wound injuries due to the ‘blast effect’ of the injury.

Table 6 – Principles of surgical repair of ureteral injury

<table>
<thead>
<tr>
<th>Principles of surgical repair of ureteral injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debridement of necrotic tissue</td>
</tr>
<tr>
<td>Spatulation of ureteral ends</td>
</tr>
<tr>
<td>Watertight mucosa-to-mucosa anastomosis with absorbable sutures</td>
</tr>
<tr>
<td>Internal stenting</td>
</tr>
<tr>
<td>External drain</td>
</tr>
<tr>
<td>Isolation of injury with peritoneum or omentum</td>
</tr>
</tbody>
</table>

Table 7 – Reconstruction option by site of injury

<table>
<thead>
<tr>
<th>Site of injury</th>
<th>Reconstruction options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper ureter</td>
<td>Uretero-ureterostomy</td>
</tr>
<tr>
<td></td>
<td>Transuretero-ureterostomy</td>
</tr>
<tr>
<td></td>
<td>Uretero-calycostomy</td>
</tr>
<tr>
<td>Mid ureter</td>
<td>Uretero-ureterostomy</td>
</tr>
<tr>
<td></td>
<td>Transuretero-ureterostomy</td>
</tr>
<tr>
<td>Lower ureter</td>
<td>Ureteral reimplantation and a Boari flap</td>
</tr>
<tr>
<td>Complete</td>
<td>Ureteral reimplantation with a psoas hitch</td>
</tr>
<tr>
<td></td>
<td>Ileal interposition graft</td>
</tr>
<tr>
<td></td>
<td>Autotransplantation</td>
</tr>
</tbody>
</table>

3.4.1 **Uretero-ureterostomy**
A uretero-ureterostomy is the most common repair performed (1), usually in the upper and mid-ureter.

3.4.2 **Uretero-calycostomy**
In pelvic-ureteral junction or upper ureteral injury, the ureter can be anastomosed to a lower pole calyx of the ipsilateral kidney.

3.4.3 **Transuretero-ureterostomy**
The distal end of the injured ureter is ligated. The proximal end is transposed across the midline through a retroperitoneal window and anastomosed to the contralateral ureter. This is a valid option in extensive ureteral loss or when pelvic injuries preclude ureteral reimplantation.

3.4.4 **Ureteral reimplantation with a psoas hitch**
Distal ureteral injuries are best managed by ureteral reimplantation because the primary trauma usually jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral reimplantation remains unresolved in the literature. The risk for clinically significant reflux should be weighed against the risk for ureteral obstruction.
A psoas hitch with non-absorbable sutures between the bladder and the ipsilateral psoas tendon is usually needed to bridge the gap and to protect the anastomosis from tension. It is important to avoid the genitofemoral nerve. The contralateral superior vesical pedicle may be divided to improve bladder mobility.

3.4.5  
**Ureteral reimplantation with a Boari flap**

In extensive mid-lower ureteral injury, the large gap can be bridged with a tubularised L-shaped bladder flap. It is a time-consuming operation and not usually suitable in the acute setting.

3.4.6  
**Ileal interposition graft**

If it is necessary to replace the entire ureter or a long ureteral segment, the ureter can be replaced using a segment of the intestines, usually the ileum. This should be avoided in patients with impaired renal function or known intestinal disease. The ileal segment is placed in the isoperistaltic orientation between the renal pelvis and the bladder. Follow-up should include serum chemistry to diagnose hyperchloremic metabolic acidosis (21). A review of long-term complications reported complication rates of 3% anastomotic stricture and 6% fistulae (22).

3.4.7  
**Autotransplantation**

In cases of extensive ureteral loss or after multiple attempts at ureteral repair, the kidney can be relocated to the pelvis. The renal vessels are anastomosed to the iliac vessels and a ureteral reimplantation is performed (23).

3.5  
**Statements and recommendations on ureteral trauma**

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic ureteral trauma gives rise to the commonest cause of ureteral injury.</td>
<td>3</td>
</tr>
<tr>
<td>Gunshot wounds account for the majority of penetrating ureteral trauma, while motor vehicle accidents account for most of blunt injuries.</td>
<td>3</td>
</tr>
<tr>
<td>Ureteral trauma usually accompanies severe abdominal and pelvic injuries.</td>
<td>3</td>
</tr>
<tr>
<td>Haematuria is unreliable and a poor indicator of ureteral injury.</td>
<td>3</td>
</tr>
<tr>
<td>The diagnosis of ureteral trauma is often delayed.</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative prophylactic stents do not prevent ureteral injury, but may assist in its detection.</td>
<td>2</td>
</tr>
<tr>
<td>Endourological treatment of small ureteral fistulae and strictures is safe and effective.</td>
<td>3</td>
</tr>
<tr>
<td>Major ureteral injuries require ureteral reconstruction following temporary urinary diversion.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual identification of the ureters and meticulous dissection in their vicinity are mandatory to prevent ureteral trauma during abdominal and pelvic surgery.</td>
<td>A*</td>
</tr>
<tr>
<td>High level of suspicion for ureteral injury should be maintained in all abdominal penetrating trauma, and in deceleration-type blunt trauma.</td>
<td>A*</td>
</tr>
<tr>
<td>Preoperative prophylactic stents do not prevent ureteral injury and therefore it is recommended that it be used in selected cases (based on risk factors and surgeon’s experience).</td>
<td>B</td>
</tr>
</tbody>
</table>

*upgraded following panel consensus

3.6  
**References**


   http://www.ncbi.nlm.nih.gov/pubmed/16406903
4. **BLADDER TRAUMA**

4.1 **Background, incidence and aetiology**

4.1.1 *External (non-iatrogenic) trauma*

Motor vehicle traffic collisions are the most common cause of bladder rupture by blunt trauma (1-6). Falls, industrial trauma/pelvic crush injuries and blows to the lower abdomen are other important causes (1,3,7).

- 60-90% of patients with bladder injuries caused by blunt trauma have associated pelvic fractures (1,3,7), and 44% of patients with bladder injuries have at least 1 other intra-abdominal injury (8).
- According to the U.S. National Trauma Data Bank, pelvic fractures are associated with bladder injuries in only 3.58% of cases (5).
- The majority of ruptures are extraperitoneal, followed by intraperitoneal ruptures and combined intra- and extraperitoneal ruptures (1,3,6-8).
- Combination of bladder and urethral injury is present in about 15% of cases (3,7).

Intraperitoneal ruptures are caused by a sudden rise in intravesical pressure, secondary to a blow to the pelvis or lower abdomen. Because the bladder dome is the weakest and most mobile point of the bladder, ruptures will usually occur at that site with disruption of the peritoneal surface and concomitant urinary extravasation (3,7).

Extraperitoneal ruptures are almost always associated with pelvic fractures (1). The bladder injury is usually caused by distortion of the pelvic ring with shearing of the anterolateral bladder wall near the bladder base (at its fascial attachments) or by a “counter-coup” bursting opposite the fracture site. Occasionally, the bladder is directly perforated by a sharp bony fragment (3,7,9).

4.1.2 *Iatrogenic trauma*

The bladder is the urologic organ most often subject to iatrogenic injury (10). Iatrogenic bladder trauma (IBT) is defined as full-thickness laceration. Table 8 shows the incidence of bladder perforation during various procedures.

**Table 8: Incidence of bladder perforation during various procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External</strong></td>
<td></td>
</tr>
<tr>
<td>Obstetrics</td>
<td></td>
</tr>
<tr>
<td>Caesarean delivery (11,12)</td>
<td>0.0016–0.94</td>
</tr>
<tr>
<td>Gynaecology</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic sterilisation (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diagnostic laparoscopy (3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Laparoscopic hysterectomy (13,14) (benign)</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>Vaginal hysterectomy (13,14) (benign)</td>
<td>0.44–6.3</td>
</tr>
<tr>
<td>Abdominal hysterectomy (13,14) (benign)</td>
<td>0.73–2.5</td>
</tr>
<tr>
<td><strong>General surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Inguinal canal surgery (3,15)</td>
<td>0.08–0.3</td>
</tr>
<tr>
<td>Tunnelling of synthetic bypass grafts (16)</td>
<td>Case reports</td>
</tr>
<tr>
<td><strong>Urology</strong></td>
<td></td>
</tr>
<tr>
<td>Retropubic male sling (17)</td>
<td>8.0–50</td>
</tr>
<tr>
<td>Laparoscopic sacrocolpopexy (18)</td>
<td>1.9</td>
</tr>
<tr>
<td>Burch colposuspension (19,20)</td>
<td>1.0–1.2</td>
</tr>
<tr>
<td>Synthetic midurethral slings (all) (19,20)</td>
<td>6.0–6.6</td>
</tr>
<tr>
<td>Transobturato route (19,21)</td>
<td>0–2.4</td>
</tr>
<tr>
<td>Retropubic route (19,20)</td>
<td>3.2–8.5</td>
</tr>
<tr>
<td>Pubovaginal sling (19)</td>
<td>2.8</td>
</tr>
<tr>
<td>Transvaginal mesh surgery (22,23)</td>
<td>1.5–3.5</td>
</tr>
<tr>
<td>Anterior colporraphy (22)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Internal</strong></td>
<td></td>
</tr>
<tr>
<td>TURB (24-28)</td>
<td>1.3–58</td>
</tr>
<tr>
<td>TURP (3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cystography (29)</td>
<td>Case reports</td>
</tr>
</tbody>
</table>

*TURB = transurethral resection of the bladder; TURP = transurethral resection of the prostate.*
External IBT mostly occurs during obstetric and gynaecologic procedures, followed by general surgical and urologic interventions (10).

Internal IBT mainly occurs during transurethral resection of the bladder (TURB) for the treatment of tumours. Large perforations requiring intervention are rare (0.16–0.57%) (30). Extraperitoneal perforations are more frequent than intraperitoneal ones.

_Iatrogenic foreign body inside the bladder_ can be caused by failure of the resectoscope, ureteric stents, bladder catheters, forgotten pieces of surgical gauze, sutures, or staples used in pelvic procedures (31,32), unrecognised perforation or erosion of mesh for urinary incontinence or pelvic organ prolapse (31).

### 4.2 Risk factors

Individuals who are driving under the influence of alcohol are more likely to have a distended bladder and an MVA. Driving after drinking alcohol is therefore a risk factor for bladder injury (33) (LE: 3). A full bladder is a risk factor for intraperitoneal ruptures (3,4,7).

The highest risk of bladder injury in pelvic fracture was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm and fractures of the rami pubis (5,6). An Isolated acetabular fracture is not likely to be associated with bladder injury (6). Risk factors for IBT are shown in table 9.

**Table 9: Risk factors for IBT associated with various procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean delivery (11,12)</td>
<td>Previous caesarean delivery&lt;br&gt;Previous pelvic surgery&lt;br&gt;Presence of labour&lt;br&gt;Station of presenting foetal part ≥ + 1&lt;br&gt;Foetal weight &gt; 4 kg</td>
</tr>
<tr>
<td>Hysterectomy (14,34)</td>
<td>Malignancy&lt;br&gt;Endometriosis&lt;br&gt;Prior pelvic surgery&lt;br&gt;Concomitant anti-incontinence or pelvic organ prolapse surgery</td>
</tr>
<tr>
<td>General surgery (10)</td>
<td>Malignancy&lt;br&gt;Diverticulitis&lt;br&gt;Inflammatory bowel disease</td>
</tr>
<tr>
<td>Midurethral sling operations (19,21,35,36)</td>
<td>Retropubic route&lt;br&gt;Previous caesarean delivery&lt;br&gt;Previous colposuspension&lt;br&gt;BMI &lt; 30 kg/m²&lt;br&gt;Rectocele&lt;br&gt;Procedures under local anaesthesia&lt;br&gt;Inexperienced surgeon</td>
</tr>
<tr>
<td>TURB (37,38,24-26,30)</td>
<td>Tumour size&lt;br&gt;Elderly patients&lt;br&gt;Pretreated bladder (previous TURB, intravesical instillation, radiotherapy)&lt;br&gt;Tumour location at the dome or in diverticulum</td>
</tr>
</tbody>
</table>

_BMI = body mass index; TURB = transurethral resection of the bladder._

### 4.3 Clinical signs and symptoms

#### 4.3.1 External trauma

Clinical presentation of bladder injury might be blurred by associated pelvic fracture, visceral and/or vascular injuries (3).

The cardinal sign of bladder injury is gross haematuria, present in 82-95% of patients (1,4,7,39). The presence of bladder injury is strongly correlated with the combination of pelvic fracture and gross haematuria (40). Thus, the classic combination of pelvic fracture and gross haematuria constitutes an absolute indication for further imaging of the bladder (3,7,39,40) (LE: 3). Approximately 5-15% of patients with bladder rupture only
have microhaematuria (6). Existing data do not support lower urinary tract imaging in all patients with pelvic fracture or microscopic haematuria alone. In case of gross haematuria without pelvic fracture, microhaematurie with pelvic fracture and isolated microhaematuria, the decision for further imaging should be based on the presence of other clinical signs and symptoms and the site of maximal trauma (3,7).

Other signs and symptoms are abdominal tenderness (up to 97%) (1), inability to void, bruises over the suprapubic region, and abdominal distension (in case of urinary ascites) (3,4,7,41). Extravasation of urine may result in swelling in the perineum, scrotum (through the inguinal canal), and thighs, as well as along the anterior abdominal wall within the potential space between the transversalis fascia and the parietal peritoneum (3,7).

In case of intraperitoneal rupture, reabsorption of urea nitrogen and creatinine through the peritoneal cavity causes uraemia and elevated creatinine levels (3,7).

In penetrating abdominal trauma, location of entrance and exit wounds at the lower abdomen, perineum or buttocks should raise suspicion of bladder injury (3,4).

Severe bladder injuries may be accompanied with soft tissue avulsion of the lower abdominal wall and/or perineum, as well as by bladder tissue loss due to trauma or infection (42).

CAUTION: in case of urinary retention and/or bloody urethrorraghy, a (concomitant) urethral injury must be suspected and a retrograde urography must be performed to assess the integrity of the urethra, before further manipulation of the urethra (e.g. urinary catheter for a cystography) (3,43).

4.3.2 Iatrogenic trauma
4.3.2.1 Perioperative: external iatrogenic bladder trauma
Direct inspection is the most reliable method of assessing bladder integrity. Suggestive signs are extravasation of urine, visible laceration, clear fluid in the surgical field, appearance of the bladder catheter, and blood and/or gas in the urine bag during laparoscopy (3,11,12). Intravesical instillation of methylene blue may be helpful (3,11,44). If bladder perforation is present, the integrity of the ureteric orifices should be checked (3,44).

4.3.2.2 Perioperative: internal iatrogenic bladder trauma
Fatty tissue, a dark space between detrusor muscle fibres, or the visualisation of bowel suggests perforation (24). Signs of major perforation are the inability to distend the bladder, a low return of irrigation fluid, and abdominal distension (26,28,45,46).

4.3.2.3 Postoperative: unrecognised bladder injury
Clinical signs and symptoms include haematuria, lower abdominal pain, abdominal distension, ileus, peritonitis, sepsis, urine leakage from the wound, decreased urinary output, and increased serum creatinine (3,28,44,46-48).

4.3.3 Intravesical foreign body
Symptoms of an intravesical foreign body include dysuria, recurrent urinary tract infection, frequency, urgency, haematuria, and perineal/pelvic pain (31,32,49-51). Bladder calculi usually develop once the foreign body has been present > 3 mo (32,49,52).

4.4 Imaging
4.4.1 Cystography (conventional or CT)
Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and in case of suspicion of a iatrogenic bladder injury in the postoperative setting (3,4,7,9,53,54). Although both conventional and CT cystography have a comparable sensitivity and specificity of respectively 90-95 and 100% (1,55), CT cystography has the advantage of diagnosing other injuries or causes of abdominal pain (1,3,53). CT or conventional cystography must be performed using slow retrograde filling of the bladder with a minimum of 350 mL of dilute contrast material (9). A plain film, a complete filling film and a post-drainage film is the absolute minimum during conventional cystography (9). With CT cystography, 3D reconstruction is helpful in delineating the location of bladder rupture and makes a postdrainage series unnecessary (56).

With intraperitoneal extravasation, free contrast medium is visualised in the abdomen, highlighting bowel loops and/or outlining abdominal viscera such as the liver (3,48). Extraperitoneal bladder injury is associated with flame-shaped areas of contrast extravasation in the perivesical soft tissues (3).

4.4.2 Cystoscopy
Cystoscopy is the preferred method to detect intra-operative bladder injuries. Routine postoperative cystoscopy after gynaecological procedures remains controversial, but it is recommended for all procedures where bladder injury is suspected (34). Vakili et al. reported that 64.7% of bladder injuries during hysterectomy
were not detected before cystoscopy and therefore, they advise the routine use of cystoscopy after hysterectomy and every major gynaecological procedure (14).

Cystoscopy is recommended after minimally invasive synthetic suburethral sling operations by retropubic route to detect any perforation of the bladder (or urethra) (20,35,57). During cystoscopy, the bladder must be adequately distended and a 70° optic or a flexible cystoscope must be used to inspect areas close to the bladder neck (31,49,58-60). The use of routine cystoscopy for insertion by obturator route is controversial as bladder injuries are rare but not impossible (20,21,36,49,57,61). Cystoscopy after transvaginal mesh procedures is preferable but not mandatory (62).

Cystoscopy with adequate distension of the bladder may directly visualise the laceration and is able to correlate the lesion with the position of the trigone and ureteral orifices (48). Inability of bladder distension during cystoscopy suggests a large perforation. Cystoscopy is the preferred examination method in case of suspicion of a iatrogenic foreign body (32,49,50,63,64).

4.4.3 Excretory phase of CT or IVP
Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is insufficient to rule out bladder injury (1,3,7,9). However, the finding of contrast extravasation during the excretory phase is suggestive of bladder injury.

4.4.4 Ultrasound
Intraperitoneal fluid or an extraperitoneal collection suggests intraperitoneal or extraperitoneal perforation, respectively. Ultrasound alone is insufficient in the diagnosis of bladder trauma (3).

4.5 Treatment
If operative bladder repair is performed, the preferred method is two-layer vesicorraphy (mucosa-detrusor) with absorbable sutures (3,7,11,12,34).

4.5.1 External trauma
4.5.1.1 Blunt trauma: extraperitoneal rupture
Most patients with uncomplicated extraperitoneal rupture can be managed safely by catheter drainage alone, even in the presence of extensive retroperitoneal or scrotal extravasation (3,4,7,8) (LE: 3). However, bladder neck involvement, the presence of bone fragments in the bladder wall, concomitant rectal injury or entrapment of the bladder wall will necessitate surgical intervention (3,4,7,33) (LE: 3).

In orthopaedic surgery, there is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthetic material. In order to prevent infection of this osteosynthetic material, there is also an increasing interest to suture an extraperitoneal rupture (1,3,7). In case of surgical exploration for other injuries, an extraperitoneal rupture should be sutured concomitantly in order to reduce infective complications (especially paravesical abscess) (1,3,7,8).

4.5.1.2 Blunt trauma: intraperitoneal rupture
Intraperitoneal ruptures occurring after blunt trauma should always be managed by formal surgical repair (1,3,4,7) (LE: 3). The rationale for this is that intraperitoneal extravasation of urine can lead to peritonitis, intra-abdominal sepsis and death (8).

Abdominal organs should be inspected for possible associated injuries and urinoma must be drained, if present. In the absence of other intra-abdominal injuries, laparoscopic suturing of the intraperitoneal rupture is possible (1).

4.5.1.3 Penetrating injuries
All bladder perforations resulting from penetrating trauma should undergo emergency exploration, debridement of devitalised bladder muscle and subsequent bladder repair (3,4,7) (LE: 3). A midline exploratory cystotomy is advised to inspect the bladder wall and distal ureters (3,7).

4.5.1.4 Bladder injuries with avulsion of lower abdominal wall or perineum and/or bladder tissue loss
In these cases, direct closure of the traumatised bladder will lead to excessive tension, resulting in ischemia and eventual break-down of the repair. Therefore, a bladder wall substitute is needed for the repair of bladder defects as well as a substitute to restore the lower abdominal wall or perineum. Use of a pedicled vastus lateralis myocutaneous flap has been reported for posttraumatic bladder reconstruction and soft-tissue coverage for the lower abdomen or perineum (42).
4.5.2 Iatrogenic injuries
Perforations recognised intraoperatively are primarily closed. For bladder injuries not recognised during surgery or for internal injuries, a distinction must be made between intraperitoneal and extraperitoneal injuries. For intraperitoneal injuries, the standard of care is surgical exploration with repair (3,48). In selected cases (in the absence of peritonitis or ileus), conservative management with continuous bladder drainage and antibiotic prophylaxis may be offered (3,48). In addition to this conservative treatment, placement of an intraperitoneal drain has been advocated, especially when the lesion is larger (26, 46, 65) . If surgical exploration is performed after TURB, meticulous bowel inspection is required to rule out concomitant injury (30).

For extraperitoneal injuries, conservative treatment with bladder drainage and antibiotic prophylaxis is advised (3,7,25,27,28). Large extraperitoneal perforations complicated by symptomatic extravesical collections require drainage, with or without closure of the perforation (28).

If perforation occurs during TURB, immediate intravesical instillation with chemotherapeutic agents should not be performed (66). If bladder perforation is encountered during midurethral sling or transvaginal mesh procedures, sling reinsertion and urethral catheterisation (1–2 d) should be performed (36).

4.5.3 Intravesical foreign body
For perforated or eroded meshes, the intravesical portion must be removed by open cystotomy or endoscopically (49-52, 60,62,63). The choice depends on the surgeon’s level of experience and the location of the mesh (49,51). For other types of foreign body, cystoscopic removal is performed or a cystotomy if that fails (32).

4.5.4 Postoperative management
Postoperative continuous bladder drainage is required to allow the bladder to heal and to prevent elevated intravesical pressure and disruption of the suture line (34). For external trauma and external iatrogenic bladder injuries, the bladder catheter is maintained for 7-14 days, depending on the extent of laceration (3,7,11,34). Cystography upon removal of the catheter is advised. In case of contrast extravasation, continuous bladder drainage is maintained for at least one week and until cystography shows no longer extravasation (3,34). For conservatively treated internal iatrogenic bladder injuries, a catheter duration is proposed of 5 and 7 days for respectively extra- and intraperitoneal perforations (25) (LE: 3)

4.6 Statements and recommendations on bladder trauma

4.6.1 Statements

| Extraperitoneal bladder perforations are more frequent than intraperitoneal perforations. | LE: 3 |
| Risk of bladder perforation during midurethral sling operations for stress urinary incontinence is lower for the obturator route compared to the retropubic route. | LE: 1a |
| The combination of pelvic fracture and gross haematuria is highly suggestive of bladder injury. | |
| Cystography should be performed with gentle filling of the bladder with at least 350 mL of dilute contrast. Passive bladder filling by clamping the catheter during the excretory phase of CT or IVP is insufficient for diagnosis. | |

4.6.2 Recommendations

| Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and in case of suspicion of a iatrogenic bladder injury in the postoperative setting. | GR: B |
| Cystoscopy, conventional or computed tomography, is required in the presence of gross haematuria and pelvic fracture. | GR: B |
| Cystoscopy is recommended after suburethral sling operations via the retropubic route and major gynaecologic operations and is optional after any other type of sling procedure or transvaginal mesh procedure. | GR: B |
| In the absence of bladder neck involvement and/or associated injuries that require surgical intervention, extraperitoneal bladder ruptures caused by blunt trauma are managed conservatively. | GR: B |
| Intraperitoneal bladder ruptures by blunt trauma, and any type of bladder injury by penetrating trauma, must be managed by emergency surgical exploration and repair. | GR: B |
| Conservative management is an option for small uncomplicated iatrogenic intraperitoneal bladder perforations. | GR: C |
4.7 References


5 URETHRAL TRAUMA

5.1 Anterior urethral injuries

Anterior urethral injuries result from blunt trauma more frequently than from penetrating trauma (Table 10). Blunt trauma accounts for more than 90% of urethral injuries (1). In blunt trauma, the relatively immobile bulbar urethra is trapped and compressed by a direct force upon it, which then presses it against the inferior surface of the symphysis pubis. One of the mechanisms responsible for such an injury is ‘fall-astride’ or ‘straddle’ injury of the bulbar urethra (2-4).

A less common cause of blunt anterior urethral trauma is penile fracture. This type of rupture of the corpus cavernosum usually occurs during intercourse. In these injuries, the urethra is involved in 20% of the cases (5). Intraluminal stimulation of the urethra with foreign objects has also been reported to cause anterior urethral trauma.

Individuals with paraplegia, who use a constriction device for urinary incontinence and then forget to release the band because of the lack of sensation, can cause severe ischaemic injuries to themselves involving the penis and urethra.

Penetrating injuries to the anterior urethra usually result from gunshot wounds and involve the pendulous and bulbar urethral segments equally. These injuries are associated with penile and testicular injury. These injuries
can also involve the rectum, which may result in pelvic abscesses and the formation of fistulae (6,7). Other less frequent causes of external anterior urethral injuries include stab wounds, penile amputation, and impalement. Iatrogenic urethral injuries caused by instruments are by far the most common cause of urethral trauma.

Table 10: Examples of urethral injury

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt trauma</td>
<td>Vehicular accidents</td>
</tr>
<tr>
<td></td>
<td>Fall astride (straddle – bicycle, fences, inspection covers)</td>
</tr>
<tr>
<td></td>
<td>Kicks in the perineum</td>
</tr>
<tr>
<td>Sexual intercourse</td>
<td>Penile fractures</td>
</tr>
<tr>
<td></td>
<td>Urethral intraluminal stimulation</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>Gunshot wounds</td>
</tr>
<tr>
<td></td>
<td>Stab wounds</td>
</tr>
<tr>
<td></td>
<td>Dog bites</td>
</tr>
<tr>
<td></td>
<td>External impalement</td>
</tr>
<tr>
<td></td>
<td>Penile amputations</td>
</tr>
<tr>
<td>Constriction bands</td>
<td>Paraplegia</td>
</tr>
<tr>
<td>Iatrogenic injuries</td>
<td>Endoscopic instruments</td>
</tr>
<tr>
<td></td>
<td>Urethral catheters/dilators</td>
</tr>
</tbody>
</table>

5.2 Posterior urethral injuries

In industrialised societies, pelvic-fracture-related urethral injuries of the posterior urethra are the commonest non-iatrogenic injuries and are usually due to MVAs.

The male posterior urethra is injured in 4-19% of pelvic fractures. The female urethra is rarely injured (0-6%), and mostly by contusion or bone fragments.

During crush or deceleration impact injury, the severe shearing forces needed to fracture the pelvis are transmitted to the prostatomembranous junction. This results in disruption of the prostate from its connection to the anterior urethra at the prostatic apex.

Typical injuries of the bladder neck and prostate in adults show several characteristic features. They occur in the midline of both the bladder neck and prostatic urethra, in association with either a lateral compression fracture of the pelvis or an open-book injury (8).

Urethral ruptures can be divided into partial and complete ones. Complete urethral ruptures can occur as distraction defects when associated with pelvic fractures. In urethral distraction defects, there is a gap between the disrupted end of the urethra. The dismembered ends of the urethra retract and fibrous tissue fills the space between them. There is no urethral wall in the scarred space, and any lumen represents merely a fistulous tract between the urethral stumps (8,9).

Injury to the posterior urethra is most likely to occur with unstable pelvic fractures (10-16), bilateral ischiopubic rami fractures (‘straddle fracture’), and symphysis pubis diastasis. In particular, the combination of straddle fractures with diastasis of the sacroiliac joint has the highest risk of urethral injury; the odds ratio is about seven times higher than for either straddle injuries or sacroiliac (‘Malgaigne’) fractures (Table 11) (4).

Table 11: Odds ratio of suffering urethral injury with different types of pelvic fracture

<table>
<thead>
<tr>
<th>Type of fracture</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ramus</td>
<td>0.6</td>
</tr>
<tr>
<td>Ipsilateral rami</td>
<td>0.8</td>
</tr>
<tr>
<td>Malgaigne’s (vertical shear)</td>
<td>3.4</td>
</tr>
<tr>
<td>Straddle</td>
<td>3.9</td>
</tr>
<tr>
<td>Straddle plus sacroiliac</td>
<td>24.0</td>
</tr>
</tbody>
</table>

Odds ratio: describes the strength of association or non-independence between urethral injury and types of pelvic fracture.

By themselves, urethral injuries are never life-threatening, except as a consequence of their close association with pelvic fractures and multiple organ injuries, which occur in about 27% of cases (17). However, they can result in very significant delayed morbidity. Strictures, incontinence and erectile dysfunction are well-recognised associated problems that interfere with the quality of life. It is important to diagnose and treat such urethral injuries efficiently to reduce the severity and duration of such complications.
Erectile dysfunction occurs in 20-60% of patients after traumatic posterior urethral rupture (9,18-20). The severity of the initial injury is the most important determining factor for impotence. The incidence of erectile dysfunction caused by the open surgical repair itself is 5% or less (9,22). King reported an incidence of 42% in cases of pelvic fracture and urethral injury, but only 5% when the urethra was not injured (19). Barbagli et al. reported an incidence of 60% in patients with posterior urethral injury compared with 14% in patients with bulbar injury (23).

Bilateral pubic rami fractures are the most frequent cause of impotence. Impotence is most commonly neurogenic, due to bilateral damage of the cavernous nerves at the prostatomembranous urethra behind the symphysis pubis (24,25). Associated vasculogenic erectile failure may occur in up to 80% of cases (26). Spontaneous return of potency may occur up to 2 years after injury (27).

5.3 Urethral injuries in women
These are rare events since the female urethra is short and mobile, without any significant attachments to the pubic bone. They are often accompanied by severe pelvic fractures, in which bony fragments of the fractured pelvis can lacerate the urethra. Urethral injuries in females often extend into the bladder neck or vagina and disrupt the normal continence mechanism (28,29). Injury to the female urethra is usually a partial tear of the anterior wall and is rarely a complete disruption of the proximal or distal urethra (30).

5.4 Penetrating injuries to the perineum
These can occur after external violence, e.g. gunshot or stab wounds, or as iatrogenic injuries caused by endoscopic instruments or during surgery for vaginal repair. In developing countries, urethral and bladder neck damage are quite often caused by ischaemic injury during obstructed labour.

5.5 Diagnosis: initial emergency assessment
5.5.1 Clinical assessment
Firstly, and most importantly, urethral bleeding and voiding difficulty should raise the suspicion of urethral trauma, although their absence does not rule out urethral injury. The presentation of clinical symptoms or signs may be delayed (2).

Table 12 lists the clinical indicators of acute urethral trauma that warrant a complete urethral evaluation.

**Table 12: Clinical signs of urethral injuries**

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood at the meatus</td>
</tr>
<tr>
<td>Blood at the vaginal introitus</td>
</tr>
<tr>
<td>Haematuria</td>
</tr>
<tr>
<td>Pain on urination - Dysuria</td>
</tr>
<tr>
<td>Inability to void</td>
</tr>
<tr>
<td>Haematoma</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>'High-riding’ or “absent” prostate</td>
</tr>
</tbody>
</table>

Blood at the meatus is present in 37-93% of patients with posterior urethral injury, and in at least 75% of patients with anterior urethral trauma (31,32). When urethral trauma is suspected an attempt of urethral catheterisation should be carried out by experienced hands and the balloon of the Foley catheter should only be inflated if clear urine flows out. It is extremely unlikely that gentle passage of a urethral catheter will do any additional damage (33,34). Although it has been suggested that passing a catheter may convert a partial tear into one that is complete (35), there are no convincing data indicating that there is a higher rate of infection or urethral stricture after a single attempt at catheterisation (1). However, the most prudent approach is to carry out urethrography prior to an attempted catheterisation. In an unstable patient, an attempt to pass a urethral catheter should be performed, but if there is any difficulty, a suprapubic catheter should be placed using ultrasound guidance and a retrograde urethrogram must be performed once the patient has been stabilised.

Blood at the vaginal introitus is present in more than 80% of female patients with pelvic fractures and co-existing urethral injuries (28).

Although non-specific, haematuria on a first-voided specimen may indicate urethral injury. The amount of urethral bleeding correlates poorly with the severity of the injury. A mucosal contusion or small partial tear may be accompanied by copious bleeding, while total transection of the urethra may result in little bleeding (36).
Urethral disruption should be suspected in patients with urethral injuries who report having trouble with voiding or an inability to void.

Urethral bleeding or urinary extravasation can cause penile/scrotal swelling, or even more extensive haematoma. An assessment for concomitant genital injuries is therefore mandatory in every case of external urethral trauma.

Rectal examination may reveal a ‘high-riding’ prostate, which is a relatively unreliable finding in the acute phase of urethral injury. This is because the pelvic haematoma associated with pelvic fractures often precludes the adequate palpation of a small prostate, particularly in younger men (1). Blood on the examination finger is suggestive of a rectal injury associated with pelvic fractures.

5.5.2 Radiographic examination (Table 13)
Retrograde urethrography is the gold standard for evaluating urethral injury (30,37). A scout film should be performed first to assess the radiographic technique and to detect pelvic fractures and foreign bodies, such as bullets.

A scout film is performed by injecting 20-30 mL of contrast material while occluding the meatus. Films are taken in a 30°-oblique position, unless this is not possible because of the severity of the pelvic fractures and associated patient discomfort. The urethrogram allows for identification of the site and assessment of the extent of any injury. The image of extravasation but still bladder filling is typical for incomplete rupture, however massive extravasation without bladder filling suggests a complete rupture.

Ultrasoundography is not a routine investigation in the initial assessment of urethral injuries, but it can be very useful in determining the position of pelvic haematomas or the exact location of the bladder when a suprapubic catheter is indicated. Furthermore, penile ultrasound can help to rule out tunica albuginea ruptures in cases of blunt traumas to the penis. Although extratunical and cavernosal hematomas can be treated conservatively, tunical ruptures need immediate surgical repair.

Computed tomography and MRI have no place in the initial assessment of urethral injuries. However, they are useful in defining distorted pelvic anatomy after severe injury and assessing associated injuries of the penile crura, bladder, kidneys, and intra-abdominal organs (38,39).

Urethroscopy does not have any role in the initial diagnosis of urethral trauma in males. In females, however, where the short urethra precludes adequate retrograde urethrography, urethroscopy is an important adjunct to the physical examination for the identification and staging of urethral injuries (40).

<table>
<thead>
<tr>
<th>Table 13: Diagnostic tools for urethral injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urologist urethrography</td>
</tr>
<tr>
<td>Ultrasonography</td>
</tr>
<tr>
<td>Computed tomography</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Urethroscopy</td>
</tr>
</tbody>
</table>

5.6 Management
The management of urethral injuries remains controversial because of the variety of injury patterns, associated injuries and treatment options available. As already mentioned, the gold standard diagnostic procedure for suspected urethral injuries is retrograde urethrography. Treatment decisions are made according to the radiological results of the urethrography.

The American Association for Surgery of Trauma has proposed a classification for urethral injury. However, it is rarely used in practical everyday use. This is because the only useful information for clinicians is whether the urethra is partially or completely disrupted and the anatomical site of the injury as well as the concomitant local tissue damage.

5.6.1 Anterior urethral injuries
Retrograde urethrography is used to identify any extravasation. The next key information for the treatment decision is whether the cause of the urethral injury is based on a blunt or penetrating trauma. According to this information, treatment decisions are being made.
5.6.1.1 Blunt anterior urethral injuries

5.6.1.1.1 Acute management
Blunt anterior urethral injuries are associated with spongiosal contusion, which makes it more difficult to evaluate the limits of urethral debridement in the acute phase. Acute or early urethroplasty is therefore not indicated, and the best management is simply suprapubic diversion. Satisfactory urethral luminal recanalisation occurs in approximately 50% of partial anterior urethral disruptions (41,42).

Partial tears can be managed with a suprapubic catheter or with urethral catheterisation (30,33,41). Extravasated blood or urine from the urethral tear produces an inflammatory reaction that can progress to abscess formation. Prompt urinary diversion, together with the appropriate administration of antibiotics, decreases the incidence of potential complications as urethrocutaneous fistulae, periurethral diverticulae and rarely necrotising fasciitis (43).

5.6.1.1.2 Delayed management
After the patient has adequately recovered from any associated injuries, and the urethral injury has stabilised, the urethra can be thoroughly re-evaluated radiographically. When necessary, the appropriate reconstructive procedure is planned.

Short and flimsy strictures are managed with optical urethrotomy or urethral dilatation. Denser strictures require formal urethral reconstruction. Anastomotic urethroplasty is indicated in strictures of less than 1 cm in length.

Longer strictures of the anterior urethra should not be repaired by an end-to-end anastomosis in order to avoid chordee. In these cases, flap/graft urethroplasty is indicated. Almost all complete ruptures of the anterior urethra require anastomotic or patch urethroplasty at 3-6 months.

5.6.1.2 Penetrating anterior urethral injuries

5.6.1.2.1 Acute management
Stab wounds, gunshot wounds and dog bites to the urethra often involve the penis and testes and often require immediate exploration. During surgery, the urethral injury can be evaluated and repaired as needed. Urethral strictures form in fewer than 15% of these patients (44).

In complete disruptions, the corpus spongiosum is mobilised at the level of the injury and the urethral ends dissected distally and proximally. Urethral ends are spatulated and end-to-end anastomosis is fashioned over a catheter. Small lacerations are being sutured with fine absorbable material. Careful overclosure of the corpus spongiosum and skin prevents the subsequent formation of fistulae (17). Urethral debridement should be kept to a minimum since the spongiosum is well vascularised and so usually heals well. Peri-operative antimicrobial therapy is mandatory.

Most female urethral disruptions can be sutured primarily. These injuries often occur together with bladder ruptures. Often, the bladder injury is repaired primarily. The urethral disruption may be repaired at the same time. For proximal urethral injuries, urethral exposure is best obtained transvesically. Distal urethral injuries can be approached vaginally (30). The early repair of post-traumatic urethral fistulae can also be accomplished transvaginally (28,29).

5.6.1.2.2 Delayed management
If the urethra is so extensively disrupted that primary anastomosis is not feasible, then primary repair should be aborted. This occurs with defects of more than 1-1.5 cm in length. Instead, the urethra should be marsupialised preparatory to a two-stage urethral repair, and a suprapubic urinary diversion should be considered. A delayed elective procedure should be performed a minimum of 3 months after injury. There is no role for acute placement of a graft or flap in the initial management of any urethral injury, since this type of repair can be compromised by contamination or a decreased blood supply (45).

5.6.2 Posterior urethral injuries

5.6.2.1 Blunt posterior urethral injuries
In cases of prostatomembranous disruption, the degree of rupture has to be assessed. It is important to distinguish between complete and partial rupture in order to proceed with treatment. Complete rupture warrants further assessment of bladder neck injury, concomitant organ injuries, etc. Partial ruptures can be treated with the insertion of a suprapubic catheter.

5.6.2.1.1 Acute management
5.6.2.1.1.1 Partial posterior urethral rupture
Partial tears of the posterior urethra can be managed with a suprapubic or urethral catheter. Urethrography should be performed at 2-weekly intervals until healing has occurred (30,33). Injuries may heal without
significant scarring or obstruction if managed by diversion alone (46,47). Residual or subsequent stricture should be managed with urethral dilatation or optical urethrotomy if short and flimsy, and with anastomotic urethroplasty if dense or long (17,33).

5.6.2.1.1.2 Complete posterior urethral rupture
For complete prostatomembranous disruption caused by blunt trauma a suprapubic catheter is the primary treatment. Further treatment depends on the patient’s comorbidity and co-existing injuries. (48,49).

Acute treatment options after position of the suprapubic catheter include:
- primary (endoscopic) realignment;
- immediate open urethroplasty, which should be considered experimental and rarely or never used in patients without associated rectal or bladder neck injury.

Primary realignment
In the absence of indications for immediate exploration, posterior urethral disruption can be managed in a delayed primary fashion. Primary realignment requires placement of a suprapubic tube at the time of initial injury, with repair undertaken when the patient is stable, usually within 7 days. At this time, patients are stable, and most pelvic bleeding has resolved. The aim of internal realignment is to correct severe distraction injuries rather than to prevent a stricture occurring, although realignment will also ensure that a stricture is easily treated if it does occur (50).

Open realignment has been described (51), but it should be performed only in patients who undergo open abdominal or pelvic surgery for associated injuries or internal bone fixation. Haematomas that prevent adequate pelvic descent can be evacuated at this time in these cases.

Concomitant bladder neck or rectal injuries should usually be repaired immediately, and open or endoscopic urethral realignment over a catheter at the same time might be advisable. The reasons for immediate repair of bladder neck and rectal injury are:
- Unrepaired bladder neck injury risks incontinence and infection of the pelvic fractures.
- Unrepaired rectal injury carries the obvious risk of sepsis and fistulae. Early exploration is indicated to evacuate contaminated haematomas and to perform colostomy if necessary. Urethral realignment over a stenting catheter is appropriate in such cases (30,36,52-54).
- The overall condition of the patient and the extent of the associated injuries greatly affect the decision to proceed with primary realignment.

The proposed benefits of primary alignment are:
- A lower stricture rate than with suprapubic catheter placement alone (69% vs. 10%) (55), which avoids a second operation for urethral reconstruction in about one-third of patients (1).
- If scarring occurs, restoration of urethral continuity is simplified and may be accomplished by endoscopic procedures or dilatation.
- If urethroplasty is required later, it is technically easier when the prostate and urethra are well aligned. However, there is the disadvantage of a higher incidence of erectile dysfunction and incontinence when compared with delayed reconstruction (55,56).

The great variation of techniques used for primary realignment procedures confuses any comparison with delayed repair procedures (57,60). Primary realignment techniques include:
- simple passage of a catheter across the defect (59);
- catheter realignment using flexible/rigid endoscopes and biplanar fluoroscopy (61,62);
- use of interlocking sounds (‘railroading’) or magnetic catheters to place the catheter (60,63);
- pelvic haematoma evacuation and dissection of the prostatic apex (with or without suture anastomosis) over a catheter;
- catheter traction or perineal traction sutures to pull the prostate back to its normal location (64).

Realignment may be insufficient to join the margins of the severed urethra completely. Defects of 1.5-4.0 cm have been observed, even after catheter realignment (65). Traction on the catheter might not improve the healing of the urethra and could in fact harm continence. Sustained traction on the Foley balloon catheter can damage the remaining sphincter mechanism at the bladder neck as a result of pressure necrosis (1,52). Series that use immediate urethral realignment with minimal traction without suture repair bolsters report the most favourable results. Endoscopic primary realignment fulfils these criteria and should be used when a primary procedure is contemplated. However it has to be kept in mind, that success rates might be low.
A recent retrospective study showed that early endoscopic realignment is only successful in up to 21% (4 of 19 patients) (66). Current literature shows that erectile dysfunction, urinary incontinence and the re-stricture rate following primary realignment are reported to be approximately 35%, 5% and 60% respectively (67-82).

Immediate open urethroplasty
Immediate open urethroplasty of posterior injuries is not indicated because of poor visualisation and the inability to assess accurately the degree of urethral disruption during the acute phase, characterised by extensive swelling and ecchymosis. The difficulty in identifying structures and planes makes it harder to achieve adequate mobilisation and subsequent surgical apposition (17). Incontinence and impotence rates are higher than with the other techniques described in these guidelines (impotence 56%, incontinence 21%, re-stricture 49%) (30,46,50,53,55,83,84).

However, in posterior urethral injuries associated with concomitant bladder neck or rectal injuries, immediate open exploration, repair and urethral realignment over a catheter is advisable (30,36,52-54).

5.6.2.1.2 Delayed management of posterior urethral injuries
Delayed treatment options include:
- delayed primary urethroplasty (which implies primary repair within 2 weeks after injury and for which there is a lack of supporting evidence in male patients);
- delayed formal urethroplasty at 3 months after injury (the most standard approach);
- delayed endoscopic incision of the scar tissue between the urethral ends (so-called ‘cut-to-the-light’ or similar procedures).

Delayed primary urethroplasty
Delayed primary urethroplasty is mainly indicated in female urethral disruption, although no large series exists. It requires placement of a suprapubic tube at the time of initial injury, with repair undertaken when the patient is stable, usually within 14 days. Fewer than 50 cases have been reported, and most of these are individual case reports only (29).

Delayed primary repair tries to preserve as much urethral length as possible, and to avoid the urethra becoming embedded in dense scar tissue with consequent incontinence. Surgical exploration should be attempted via the retropubic route for proximal injuries, and the vaginal route for distal injuries (30).

Delayed formal urethroplasty
Delayed formal urethroplasty is the procedure of choice and the gold standard for the treatment of posterior urethral distraction defects. Most posterior urethral distraction defects are short, and can generally be resolved by a perineal approach anastomotic repair, provided that they are not associated with extensive haematoma-fibrosis and the bladder neck mechanism is occlusive and competent. After division of the bulbular urethra at the distal point of obliteration, mobilisation of a normal bulbular urethra to the base of the penis generally achieves 4-5 cm of elastic lengthening. This is usually sufficient to achieve a tension-free 2-cm spatulated overlap anastomosis, after bridging a gap of 2.0-2.5 cm without rerouting (17).

This technique has the advantage that associated injuries, damaged skin and tissues and pelvic haematoma have resolved by the time it is performed.

When the prostatobulbar gap is longer than 2-3 cm as a result of a high dislocation of the prostate, or when the available elongation of the mobilised urethra has been foreshortened by damage caused by a previous surgical procedure, additional procedures may be required. The following manoeuvres are carried out sequentially to gain sufficient anterior urethral mobility to bridge up to 8 cm of separation, and are referred to as the ‘progressive perineal approach’ (85):
- midline separation of the proximal corporal bodies;
- inferior pubectomy;
- supracorporal urethral rerouting.

In addition to its use as an initial therapy for posterior urethral distraction injuries, the progressive perineal approach can also be applied successfully to salvage procedures following failed repair. There are a number of circumstances that might preclude successful perineal anastomotic repair as either initial or salvage therapy. These circumstances probably represent fewer than 5% of cases and are shown in Table 14 (86,87).
Table 14: Circumstances that might preclude successful perineal anastomotic repair as either initial or salvage therapy (86,87)

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Alternative procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distraction defects longer than 7-8 cm</td>
<td>A tubed interposition flap of penile or perineal skin can be used for reconstruction. This is seldom required and most patients that require the use of flap urethroplasties have previous failed repairs of posterior urethral rupture.</td>
</tr>
<tr>
<td>Fistulae</td>
<td>These might require a combined abdominoperineal approach to secure adequate closure.</td>
</tr>
<tr>
<td>Synchronous anterior urethral stricture</td>
<td>The presence of anterior urethral stricture may compromise the blood supply to the bulbar urethra following division of the bulbar arteries, and these patients should be treated cautiously.</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>The distal urethral sphincter mechanism could be defunctionalised by urethral distraction, so urinary continence may be maintained primarily by the proximal bladder neck sphincter. Concomitant bladder neck injury might increase incontinence and could require an abdominoperineal procedure to allow simultaneous bladder neck and urethral reconstruction. (49,88).</td>
</tr>
</tbody>
</table>

The results of various techniques are reviewed by Koraitim (54) in a personal series of 100 patients combined with a review of 771 patients from published reports. Immediate and early realignment (n = 326) was associated with rates of 53% for stricture, 5% for incontinence and 36% for impotence. Of the patients successfully managed with immediate realignment, 42% needed subsequent instrumentation to attempt stabilisation of the stricture. Urethroplasty was required eventually in 33%.

Primary suturing (n = 37) was associated with rates of 49% for stricture, 21% for incontinence, and 56% for impotence. In comparison, inserting a suprapubic catheter before delayed repair (n = 508) was associated with rates of 97% for stricture, 4% for incontinence, and 19% for impotence. The restricture rate after delayed anastomotic urethroplasty was less than 10% (9,21,34,48,89-93), while the risk of impotence caused by delayed urethroplasty was about 5% (9,21,22,33,53,94-96). The gold standard therapy is still a delayed urethral repair at a minimum of 3 months after trauma, using a one-stage perineal approach.

Delayed endoscopic optical incision
The principles of the procedure were described by Sachse in 1974 (97). A curved metal sound is passed through the suprapubic cystostomy into the blind-ended proximal urethra. The direct vision urethrotome is inserted into the urethra, and cuts are made towards the sound. Blandy described a modification of this procedure, involving suprapubic passage of a cystoscope for transillumination of the thin perineal membrane and transurethral ‘cutting-to-the-light’ with an electrode (98).

Today, the cut-to-the-light technique is sometimes carried out using C-arm fluoroscopy for stereotactic guidance. The urethral catheter is left in place for between 1 and 3 weeks and suprapubic drainage for an additional 2 weeks to confirm consistent voiding (99). The results of several small series suggest that almost 95% of patients following optical urethrotomy for traumatically obliterated pelvic urethra require repeat urethrotomies (72,100-111). Thus, the procedure is only indicated if the urethral defect is short, the bladder neck is competent and there is minimal displacement of the prostate and proximal bulbous urethra (104).

Although immediate restoration of urethral continuity is commonly possible, failure is common. About 80% of patients will require urethral dilatation, optical urethrotomy and transurethral resection of stricture. Most repeat urethrotomies are performed in the first year of follow-up. It should be noted that after failure of the initial urethrotomy, alternative treatments should be considered, as repeat urethrotomy achieves only temporary improvement (112). Urethral false passage and rectal perforation have been reported (100,104,107). Stents are not currently recommended for patients with strictures following pelvic trauma, as fibrotic tissue tends to grow through into the lumen of the stent (48,113-115).

5.6.2.2 Penetrating posterior urethral injuries
In cases of penetrating trauma associated with prostatomembranous disruption primary, open repair should be performed, regardless of the degree of the urethral disruption. If the patient is unstable, or acute intervention is required for associated non-urological injuries, open repair can be postponed and the urethral injury can be managed with the placement of a suprapubic cystostomy.
5.6.2.3 Management of failed repair of posterior urethral rupture

Re-stenosis after delayed urethral repair mostly occurs within 6 months. If the anastomosis has a normal calibre at 6 months, then it is extremely unlikely that the patient will develop further stricturing (34). The principles of salvage repair are similar to those of the initial procedure. Salvage repair should be performed in referral centres to minimise potential side effects. Progressive perineal anastomotic repair alone can be successful in 85% of salvage urethroplasties (8). If an anastomotic repair cannot be performed, a one-stage substitution urethroplasty using a pedicle island of penile skin might be possible. Alternatively two-stage inlay procedures, usually with buccal mucosa or mesh split-thickness skin graft, should be performed (51,116,117). Optical urethrotomy is an alternative, particularly for a short and narrow stricture.

5.7 Treatment algorithms

The following algorithms are suggested for the treatment of anterior and posterior urethral injuries in men (Figures 3 and 4).
Figure 3: Management of anterior urethral injuries in men

Suspected urethral injury

Retrograde urethrography

Extravastion

Complete disruption

Penetrating

Primary urethral repair

If associated with penile rupture

Penetrating

Suprapubic cystostomy

Partial disruption

Blunt

Endoscopic optical incision

Successful

If stricture is short (< 1 cm) and flimsy

Endoscopic optical incision if failure

If stricture is long or denser

Formal urethral reconstruction

Gentle catheterisation

Normal

No stricture

Follow-up
Figure 4: Management of posterior urethral injuries in men

Suspected urethral injury

Retrograde urethrogram

Prostatomembranous disruption

Complete rupture

Penetrating

Primary open repair.
If patient unstable or important associated non-urological injuries, suprapubic cystostomy

Partial rupture

Blunt

Assess for acute surgical indications: bladder neck injury, rectal tear, pie-in-the-sky bladder

Suprapubic cystostomy

Penetrating

Primary open repair.
If patient unstable or important associated non-urological injuries, suprapubic cystostomy

No stricture

Suprapubic cystostomy

Yes

Suprapubic tube + endoscopic re-alignment.
Open if rectal or bladder injury.

No stricture

Option:
endoscopic realignment if patient is stable (< day 14)

Stricture

Urethotomy

Delayed urethroplasty

5.8 Statements and recommendation on trauma of the urethra

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt trauma accounts for more than 90% of urethral injuries.</td>
<td>3</td>
</tr>
<tr>
<td>In penile fracture the urethra is involved in 20% of cases.</td>
<td>4</td>
</tr>
<tr>
<td>The male posterior urethra is injured in 4-19% in cases of pelvic fractures. In industrialized societies pelvic fracture related injuries of the posterior urethra are the most common non iatrogenic injuries.</td>
<td>3</td>
</tr>
<tr>
<td>Erectile dysfunction occurs in 20-60% of patients after traumatic urethral rupture.</td>
<td>3</td>
</tr>
</tbody>
</table>
5.9  Iatrogenic urethral trauma

5.9.1  Introduction

The most common type of urethral trauma seen in modern urological practice is iatrogenic, due to catheterisation, instrumentation, or surgery (2,118). New treatment methods and applied energy sources can also injure the urethra. In most cases, iatrogenic urethral lesions require surgery due to strictures, which vary in their location and degree and require different management strategies (119).

5.9.2  Causes of iatrogenic urethral trauma

5.9.2.1  Transurethral catheterisation

Iatrogenic urethral trauma usually results from improper or prolonged catheterisation and accounts for 32% of strictures. Most of these strictures affect the bulbar urethra (119).

In incorrectly placed transurethral catheters, the pressure needed to fill the balloon and the force associated with manual extraction are much greater than when the catheter is placed correctly. This leads to a greater probability of urethral lesions (120). Improper urethral catheter insertion is a preventable source of urethral trauma in male patients (121). The risk of this type of urethral injury occurring during a hospital stay has been estimated at 3.2 per 1000 cases (119).

Stricture formation due to indwelling catheters is a common problem (118) that primarily affects the anterior urethra. The bladder neck is rarely affected in such cases (122).

It is possible to prevent or reduce the frequency of a wide range of iatrogenic urethral injuries. Implementing training programmes may significantly decrease the incidence, increasing patient safety and reducing the negative long-term effects (118,123) (LE: 2b).

Male patients undergoing cardiac surgery, such as bypass and other major operations associated with a need for catheterisation, are at risk for urethral trauma and stricture formation. Women undergoing abdominal surgery are also at risk during catheterisation. The size and type of catheter used have an important impact on urethral stricture formation. Current data indicate that silicone catheters and small-calibre Foley catheters are associated with less urethral morbidity (124).
5.9.2.2 Transurethral surgery

Transurethral procedures are a common cause of iatrogenic urethral trauma (IUhT). Factors that may influence the development of iatrogenic endoscopic urethral strictures include electrical dispersion generated by unipolar current and the diameter of the instruments used (125) (LE: 1b).

Predisposing factors most strongly associated with stricture formation in patients undergoing TURP are increasing prostate volume, prostate cancer and the surgeon’s experience (126).

Meatal strictures occur as a result of a mismatch between the size of the instrument and the diameter of the urethral meatus. Bulbar strictures occur due to insufficient insulation by the lubricant, causing the monopolar current to leak. To prevent strictures, lubricant gel should be applied carefully in the urethra. The lubricant must be reapplied when the resection time is prolonged (127). Internal urethrotomy must be performed before TURP if there are pre-existing meatal or urethral strictures (127).

There appears to be no relationship with the duration of procedures or the method used (holmium laser or traditional TURP) on the rate of stricture formation (128).

5.9.2.3 Surgical treatment for prostate cancer

Urethral stricture following prostate cancer treatment can occur anywhere from the bladder neck to the urethral meatus. The rate of bladder neck constriction after radical prostatectomy varies with the definition of the stricture used and individual practice (129,130) (LE: 2a). The Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) database shows an incidence of urethral stricture after various forms of prostate cancer therapy of 1.1-8.4%. The risk is greatest after radical prostatectomy if combined with external-beam radiation therapy. In a multivariate analysis, primary treatment type, age, and obesity were found to be significant predictors for stricture development (129) (LE: 2b).

Robot-assisted prostatectomy also affects urinary function and the risk of iatrogenic trauma. Iatrogenic complications involving the bladder neck account for 2.2%, similar to the stricture rate found with conventional treatment for localised prostate cancer (131) (LE: 2b).

Anastomotic stricture is also a complication in conventional laparoscopic prostatectomy. If prospective studies only are taken into account, there is no significant difference in the anastomotic stricture rate between laparoscopic and robot-assisted radical prostatectomy (132) (LE: 3b).
5.9.2.4 Radiotherapy for prostate cancer
The development of urinary fistulae has been reported after brachytherapy and radical prostatectomy, with incidences of 0.3-3.0% and 0-0.6%, respectively. Most fistulae involve the rectum (133,134) (LE: 3). Brachytherapy is a recognised cause of strictures in patients with localised prostate cancer, as the CaPSURE study has shown (135). Previous TURP increases the risk of stricture formation (136,137).

5.9.2.5 Major abdominal surgery and cystectomy
Iatrogenic injuries to the urethra are not a rare complication of abdominal and pelvic procedures. Bladder and urethral catheterisation must therefore be carried out preoperatively to prevent these complications (138) (LE: 2). Radical cystectomy and subsequent urinary diversion may also cause urethral trauma (139). Table 15 lists the most common causes of urethral trauma.

Table 15: Most common causes of urethral trauma

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterisation</td>
<td>32% of iatrogenic urethral strictures (52% bulbar urethra)</td>
</tr>
<tr>
<td>Urethral instrumentation for therapy and/or diagnosis</td>
<td>1.1-8.4% urethral stricture rate</td>
</tr>
<tr>
<td>Treatment for prostatic disease</td>
<td>2.2-9.8% urethral stricture rate</td>
</tr>
<tr>
<td>Transurethral surgery (e.g. TURB/TURP)</td>
<td>0.5-32% bladder neck constriction; no difference between LRP and RALP (relative risk: 1.42; 95% confidence interval for relative risk, 0.40-5.06; p = 0.59)</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>6% urethral stricture rate, 0.3-3.0% urinary fistula rate</td>
</tr>
<tr>
<td>Radiotherapy (percutaneous or brachytherapy)</td>
<td>Greatest risk for urethral stricture is found for the combination of radical prostatectomy and EBRT</td>
</tr>
<tr>
<td>Greatest risk for urethral stricture is found for the combination of radical prostatectomy and EBRT</td>
<td>0.5-32% bladder neck constriction; no difference between LRP and RALP (relative risk: 1.42; 95% confidence interval for relative risk, 0.40-5.06; p = 0.59)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>HIFU</td>
</tr>
<tr>
<td>Treatment for bladder disease</td>
<td>TURB</td>
</tr>
<tr>
<td>Cystectomy</td>
<td>Injury during major abdominal and pelvic operations</td>
</tr>
</tbody>
</table>

TURB = transurethral resection of the bladder; TURP = transurethral resection of the bladder; LRP = radical prostatectomy; RALP = robot-assisted laparoscopic prostatectomy; EBRT = external-beam radiation therapy; HIFU = high-intensity focused ultrasound.
5.9.3 Symptoms of iatrogenic urethral injury
Symptoms of urethral lesions caused by improper catheterisation or instrumentation are penile and/or perineal pain (100%) and urethral bleeding (86%) (122) (LE: 2b). Failure to diagnose accurately and treat urethral injuries may lead to significant long-term sequelae, in most cases presenting as strictures (140,141).

5.9.4 Diagnosis
Uroflowmetry, urethrography, and/or urethroscopy are the key investigations in diagnosis, and the algorithm is the same for acute and delayed symptoms. In the acute phase, the symptoms are bleeding and difficulty during catheterisation. Delayed symptoms include worsening of flow and other symptoms of obstruction.

5.9.5 Treatment
The value of temporary stenting in minor urethral injuries is unproven. Temporary stenting with an indwelling catheter is the conventional treatment option for an acute false passage (142). In difficult cases, it may be assisted by cystoscopy and guidewire placement (143) (LE: 3). Suprapubic catheterisation is an alternative.

Endoscopic management, either with incision or resection, can successfully treat iatrogenic prostatic urethral strictures. Indwelling catheter placement or an open procedure, associated with increased morbidity, are alternatives (144) (LE: 2b).

Urethral lesions following radiotherapy are often more difficult to treat and may require complex reconstructive surgery (133,134). Table 16 lists the statements and recommendations regarding the iatrogenic causes of urethral trauma.

Table 16: Statements and recommendations regarding iatrogenic urethral trauma

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic causes are the most common type of urethral injury in Europe and therefore the most common cause of urethral stricture formation.</td>
<td>2a</td>
</tr>
<tr>
<td>Implementing training programmes on urinary catheter insertion significantly improves the rate of catheter-related complications.</td>
<td>2b</td>
</tr>
<tr>
<td>New technologies represent an additional source of urethral injury.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper training should be provided to reduce the risk of traumatic catheterisation.</td>
<td>A</td>
</tr>
<tr>
<td>Urethral instrumentation should only be carried out when there are valid clinical indications.</td>
<td>A</td>
</tr>
<tr>
<td>When catheterisation is necessary, its duration should be kept to a minimum.</td>
<td>B</td>
</tr>
</tbody>
</table>

LE = level of evidence; GR = grade of recommendation.

5.9.6 References


6. GENITAL TRAUMA

6.1 Introduction and background
Genitourinary trauma is seen in both sexes and in all age groups. Of all genito-urinary injuries, 1/3rd to 2/3rds involve the external genitalia (1). Genital trauma is much more common in males (especially between the ages of 15 and 40) than in females. This is due to anatomical differences, increased frequency of road traffic accidents and more frequent participation in physical sports, violent crime, and war-fighting.

Genital trauma is commonly caused by blunt injuries (80%). The risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum and bowel) after blunt trauma is higher in females than in males. In
males, blunt genital trauma frequently occurs unilaterally. Only 1% present as bilateral scrotal or testicular injuries (2).

Any kind of contact sport, without the use of necessary protective aids, may be associated with genital trauma. Off-road bicycling and motorbike riding, especially on bikes with a dominant petrol tank, rugby football and hockey are all activities which have been associated with blunt testicular trauma (3-6).

Penetrating injuries account for 20% of genito-urinary trauma and 40-60% of all penetrating genitourinary lesions involve the external genitalia (1,7,8). 35% of all genito-urinary gunshot wounds involve the genitalia (2). In a recent series of wartime genito-urinary injuries 71.5% of 361 operations involved the external genitalia and the majority of trauma was due to Improvised Explosive Devices (IEDs) and other explosive ordinance with a smaller number of gunshot injuries (9). An increase in domestic violence has led to an increase in gunshot and stab wounds over the last several years (10-13). In both males and females, penetrating genital injuries occur with other associated injuries in 70% of patients. In males, penetrating scrotal injuries affect both testes in 30% of cases (2,14) cf. blunt scrotal injuries.

Self-mutilation of the external genitalia has also been reported in psychotic patients and transsexuals (15). Genital burns are rare in isolation, usually due to industrial flame or chemicals in adults and all but the full thickness type are treated conservatively (16). Both male and female genital piercing may also cause unexpected genital trauma (17). This was significantly higher than the risk in the normal population. Although there is an increased risk of Hep B and C risk in genital injured patients, there is no higher incidence of STIs found in the population with controlled, self-directed trauma in the form of genital piercing (17).

6.2 General principles and pathophysiology

In genital trauma, a urinalysis should be performed. The presence of macro- and or microhaematuria requires a retrograde urethrogram in males. In females, flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury (18,19). In women with genital injuries and blood at the vaginal introitus, further gynaecologic investigation is needed to exclude vaginal injuries (19). The potential for significant injury should never be discounted in those patients who also may have blood in the vaginal vault from menstruation. Complete vaginal inspection with specula is mandatory. Depending on the nature of the injury, this may require sedation or general anaesthesia to be completed comfortably.

6.2.1 Gunshot wounds

In patients with gunshot wounds to the genitals several pieces of additional information will be useful – in particular the range, calibre and type of weapon. As high–velocity missiles transmit large amounts of energy to the tissues and can produce trauma to structures outwith the wound track by creating an expansive cavity of sub-atmospheric pressure which then collapses and in so doing, creates shear forces and induction of other foreign bodies and (usually) infected material (1).

6.2.2 Bites

Animal

Although animal bites are common, bites injuring the external genital are rare. Wounds are usually minor, but have a risk of wound infection. The most common bacterial infection by a dog bite is *Pasteurella Multicida*, which accounts for up to 50% of infections (20). Other commonly involved organisms are *Escherichia coli*, *Streptococcus viridans*, *Staphylococcus aureus*, *Eikenella corrodens*, *Capnocytophaga canimorsus* *Veillonella parvula*, *Bacteroides* and *Fusobacterium spp*. (15,20,21).

The first choice of antibiotics is penicillin-amoxiclavulanic acid followed by doxycycline, cephalosporine or erythromycin for 10-14 days (22-24). After any animal bite, one has to consider the possibility of rabies infection. In cases where rabies is locally present, vaccination must be given to prevent life-threatening infection (25). Besides vaccination, local wound management is an essential part of post-exposure rabies prophylaxis. If rabies infection is suspected, vaccination should be considered in relation to the animal involved, specific nature of the wound and attack (provoked/unprovoked) and the appearance of the animal (aggressive, foam at the mouth). In high risk patients, vaccination with human rabies immunoglobulin and human diploid cell vaccine is recommended (25,26).

Human

Human bites are much less common but should be considered especially in risk groups. Since transmission of viral diseases may occur, risk assessment should be made and, if appropriate, hepatitis B vaccine/ immunoglobulin and/or HIV post-exposure prophylaxis offered. For further details see Guidelines for the Management of Human Bite Injuries (27).
6.2.3 **Sexual assault**
Genital injury is seen frequently (42%) after sexual abuse, and must be considered when such injuries present at any age (28). In these cases, the extraordinary emotional situation of the patient must be considered and the privacy of the patient respected. In suspicious cases, gynaecological and forensic support and advice is necessary. Swabs or vaginal smears should be taken for detection of spermatozoa (29) and local legal protocols followed closely. A thorough history and examination (in some cases under anaesthesia), photo documentation, and identification of forensic material may be important. In a recent report, only 38% of the forensic samples tested positive for an ejaculate and/or sperm. This may be due to delayed presentation or lack of vaginal/anal ejaculation (30,31).

**Organ specific genital trauma**

6.3 **Penile trauma**

6.3.1 **Blunt penile trauma**
Blunt trauma to the flaccid penis does not usually cause tearing of the tunica. In these cases, only subcutaneous haematoma with intact tunica albuginea may be seen.

6.3.1.1 **Penile fracture**
The most important and common presentation of blunt penile trauma is in penile fracture. This results from trauma to the erect penis during sexual intercourse, masturbation, rolling over in bed (rarely) and as a result of self-inflicted bending to produce detumescence in some Middle Eastern Cultures – a practice known as taqaandan (which, when translated, means “to click”) (32).

The most common mechanism of injury is when the penis slips out of the vagina and strikes against the symphysis pubis or perineum. This most frequently (60%) occurs during consensual intercourse (33), and more prevalent when the partner is on top. Penile fracture is caused by rupture of the cavernosal tunica albuginea, and may be associated with subcutaneous haematoma, and lesions of the corpus spongiosum or urethra in 10-22% (34,35).

The thickness of the tunica albuginea in the flaccid state (approximately 2 mm) decreases in erection to 0.25-0.5 mm, and is therefore more vulnerable to traumatic injury (36,37).

Penile fracture is associated with a sudden cracking or popping sound, pain and immediate detumescence. Local swelling of the penile shaft develops quickly, due to enlarging haematoma. Bleeding may spread along the fascial layers of the penile shaft and extend to the lower abdominal wall if Buck’s fascia is also ruptured. The rupture of the tunica may be palpable.

A thorough history and examination usually confirm the diagnosis, but in some cases imaging may be useful. Cavernosography, USS (ultrasound scanning) or MRI (38-40) can identify lacerations of the tunica albuginea in unclear cases (41), or provide reassurance that the tunica is intact. If there is suspicion of a concomitant urethral injury, a RUG (retrograde urethrogram) may be performed but flexible cystoscopy under anaesthesia during exploration/repair is more usually employed.

Subcutaneous haematoma, without associated rupture of the cavernosal tunica albuginea does not require surgical intervention. In these cases, nonsteroidal analgesics and ice-packs are recommended (8). Less severe penile injuries can be distinguished from penile fracture, as penile fracture is classically associated with rapid post-traumatic detumescence.

In penile fracture, early surgical intervention with closure of the tunica albuginea is recommended. The approach is usually by a circumferential incision proximal to the coronal sulcus to deglove the penis entirely. Increasingly local longitudinal incisions centred on the area of fracture are employed and further localisation may be gained with a flexible cystoscopy prior to incision if urethral trauma is suspected and proven. Closure can be obtained by using absorbable sutures, with good long-term outcome and protection of potency. Post-operative complications were reported in 9%, including superficial wound infection and impotence in 1.3% (33,42). Conservative management of penile fracture is not recommended. It increases complications such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention (42). Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% (33,42).

6.3.2 **Penetrating penile trauma**
Penetrating penile trauma is rarely seen in isolation. Most cases are associated with multiple injuries. The causes of penetrating penile trauma are gunshot/knife injury, animal or human bites, assault and industrial or self-inflicted mutilation/avulsion/amputation.
Non-operative management is recommended in small superficial injuries with intact Buck’s fascia (8). In more significant penetrating penile injuries surgical exploration and conservative debridement of necrotic tissue is recommended in most severe injuries. Even in extended injuries of the penis, primary alignment of the disrupted tissues may allow for acceptable healing because of the robust penile blood supply (15).

Because of the elasticity of genital skin, loss of only a moderate amount of penile skin is usually manageable, although in extensive injuries when significant skin loss is encountered the management is more difficult. The tissue chosen for reconstruction following trauma needs to provide good coverage, and be suitable for reconstruction. Split-thickness skin grafting provides good coverage and dependable take that is reproducible and durable, but these grafts contract more than full-thickness skin grafts and their use on the shaft should be kept to a minimum. McAncinch et al. recommended the use of a skin graft thickness of at least 0.015 inch (0.4 mm) in order to reduce the risk of contraction (15). Full thickness skin grafting onto the penile shaft gives less contracture, a better cosmetic appearance and more resistance to trauma from intercourse, when eventually re-established (43) The donor site may be taken from the abdomen, buttock, thigh or axilla - chosen according to surgeon preference and injury pattern.

The principles of care are debridement of devitalised tissue with the preservation of as much viable tissue as possible, haemostasis, diversion of urine in selected cases and the removal of foreign bodies. Tissues of questionable viability may be left for subsequent definitive surgery. Subsequent immediate or delayed repair is needed depending on the injury and extent of tissue damage, and usually takes place 4–6 weeks after trauma occurrence.

If there has been extensive destruction of deeper tissues, or if later prosthetic placement is being considered, skin flaps, with their secure vascular supply can be employed. The surgical approach will be dependent upon the site and extent of the injury, but a sub coronal incision with penile degloving usually gives good exposure. A defect in the tunica albuginea can be closed primarily, after copious irrigation. If there is too much tissue loss, the defect can be repaired with a patch (either from autologous saphenous vein or xenograft), either initially or delayed. If a concomitant urethral injury is suspected, a pre- or perioperative urethrogram or cystoscopy is useful in the diagnosis and localisation of any urethral involvement.

6.3.3 Penile avulsion injuries and amputation
Most of these injuries are self-inflicted, but some are a result of industrial accidents or assault. The acute management involves the resuscitation of the patient (who might be compromised from blood loss) and preparation for the surgical re-implantation of the penis if it has been recovered and not too badly damaged. Surgical re-implantation should be considered for all patients, and should be performed within 24 h of amputation. If the injury occurred during a psychotic episode, early psychiatric advice and support should be sought.

The severed penis should be washed with sterile saline, wrapped in saline-soaked gauze, placed in a sterile bag and immersed in iced water. The penis must not come into direct contact with the ice. A pressure dressing or a tourniquet should be placed around the penile stump to prevent excessive blood loss. Reattachment can be achieved in a non-microsurgical way, but this technique gives a higher postoperative urethral stricture rate and more problems with loss of sensation. The best results are seen with microsurgical re-implantation. Firstly the corpora cavernosa and urethra are aligned and repaired, and then the dorsal penile arteries, the dorsal vein and the dorsal nerves are repaired with the use of an operating microscope. The cavernosal arteries are generally too small to anastomose. The fascia and skin are closed in layers, and both a urethral and a suprapubic catheter placed. If the severed penis cannot be found, or is unsuitable for reattachment, then the end should be closed as if for a partial penectomy. Later reconstruction may be employed to lengthen the penis (e.g suspensory ligament division and v–y plasty, pseudo-glans formation with split-thickness skin grafting etc.)

A delayed major reconstructive procedure – phalloplasty (either radial artery or pubic) is sometimes required for injuries which leave very little or no functioning penile stump.

6.4 Scrotal trauma
6.4.1 Blunt scrotal trauma
Blunt trauma to the scrotum can cause testicular dislocation, testicular haematocoele, testicular rupture and/or scrotal haematoma.

6.4.1.1 Testicular dislocation
Traumatic dislocation of the testicle occurs rarely. It is most common in victims of MVAs or auto-pedestrian accidents (44-47). Bilateral dislocation of the testes has been reported in up to 25% of cases (47). It can be
either a subcutaneous dislocation with epifascial displacement of the testis or an internal dislocation. In the latter the testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity. Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.

6.4.1.2 Haematoceles
Conservative management is recommended in haematoceles smaller than three times the size of the contralateral testis (10). In large haematoceles, non-operative management often fails, and often requires delayed surgery (> 3 days). These patients suffer from a higher rate of orchiectomy than acutely-operated patients, even in non-ruptured testis (2,15,48-50). Early surgical intervention resulted in > 90% preservation of the testis whereas delayed surgery necessitates orchiectomy in 45-55% (48). Additionally, non-operative management is associated with prolonged hospital stays. Large haematoceles should be treated surgically, irrespective of testicle contusion or rupture. At the very least, the blood-clot should be evacuated from the tunica vaginalis sac to relieve disability and hasten recovery. Patients initially treated non-operatively may need delayed surgery if they develop infection or undue pain.

6.4.1.3 Testicular rupture
Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma (48). It may occur under intense, traumatic compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea of the testis. Wasko and Goldstein estimated that a force of approximately 50kg is necessary to cause testicular rupture (51). Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting. The hemiscrotum is tender, swollen, and ecchymotic. The testis itself may be difficult to palpate. High-resolution, real-time ultrasonography with a high resolution probe (minimum 7.5 MHz or higher) should be performed to determine intra- and/or extratesticular haematoma, testicular contusion, or rupture (52-60). The literature is contradictory as to the real usefulness of US over exam alone. Some studies report convincing results with a specificity of up to 98.6% (15,52,57,58,61). Others reported poor specificity (78%) and sensitivity (28%) for differentiation of testicular rupture or haematocele, and accuracy as low as 56% (55). Colour Doppler-duplex ultrasonography may provide useful information when used to evaluate testicular perfusion. In case of inconclusive scrotal sonography, testicular CT or MRI may be helpful (62). However, these techniques did not specifically increase the detection of testicular rupture. It may be most prudent to surgically explore these equivocal patients. If imaging studies cannot definitively exclude testicular rupture, surgical exploration is indicated. This involves exploration with evacuation of clot and haematoma, excision of any necrotic testicular tubules and closure of the tunica albuginea usually with running absorbable sutures (such as 3/0 vicryl). This results in a high rate of testicular preservation and normal endocrine function.

6.4.2 Penetrating scrotal trauma
Penetrating injuries to the scrotum require surgical exploration with conservative debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of testis and scrotum can be performed in most cases. In complete disruption of the spermatic cord, realignment without vaso-vasostomy may be considered if surgically feasible (63). Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although there are only a few cases reported (63). If there is extensive destruction of the tunica albuginea, mobilisation of a free tunica vaginalis flap can be performed for testicular closure. If the patient is unstable or reconstruction cannot be achieved, orchiectomy is indicated.

Prophylactic antibiotics are recommended by experts after scrotal penetrating trauma, although data to support this approach is lacking. Tetanus prophylaxis is mandatory. Postoperative complications were reported in 8% of patients who underwent testicular repair after penetrating trauma (8).

Extended laceration of scrotal skin requires surgical intervention for skin closure. Due to the elasticity of the scrotum, most defects can be primarily closed, even if the lacerated skin is only minimally attached to the scrotum (15). Local wound management with extensive initial wound debridement and washout is important for scrotal convalescence.

In IED blast injury, the extensive loss of genital tissue often requires complex and staged reconstructive surgical procedures (9).
6.5  Genital trauma in females

In females with blunt trauma to the external genitalia, imaging studies of the pelvis with US, CT, or MRI should be performed since additional injuries and extensive intrapelvic haematoma are frequently found (19,29).

6.5.1  Blunt vulvar injuries

Blunt trauma to the vulva is rarely reported and commonly present as a large haematoma. The incidence of traumatic vulvar haematomas after vaginal deliveries has been reported as 1 in 310 deliveries (64). The frequency in non-obstetric vulvar haematomas is even lower, with only individual cases reported (65). Although blunt trauma to the female external genitals is rarely reported, the presence of vulvar haematoma is closely related to an increased risk of associated vaginal, pelvic or abdominal injuries. Goldman et al. reported that blunt injuries of the vulva and vagina were associated with pelvic trauma in 30%, after consensual intercourse in 25%, sexual assault in 20%, and other blunt trauma in 15% (18).

However, in contrast to men, blunt vulvar or perineal trauma may be associated with voiding problems. Bladder catheterisation will usually be required. Vulvar haematomas usually do not require surgical intervention, although they can cause significant blood loss, even requiring red blood cell transfusions. Data are scarce (18,19,29,65), but in haemodynamically stable women, non-steroidal anti-inflammatory medication and cold packs are used. In massive vulvar haematoma or haemodynamically unstable patients, surgical intervention, lavage and drainage is indicated (66).

Antibiotics are recommended by experts after major vulvar trauma, but data supporting this approach are lacking. It is important to emphasise that vulvar haematoma and/or blood at the vaginal introitus are an indication for vaginal exploration under sedation or general anaesthesia in order to identify possible associated vaginal and/or rectal injuries (19). Flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury (18,19). In case of vulvar laceration, suturing after conservative debridement is indicated. If there are associated injuries to the vagina, these can be repaired immediately by primary suturing. Additional injuries to the bladder, rectum or bowel may require laparotomy for closure. The rectal injuries may also require colostomy.

6.6  References

5. Physical examination and assessment of the injury.
6. Antibiotic prophylaxis for bites.
8. Recommendations for managing animal bites.
15. Prevention programs for animal bites.
17. Prevention and management of animal bites.
19. Prevention programs for animal bites.
23. Prevention programs for animal bites.
27. Prevention programs for animal bites.


7. MASS CASUALTY EVENTS, TRIAGE AND DAMAGE CONTROL

7.1 Definition
A mass casualty event is one in which the number of injured people is significantly higher than the number of healthcare providers available (1). A mass casualty disaster does not therefore necessarily involve a large number of victims, but is related to the disproportion between the number of victims and the size of the medical team available (2,3). There is little published data on how best to handle these events.

7.2 Causes of mass casualty events
Potential mass casualty events include:
- the collapse of buildings or bridges;
- earthquakes;
- floods;
- tsunamis;
- train collisions;
- aircraft catastrophes;
Most mass injury caused by civilian terrorism is caused by explosions. The combined effects of blast, shrapnel, bomb projectiles, and burns result in multiple penetrating injuries involving several body systems and unpredictable degrees of damage.

7.3 Mechanisms of explosive injury

The mechanism of injury in explosions is divided into three phases:

- **Primary blast injury**: this is caused by the powerful shock wave that spreads from the site of the explosion. The most commonly injured organs are those containing air (lungs and ears), but any tissue can be damaged by the pressure wave passing through the body. Urogenital injuries as a direct result of primary blast have not been described in survivors of blast injuries.

- **Secondary blast injury**: this is produced by the debris and projectiles set in motion by the explosion. Penetrating injuries to the urogenital system, as to any organ, have been described.

- **Tertiary injury**: this occurs when the victim displaced by the blast wave hits a fixed object. An acceleration-deceleration mechanism produces severe injuries to organs, large blood vessels, and bones. Blunt renal, ureteral, and bladder injuries are induced by this mechanism. The patterns and severity of injury after explosions differ according to the location of the event. Explosions in confined spaces (e.g., buildings or buses) are more devastating than those that occur in open spaces because of amplification of the blast wave by reflection, and structural collapse, which can cause further injury.

7.4 Triage

Triage after mass casualty events is difficult, controversial, and full of difficult ethical and moral questions. Disaster triage requires one to differentiate the few critically injured that can be saved by immediate intervention from the many with non-life-threatening injuries for whom treatment can be delayed.

Triage divides patients into four groups (4,5):

1. Patients with life-threatening injuries that require immediate intervention, presenting with airway compromise, Breathing failure and/or circulatory compromise from ongoing external haemorrhage.
2. Patients with severe but non-life-threatening injuries, in whom treatment can be acceptably delayed: major fractures, vascular injuries of the limbs and large soft tissue wounds.
3. ‘Walking wounded’ with minimal injuries.
4. Patients who are so severely injured that treatment would require allocation of resources and time that would deny other, more salvageable patients, timely care. These patients are given minimal or no treatment, and are re-evaluated when resources become available. There is no absolute definition for this group because triage is individualised according to the number and severity of casualties related to the available resources.

Triage contradicts the everyday principles of care, in which the goal is maximal and optimal care for every individual patient. Triage is necessary in mass casualty scenarios because of the need to provide effective treatment to the maximum number of salvageable patients within the limited resources.

7.4.1 Primary triage

Primary triage begins when trained medical teams arrive at the event. It is concerned with the initial stabilisation and rapid evacuation of the prioritised victims to the nearest hospital.

7.4.2 Secondary triage

Secondary triage begins at the medical facility that is receiving the mass casualties. The most experienced trauma surgeon who is not taking part in surgical or resuscitation procedures performs triage.

7.4.3 Re-triage

Re-triage is performed frequently. After all the victims have undergone triage, the senior surgeon repeats triage and reclassifies patients as necessary. Repeat triage is important. It avoids under-triage, which results in serious injury being missed, or overtriage, which results in some patients being assigned for immediate care when in fact they do not have critical injuries. The surgeon in charge is responsible for directing specialty surgical consultants, including urologists, and assigning them responsibility for specific patients as dictated by the specific injuries.

7.5 Principles of ‘damage control’

Damage control is a prioritised three-phase approach to patients with major injuries (6). The first phase...
consists of rapid control of haemorrhage, wound contamination, and faecal spillage using simple measures and temporary abdominal closure. The second phase is resuscitation in the intensive care unit (ICU), with the goal of restoring normal temperature, coagulation, perfusion, and oxygenation of tissues. Then, in the third stage, definitive surgery and abdominal wall closure is performed in stable patients.

Damage control is a life-saving strategy for patients with multiple injuries that has been adopted by trauma surgeons as a result of the observation that such patients often die from hypothermia, coagulopathy, and acidosis-induced physiological insults (7-9). In unstable patients, extensive and time-consuming reconstructive procedures could further destabilise the patient beyond recovery. Identifying those critically injured patients who are candidates for damage control is difficult. The most senior trauma surgeon should make the decisions, in co-operation with other specialist surgeons.

Damage control principles have also been successfully adopted in the context of civilian mass casualty events, military field surgery, and initial treatment in rural areas with long-range transfers (9,10).

7.6 Urological aspects of ‘damage control’

In events involving mass casualties, the principles of triage and damage control are the same. Damage control can theoretically lower the mortality rates by allowing a limited number of qualified personnel to treat more patients.

Urologists are frequently consulted in patients with multiple injuries, and should be familiar with the damage control approach. Damage control is well suited to urological trauma, and should result in more efficient interaction with the trauma team, improved patient survival and lower morbidity. In fact, because urological surgery is often elective, management of urological trauma has traditionally consisted of temporary measures followed by definitive surgery later on, which meshes well with modern damage control principles (8). It is important to be aware of damage control opportunities, and to maximise the quality of care with creative improvisation.

7.6.1 The urological consultation in the emergency room during mass casualty events

7.6.1.1 Responsibility and primary overall assessment

After primary assessment and triage by the surgeon in charge, a urological consultation might be required for patients triaged to groups 2 (severe but not immediately life-threatening injuries) and 3 (‘walking wounded’ with mild injuries). The urologist might even become primarily responsible for these patients if they are stable and have few other injuries.

It is important to remember that under-triage can happen during a mass casualty event. A complete re-assessment of the patient assigned must therefore be performed, paying attention to the whole body so as to detect previously unnoticed injuries. This assessment should be quick but comprehensive. Conduct a rapid ABCDE survey (Airway, Breathing, Circulation, Disability or neurological status, Exposure) as dictated by advanced trauma life support (ATLS) principles (3). Urological care should begin only after the patient is cleared for the presence of other injuries.

7.6.1.2 Imaging

Evaluation of patients with penetrating and blunt abdominal or pelvic trauma usually includes imaging procedures such as contrast CT scans or retrograde cystourethrography (11,12). However, when mass casualty protocols are instituted, decisions on care must be made with a minimum of imaging procedures. In those situations, create a unidirectional flow of patients in order to avoid the bottleneck that usually occurs in imaging departments. The ‘normal’ pattern of sending patients for imaging and then returning them to the accident and emergency department for re-evaluation may not be feasible.

7.6.1.3 Primary management

Following initial primary evaluation, there are several possible scenarios:

1. Haemodynamically unstable patients with suspected intra-abdominal bleeding are transferred urgently to the operating theatre without any pre-operative imaging.

2. Stable patients with suspected renal injuries (penetrating trauma to the upper abdomen/flanks/lower chest, blunt abdominal trauma, and gross haematuria) should have delayed imaging once the protocols of mass casualties are cancelled, or when resources become available. These patients should be transferred to surgical wards and re-evaluated by the urologist as soon as possible.

3. Patients with suspected bladder or urethral injuries (pelvic fractures, high riding prostate on rectal examination, blood at the urethral meatus and/or inability to void) need to undergo imaging of the lower urinary tract, but this is not urgent as these injuries are not considered life-threatening (13).

4. In cases of suspected urethral injuries, the ‘minimal acceptable treatment’ will be one gentle trial of
catheterising the bladder or insertion of a suprapubic cystostomy, followed by transfer of the patient
to the surgical ward for later evaluation (14).

5. Bladder injuries following blunt or penetrating trauma are usually associated with other severe injuries
(15) and thus require a prioritising surgical approach. The first priority in this scenario is the treatment
of the associated life-threatening injuries. Bladder drainage is a sufficient first measure, but should
be followed by delayed evaluation aiming to obtain accurate diagnosis and to distinguish between
intraperitoneal and extraperitoneal bladder rupture.

6. Blunt injuries of the external genitalia are often isolated and can be managed conservatively. On
the other hand, penetrating injuries of the genitalia are often associated with injuries of adjacent
abdominal organs and haemodynamic instability (7). In mass casualty scenarios, external genital
injuries should be operated on only if they have resulted in major haemorrhage. Surgery can be
performed in the operating theatre or in a well-equipped shock room in the accident and emergency
department. Compression dressings, or clamping/ligation of bleeding vessels are highly efficient
manoeuvres that require a minimum of time. When severe haemorrhage is not present, any further
diagnostic steps can be postponed. The patient can be transferred to the surgical ward for later
re-evaluation followed by delayed reconstruction.

Urological consultations during a mass casualty scenario should be performed according to the following
principles:

1. Rule out under-triage by the surgeon in charge, and perform a rapid primary survey of every patient.
2. Avoid unnecessary imaging procedures such as CT scans and retrograde urethrography. These
procedures should be performed later, after re-evaluation of the patient, and after mass casualty
protocols have been suspended.
3. Treat unstable patients who are to have surgery using damage control principles.
4. Stable patients with suspected renal injuries should be transferred to the surgical ward without
imaging procedures. Re-evaluate if there is any change in their haemodynamic status, or when
possible as dictated by the constraints of the mass casualty event. Patients managed in this delayed
fashion should be treated according to traditional trauma management protocols.
5. ‘Minimal acceptable’ procedures should be performed in order to transfer patients to the surgical
wards, e.g. suprapubic drainage of the bladder when bladder or urethral injuries are suspected,
clamping and ligation of bleeding vessels from wounds to the external genitalia, etc.

7.6.2 The urological consultation in the operating room during mass casualty events
During emergency laparotomy, urologists are usually present in the operating theatre along with the general
surgeons. During mass casualty events, the principle of ‘minimum acceptable intervention’ for the ‘maximum
salvageable outcome’ applies. Procedures should be directed at the rapid control of active bleeding,
and management of urinary extravasation by simple diversion measures. Complex and time-consuming
reconstructive procedures should be delayed whenever possible.

7.6.2.1 Renal trauma
The ultimate goal of all renal exploration in the setting of major traumatic renal injury is to control life-
threatening bleeding and to preserve the maximal amount of viable renal parenchyma (16).
Renal reconstruction might be too time-consuming in the context of an unstable, multiply injured
patient, or in the scenario of mass casualties in which the operating theatre should not be occupied by time-
consuming reconstructive procedures (17).

Whenever major active haemorrhage of renal origin can be ruled out, it is best not to explore the injured kidney,
even if a secondary delayed laparotomy will eventually be needed (18).
In unstable patients, packing the renal fossa with laparotomy pads and transferring the patient to the
surgical ICU is best. Later, a planned second-look laparotomy is better than time-consuming reconstruction
(19). Alternatively, especially in briskly bleeding patients, speedy nephrectomy may be required.

Haemostatic techniques, many of which were developed for hepatic surgery and splenic trauma, can be used
to control renal parenchymal bleeding (20):

- Mattress sutures through the parenchyma (renorrhaphy), similar to the sutures used in extensive
  hepatorrhaphy (7).
- Packing with dry folded laparotomy pads as described for peri-hepatic tamponade (7).
- Fibrin hemostatic agents, may be used to control bleeding.
- Absorbable mesh kidney bags maintain renal parenchymal fragments in contact with each other and
Ensure lasting haemostasis (21).

- Urinary extravasation may be ignored during the acute phase; acutely, urine leak will be drained by intraoperatively placed drains; defer ureteral stents or percutaneous nephrostomies.
- The abdomen is temporarily closed with towel clips or other measures.

Following urgent primary exploration, patients should be carefully monitored in an ICU. When they are sufficiently stable, begin radiological assessment of their injuries and plan their definitive operative management accordingly.

Delayed imaging is obtained by CT scan. If the extent of renal injury has not been clearly defined at the initial laparotomy (by choosing not to explore the retroperitoneal haematoma), a CT scan performed before the second laparotomy can help in decision-making. Computed tomography allows the existence and function of the contralateral kidney to be documented, the kidney injury to be graded according to traditional protocols, and a clinical plan to be created, which will then determine the selection of operative or non-operative management of the renal trauma, and whether nephrectomy or reconstruction is to be attempted.

In patients who are haemodynamically unstable after the initial acute damage control laparotomy, or in patients with deteriorating haemodynamic parameters (indicating ongoing or delayed bleeding), the management options are angiographic embolisation of the bleeding kidney or re-operation. This decision should be made according to several factors:

- The general status of the patient.
- The presence of associated injuries that have been treated according to damage control principles (bowel injuries, packed liver, or splenic injuries) and that need re-operation irrespective of the renal injury.
- The availability of angiography.

7.6.2.2 Ureteral injuries

Although excellent results can be achieved with acute ureteral reconstruction, the surgery is time-consuming and might not be appropriate in the mass casualty setting.

During mass casualty events, diagnostic procedures such as the intraoperative injection of indigo carmine, intraoperative IVP or retrograde ueretropolyegraphy that are intended to evaluate ureteral injuries should be discouraged.

If a ureteral injury is suspected but not clearly identified, a drain may be left in place. If urine leaks, a nephrostomy tube can be placed postoperatively.

If a partial ureteral tear is identified (less than half circumference) and the ureter looks viable, a double J-stent may be inserted over a guide wire through the tear, and the tear quickly closed with interrupted absorbable stitches.

When complete ureteral injuries are identified, definitive repair should not be performed. Dissection of the ureteral stumps should be avoided as it interferes with the blood supply. Instead:

- place a single J or 8 French feeding tube into the ureter;
- tie the distal end of the ureter over the tube;
- exteriorise it through a small stab incision;
- tie it to the skin.

The distal ureteral stump does not need to be ligated, and any unnecessary manipulation should be avoided.

Tying off the injured ureteral segment and inserting a percutaneous nephrostomy postoperatively (22,23) is a viable alternative, but is not the procedure of choice.

In rare, selected cases, nephrectomy is required to treat ureteral injury, but only in cases of severe associated injuries of the ipsilateral kidney (24).

Ureteral injuries are rarely life-threatening and should be addressed only after other injuries have been attended to. In an unstable patient, temporary measures to control urine spillage should be performed, for example:

- tying off of the injured ureteral segment and post-operative insertion of percutaneous nephrostomy (15,19);
- placement of a single J or feeding tube into the ureter, tying the distal end of the ureter over the tube and exteriorising it (15,19,23).

Intraoperative placement of a nephrostomy tube is time-consuming and should be avoided (15,19).
7.6.2.3 Bladder injury
Bladder injuries should be classified, when time and resources allow, as extraperitoneal or intraperitoneal. Extraperitoneal injuries can usually be managed with bladder drainage alone. Intraperitoneal injuries require surgical exploration and layered closure of the bladder wall (13). The degree to which penetrating bladder injury can be treated non-surgically is not known. However, non-surgical management of iatrogenic bladder injuries has been reported, and could be effective after penetrating injury (11,19).

Bladder injury was present in 1.15% of soldiers suffering a combat trauma. The main causes of injury were explosive devices, followed by high-velocity weapons (25).

- The majority of ruptures are extraperitoneal (54-86%), while 14-40% are intraperitoneal, with combined intra- and extraperitoneal ruptures account for 1.7-8% of all bladder ruptures (26-31).

7.6.2.3.1 Auxiliary damage control measures
Examples of auxiliary damage control measures that could be applicable include:
- the placement of externalised ureteral stents can provide external urinary drainage in extensive bladder rupture (19);
- packing or arteriography and selective embolisation can be applied in cases of bladder haemorrhage in patients who are unsuitable for urgent pelvic exploration (13,19);
- the placement of a pelvic suction drain for urinary evacuation (19).

7.6.2.4 Urethral injury
Urethral injury of any kind is never life-threatening per se, but the associated injuries might cause haemodynamic instability. The patient is usually seen by the urologist during an operation performed because of the other injuries. In this situation, no matter whether the urethral tear is posterior or anterior, partial or complete, drainage through a suprapubic or urethral catheter should be obtained without prior imaging.

7.6.2.5 Injury of the external genitalia
Traumatic injuries of the external genitalia are much more common in men than in women, probably because of the anatomical differences (11,31). Blunt injuries of the genitalia are usually isolated, and can be managed conservatively. Penetrating injuries of the genitalia are often associated with injuries of adjacent abdominal organs and related haemodynamic instability (12). In mass casualty events, both types of injury should be managed by watchful waiting. Urethral or testicular imaging and surgical exploration should be deferred.

7.6.2.5.1 Temporary damage control measures
Temporary damage control measure that might be applicable include:
- compression dressing of the penis;
- packing of penetrating testicular injuries;
- tampons for vulvar lacerations.

7.7 Summary
- Damage control surgery has become the standard approach in the management of unstable patients, and is especially useful in a mass trauma event.
- Medical teams should be well prepared ahead of time to deal with mass casualty events.
- All surgical sub-specialists involved in trauma management should be very familiar with the principles of triage and damage control.

7.8 References


8. **ABBREVIATIONS USED IN THE TEXT**

This list is not comprehensive for the most common abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAST</td>
<td>American Association for the Surgery of Trauma</td>
</tr>
<tr>
<td>ATLS</td>
<td>advanced trauma life support</td>
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<tr>
<td>AVF</td>
<td>arteriovenous fistulae</td>
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<td>BT</td>
<td>transperineal, interstitial, permanent prostate brachytherapy</td>
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<td>BUN</td>
<td>blood urea nitrogen</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>DMSA</td>
<td>dimercaptosuccinic acid</td>
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<td>EBRT</td>
<td>external beam radiotherapy</td>
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<tr>
<td>ePTFE</td>
<td>polytetrafluoroethylene</td>
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<tr>
<td>FAST</td>
<td>focused assessment with sonography for trauma</td>
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<td>GR</td>
<td>grade of recommendation</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>hpf</td>
<td>high-power field</td>
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<td>IBT</td>
<td>iatrogenic bladder trauma</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>IED</td>
<td>improvised explosive device</td>
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<td>IRT</td>
<td>iatrogenic renal trauma</td>
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<td>ISS</td>
<td>injury severity score</td>
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<td>IVP</td>
<td>intravenous pyelography/pyelogram</td>
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<td>intravenous urography</td>
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<td>KUB</td>
<td>kidney-ureter-bladder</td>
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<td>LE</td>
<td>level of evidence</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>m/s</td>
<td>metres per second</td>
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<td>motor vehicle accident</td>
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<td>rbc/hpf</td>
<td>red blood cells per high-power field</td>
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<td>TOT</td>
<td>transobturator tape</td>
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<td>transurethral resection of the prostate</td>
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<td>tension-free vaginal tape</td>
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<td>UPJ</td>
<td>ureteropelvic junction</td>
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<td>US</td>
<td>ultrasonography</td>
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**Conflict of interest**

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Guidelines on Pain Management & Palliative Care

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1. INTRODUCTION

1.1 The Guideline
The new European Association of Urology (EAU) Guidelines expert panel for Pain Management and Palliative Care have prepared this guidelines document to assist medical professionals in appraising the evidence-based management of pain and palliation in urological practice. These guidelines include general advice on pain assessment and palliation, with a focus on treatment strategies relating to common medical conditions and painful procedures.

The multidisciplinary panel of experts responsible for this document include a urologist, a radiotherapist-oncologist, an anaesthesiologist and a nurse specialised in palliative care.

1.2 Methodology
The recommendations provided in the current guidelines are based on systematic literature search using Embase/Medline and the Cochrane Central Register of Controlled Trials.

It has to be emphasised that these guidelines contain information for the treatment of an individual patient according to a standardised general approach.

1.3 Publication history
The Pain Management Guidelines were first published in 2003, with a partial update in 2007, followed by a full text update in 2009. In 2010 two new topics were added, Section 5.6 “Perioperative pain management in children” and Chapter 6 “Non-traumatic acute flank pain”. The quick reference guide was completely reworked. In the 2011 print all chapters were abridged.

The current 2013 edition contains partial updates based on the available literature. Section 3.5 on Palliative Care was moved and expanded to a new Chapter 7, which deals with the subject of Palliative Care.

A quick reference document presenting the main findings of the former Pain Management guidelines is also available. All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/

1.4 Acknowledgements
The Expert Panel would like to express its gratitude to Dr. Juan Guerra Martínez (JGM), medical oncologist at the University Hospital of Fuenlabrada, Spain, for his guidance on palliation matters. His assistance and expertise proved most valuable.

1.5 Level of evidence and grade of guideline recommendations*
References used in the text have been assessed according to their level of scientific evidence (Table 1) and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence (LE)*

<table>
<thead>
<tr>
<th>LE</th>
<th>Type of evidence</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (1).

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.
Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can it address local/national preferences in a systematic fashion. However, whenever these data are available, the expert panels will include the information.

Table 2: Grade of recommendation (gR)*

<table>
<thead>
<tr>
<th>GR</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (1).

1.6 References

2. BACKGROUND

2.1 Definition of pain
Pain is the most common symptom of any illness, and is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage” (1).

The alerting function of pain evokes protective responses, and is intended to keep tissue damage to a minimum. The capacity to experience pain has a protective role. If tissue damage is unavoidable, a cascade of changes occurs in the peripheral and central nervous system (CNS) responsible for the perception of pain (2).

Acute pain has a time-limited course during which treatment, if necessary, is aimed at correcting the underlying pathological process. In contrast, maladaptive (pathological) pain offers no biological advantage because it is uncoupled from a noxious stimulus or tissue healing, and is usually persistent or recurrent. It may occur in response to damage to the nervous system. It is known as neuropathic pain, and is pain as a disease (3-5).

2.2 Pain evaluation and measurement
2.2.1 Pain evaluation
Health professionals should ask about pain, and the patient’s self-report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales, and should document the
efficacy of pain relief at regular intervals after starting or changing treatment.

Systematic evaluation of pain involves the following steps:

- evaluate its severity;
- take a detailed history of the pain, including an assessment of its intensity and character;
- evaluate the psychological state of the patient, including an assessment of mood and coping responses;
- perform a physical examination, emphasising the neurological examination;
- perform an appropriate diagnostic work-up to determine the cause of the pain, which may include tumour markers;
- perform radiological studies, scans, etc;
- re-evaluate therapy.

The initial evaluation of pain should include a description of the pain using the OPQRSTUV characteristics:

**O** Onset: ‘When did it start? How long does it last? How often does it occur?’

**P** Palliative or provocative factors: ‘What makes it less intense?’

**Q** Quality: ‘What is it like?’

**R** Radiation: ‘Does it spread anywhere else?’

**S** Severity: ‘How severe is it?’

**T** Temporal factors: ‘Is it there all the time, or does it come and go?’

**U** Understanding/Impact on you
- What do you believe is causing this symptom?
- How is this symptom affecting you and/or your family?

**V** Values
- What is your goal for this symptom?
- What is your comfort goal or acceptable level for this symptom (on a scale of 0 - 10 with 0 being none and 10 being the worst possible)?
- Are there any other views or feelings about this symptom that are important to you or your family?

Pain in patients with cancer is a complex phenomenon. Not all pain is of malignant origin. Patients often have more than one pain problem, and each must be individually assessed and evaluated. A key principle is to constantly re-evaluate pain and the effects and side effects of analgesic therapy.

Pain in cancer patients could be caused by the cancer itself, be due to secondary muscular spasm, be secondary to cancer treatments, or have no relation to the cancer, e.g., arthritis.

In general, cancer pain consists of two broad diagnostic types: nociceptive and neuropathic pain.

When evaluating pain, it is useful to try to determine whether the pain is one of these types or a mixture of the two. Nociceptive pain includes bone pain and soft tissue pain. Typically, it is described as a dull, aching pain. This type of pain will be largely sensitive to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.

Neuropathic pain results from damage to the peripheral or CNS. It is usually described as a burning or sharp, shooting pain. Neuropathic pain is usually not particularly responsive to NSAIDs or opioids.

Adjuvant analgesics such as anti-depressants and anticonvulsants should be used in the first instance.

### 2.2.2 Assessing pain intensity and quality of life (QoL)

There are several rating scales available to assess pain. Rating pain using a visual analogue scale (VAS) or collection of VAS scales (such as the brief pain inventory) is an essential part of pain assessment. Its ease of use and analysis has resulted in its widespread adoption. It is, however, limited for the assessment of chronic pain.
Other common ways of pain assessment are numerical scales (NRS rating 1-10, “Faces”-Wong Baker scale, mostly used in children and verbal scales (rating from absence to severe pain) (Figure 1). To study the effects of both physical and non-physical influences on patient wellbeing, an instrument must assess more dimensions than the intensity of pain or other physical symptoms. Several validated questionnaires to assess various QoL dimensions are available, including the Medical Outcomes Short-Form Health Survey Questionnaire 36 (SF-36), and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) (6-10).

For cognitively impaired and elderly patients Doloplus-2 offers pain assessment by rating somatic, psychomotor and psychosocial behaviour. The tool consists of 10 items with four behavioural descriptions representing increasing severity of pain from 0 to 3. Individual item scores are summed to arrive at a total score ranging from 0 to 30 points. Five points is the threshold indicating pain (11).

2.3 References

3. CANCER PAIN MANAGEMENT (GENERAL)

3.1 Classification of cancer pain
Cancer pain is classified as mild (1-3), moderate (4-6) and severe (7-10) (1). The physical causes of pain are either nociceptive or neuropathic. In cancer patients, nociceptive pain tends to be caused by invasion of the bone, soft tissues or viscera (e.g. bowel, bladder), and neuropathic pain by nerve compression or infiltration.

Urogenital neoplasms frequently metastasise to bone (e.g., spine, pelvis, and skull). Bone metastases are associated with pathological fractures, hypercalcaemia and neurological deficits, leading to substantial impairment of QoL. The release of algogenic substances in the tissue, microfractures and periosteal tension are the main mechanism for pain sensation (2).

Pain caused by bone metastasis is nociceptive, but can become neuropathic if the tumour invades or compresses a nerve, neural plexus or spinal cord. One-third of patients with tumour-related pain are affected by neuropathic pain components (3). Nociceptive pain is well localised. Initially, it occurs on physical movement, but later might also occur at rest.

Neuropathic pain frequently has a constant ‘burning’ character. The efficacy of opioids may be diminished in neuropathic pain, making co-analgesia necessary (4). Patients with severe neuropathic pain are a special challenge. Psychological changes frequently occur, and specific therapeutic intervention may be necessary (5).

The World Health Organization (WHO) recommends a stepwise scheme for the treatment of cancer pain syndromes and neoplastic bone pain. Bisphosphonates and calcitonin are helpful for stabilising bone metabolism. Epidural and intrathecal opioids are sometimes useful in managing metastatic bone pain. Selected patients with neuropathic pain sometimes benefit from nerve destruction by intrathecal or epidural phenol (6).

3.2 General principles of cancer pain management
The four goals of care are:
• prolonging survival;
• optimising comfort;
• optimising function;
• relieving pain.

Pain leads to a vicious cycle of sleeplessness, worry, despair, isolation, hopelessness, depression, and escalation of pain. The following hierarchy of general treatment principles is useful in guiding the selection of pain management choices.
1. Individualised treatment for each patient.
2. Causal therapy to be preferred over symptomatic therapy.
3. Local therapy to be preferred over systemic therapy.
4. Systemic therapy with increasing invasiveness (the WHO ladder).
5. Conformance with palliative guidelines.
6. Both psychological counselling and physical therapy from the very beginning.

The fundamental principle is the individualisation of therapy. Repeated evaluations allow the selection and
administration of therapy to be individualised in order to achieve and maintain a favourable balance between
pain relief and adverse effects.

The next steps in the hierarchy, especially points 2-4, necessitate a continuing risk-to-benefit assessment
between therapeutic outcome versus tolerability and willingness to accept adverse effects. The more invasive
the therapy, the more difficult the decisions become. This is particularly true with palliative medicine, where the
prospects of healing are limited and there is the problem of working against time.

If local therapy is not feasible or cannot be well tolerated, then symptomatic measures are appropriate,
although local therapy is to be preferred over systemic treatment. In simple cases, measures such as drainage
and stenting can make analgesic medication redundant, e.g., gastric probe, ureteral stent, percutaneous
nephrostomy, and bladder catheter. Patients with recurrent subileus caused by peritoneal carcinomatosis are
immediately relieved of their pain when they are given an artificial anus.

The indication is in direct relation to the severity of the disease and the operation, especially if the aim is
palliative, although such cases sometimes require invasive measures, not only to relieve pain in the terminal
phase, but also to improve QoL, although surgery can have a negative impact on patients’ wellbeing.
Examples include evisceration to prevent cloaca in cervical carcinoma, or implanting a prosthetic hip due to a
pathological fracture originating in metastasised bladder or kidney cancer.

When dose escalation of a systemically administered opioid proves unsatisfactory, the following gradual
strategy can be considered:

- Switch to another opioid.
- Intervene with an appropriate primary therapy or other non-invasive analgesic approach.
- Pursue psychological, rehabilitative and neurostimulatory techniques (e.g. transcutaneous electrical
  nerve stimulation (TENS).
- Use invasive analgesic techniques after careful evaluation of the likelihood and duration of the
  analgesic benefit, the immediate risks, and the morbidity of the procedure (epidural infusion).
- Use neurodestructive procedures (chemical or surgical neurolysis, coeliac plexus blockade).
- Some patients with advanced cancer and treatment refractory symptoms where comfort is the
  overriding goal can elect to be deeply sedated (see chapter 7, section 7.5.3 Palliative sedation).

The importance of physiotherapy and psychological counselling cannot be emphasised too strongly.

3.3 Non-pharmacological therapies

3.3.1 Surgery
Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow
viscus, unstable bony structures and compression of neural tissues or draining of symptomatic ascites (7-9).
The potential benefits must be weighed against the risks of surgery, the anticipated length of hospitalisation
and convalescence, and the predicted duration of benefit. Radical surgery to excise locally advanced disease
in patients with no evidence of metastatic spread may be palliative, and potentially increase the survival of
some patients (10-13).

### Recommendation

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<th>LE</th>
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Palliation is not equivalent to minimal invasion. Consider aggressive surgery under certain
circumstances.

3.3.2 Radionuclides

3.3.2.1 Clinical background
For patients presenting with multiple painful bone metastases, both β- and α-emitting, radionuclides can be
used to obtain pain relief.

3.3.2.2 Radiopharmaceuticals

β-Emitting isotopes
The most important β-emitting radiopharmaceuticals are: strontium-89 chloride (89Sr) and samarium-153
lexidronam (153Sm ethylenediaminetetramethylenephosphonate [EDTMP]). They are indicated for the treatment
of bone pain resulting from skeletal metastases with an osteoblastic response on bone scan but without spinal
cord compression (14-22) (LE: 2) or pathological fracture (14,17,23) (LE: 2).

These radiopharmaceuticals are delivered intravenously. The patient can pose a radiation
exposure risk for 2-4 days after 153Sm, and 7-10 days after 89Sr (17,19-21,23-30) (LE: 2). Information about
radioprotection should be provided. If the pain responds to the initial treatment, administration of $^{153}$Sm can be repeated at intervals of 8-12 weeks in the presence of recurrent pain (14,30,31) (LE: 2). The response rate for second and subsequent treatments may be lower than for the first (14,18,23,30) (LE: 2).

Side effects:
About 10% of patients experience a temporary increase in bone pain (pain flare) (32-35), generally 2-4 days after $^{153}$Sm, and 1-2 weeks after $^{89}$Sr (acute side effect) (17,18). Pain flare is associated with a good clinical response (LE: 2) (32-35), and sometimes requires a transient increase in analgesia. Pain reduction is unlikely to occur within the first week, and can occur as late as 1 month after injection. Late side effects include temporary myelosuppression (platelets and white blood cells). Recovery occurs 4-6 weeks later, depending on bone marrow reserve. There is generally no significant effect on haemoglobin.

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tr>
<td>Radiopharmaceuticals are an option for patients with multifocal pain bone metastases when other treatments such as radiotherapy, hormone therapy or bisphosphonates have failed.</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>$\beta$-Emitting radiopharmaceutical are contraindicated within 4 weeks of myelotoxic chemotherapy (except for cisplatin), or within 12 weeks of hemi-body radiotherapy.</td>
<td>3</td>
<td>C</td>
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<tr>
<td>$\beta$-Emitting radiopharmaceuticals are mainly excreted in urine so precautions must be taken with urine or blood spills for the first 10 days after treatment.</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>$\beta$-Emitting radiopharmaceuticals provide an overall survival benefit in patients with CRPC and bone metastases.</td>
<td>1b</td>
<td>A</td>
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CRPC = castration-resistant prostate cancer

Absolute contraindications:
- During or within 4 weeks of myelotoxic chemotherapy (all compounds except cisplatin), or within 12 weeks of hemi-body external radiotherapy in order to avoid severe haematopoietic toxicity.
- Known hypersensitivity to EDTMP or similar phosphonate compounds for $^{153}$Sm (14).
- Glomerular filtration rate (GFR) < 30 mL/min (14,31).
- Pregnancy; continued breastfeeding (31).

Relative contraindications:
- In acute or chronic severe renal failure (GFR 30-60 mL/min), the dose administered should be adapted.
- With a single painful lesion: external limited field radiotherapy should be performed (36,37).

Caution must be used in the following circumstances:
- Urinary incontinence: special recommendations apply, including catheterisation before administration of the radionuclide (32).
- White blood cell count of < 2500/μL (31).
- Platelets < 80,000/μL (31).
- Haemoglobin < 90 g/L (31).

$\alpha$-Emitting isotopes: radium-223
$\alpha$-Particle therapy represents a new concept that has also been successful in prolonging survival in phase III clinical trials (38). Unlike $\beta$-emitting radiopharmaceuticals, $\alpha$-pharmaceuticals, such as $^{223}$Ra, deliver an intense and highly localised radiation dose to bone surfaces (39). $^{223}$Ra thus has potentially better efficacy and tolerability when compared to $\beta$-emitters.

In clinical trials, treatment is administered by iv injection once monthly for 4 or 6 months (40-42). No imaging dose or premedication are required. No radiation protection procedures are required.

Pain response was seen in up to 71% of the patients with a dose response observed 2 weeks after administration (43). $^{223}$Ra has a favourable safety profile with little or no myelotoxic effect (44,45).

A recently completed phase III study has proven that $^{223}$Ra provides an overall survival benefit in patients with CRPC and bone metastases (38). $^{223}$Ra is expected to receive approval by various regulatory agencies in the near future.
3.3.3  Radiotherapy for metastatic bone pain

3.3.3.1 Clinical background

Radiotherapy alleviates metastatic bone pain in approximately 70% of patients, with complete pain relief at the treated site in up to 40% of patients (46-48) (LE: 1a). The onset of pain relief varies from a few days to 4 weeks (48) (LE: 2b). The median duration of pain relief reported by most studies is 3-6 months (48) (LE: 1a).

3.3.3.2 Radiotherapy scheme

Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (47-53) (LE: 1a). However, the rates of retreatment and pathological fractures are significantly higher after single-fraction radiotherapy (47,48,54) (LE: 1a).

Single-fraction radiotherapy remains the treatment of choice for alleviating bone pain because of its greater convenience for patients (LE: 1a), faster patient turnover for the radiotherapy unit (55) and lower costs (53,56) (LE: 3). The recommended dose is 8 Gy (48-53,57,58) (LE: 1a). Pain relief can be achieved with lower doses (1) (LE: 1b). These lower doses should be borne in mind if a third retreatment is necessary, or if there is concern about radiation tolerance (48) (LE: 2b).

In cases of oligometastases (< 5), a case can be made for aggressive therapy, such as radiosurgery or high-dose radiotherapy, to improve survival (LE: 3).

3.3.3.3 Spinal cord compression

Metastatic epidural spinal cord compression (MSCC) is a common, severe complication of malignancy. The most common symptom is back pain (83-95%), and weakness is present in 35-75%. When spinal cord compression is suspected, magnetic resonance imaging (MRI) is currently the gold standard for detection and therapeutic management (59-63) (LE: 2b), with sensitivity of 93% (64) (LE: 3) and specificity of 96% (64) (LE: 3). The level of neurological function at the start of treatment determines the functional outcome (65).

Corticosteroids reduce oedema and may have an oncolytic effect on certain tumours. However, the extent of the benefit and the optimal dosage are unclear. High-dose corticosteroids carry a significant risk of adverse effects. One RCT of patients with MSCC showed significantly better functional outcome when radiotherapy was combined with dexamethasone (66) (LE: 1b).

Radiotherapy is generally the treatment of choice. A multifraction regimen (10 × 3 Gy) is preferable in these patients because it allows for a higher dose and thus greater reduction in tumour size. For patients whose chances of survival are estimated to be poor, a short course of radiotherapy is advised (67) (LE: 1b).

Several uncontrolled surgical trials (59,61,63) and one meta-analysis (60) have indicated that direct decompressive surgery is superior to radiotherapy alone with regard to regaining ambulatory and sphincter function, and obtaining pain relief (LE: 1a). However, the decision to pursue surgery must be tempered by awareness of the attendant significant morbidity and mortality risks. Careful patient selection is of utmost importance; the criteria are shown in Table 3 (LE: 3).

Table 3: Criteria for selecting patients for primary therapy for spinal cord compression

<table>
<thead>
<tr>
<th>Absolute criteria</th>
<th>Surgery</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operability</td>
<td>Medically operable</td>
<td>Medically inoperable</td>
</tr>
<tr>
<td>Duration of paraplegia</td>
<td>&lt; 48 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>&gt; 3 months</td>
<td>&lt; 3 months</td>
</tr>
<tr>
<td>Radiosensitivity</td>
<td></td>
<td>Highly sensitive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative criteria</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Diagnosis of primary tumour</td>
<td>Unknown</td>
<td>Known</td>
</tr>
<tr>
<td>Bone fragments with compression</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Number of foci of compression</td>
<td>1 focus</td>
<td>&gt; 1 foci</td>
</tr>
</tbody>
</table>

A randomised prospective trial has demonstrated that patients treated with a combination of surgery followed by radiotherapy can remain ambulatory longer, and those who are not ambulatory at presentation have a better chance of regaining ambulatory function than those treated with radiotherapy alone (62) (LE: 1b).
3.3.3.4 Pathological fractures
In patients with impending pathological fractures (e.g., femoral lesion with an axial cortical involvement > 30 mm), a prophylactic orthopaedic procedure should be considered (64).

3.3.3.5 Side effects
Side effects are related to the total dose, fractionation size, and the localisation of the metastases. Acute grade 2-4 toxicity is more frequent after multifraction radiotherapy regimens. The incidence of late toxicity is low (54). The side effects are mostly transient, lasting a few days and include:
1. Pain flare (within 24 h and due to oedema). Patients should be counselled accordingly and given breakthrough opioids. Patients receiving single-fraction radiotherapy may be at higher risk than those receiving multifraction radiotherapy (68). A small phase II study has shown that 8 mg dexamethasone is effective for prophylaxis of radiotherapy-induced pain flare after palliative radiotherapy for bone metastases (69) (LE: 3).
2. Symptoms depending on the treatment field and location: nausea (especially with larger fields), vomiting, diarrhoea, irritation of the throat and oesophagus.

3.3.4 Psychological and adjunctive therapy
3.3.4.1 Psychological therapies
The perception of pain and the suffering it causes derive from a combination of physical, emotional, spiritual, and social constructs. Psychological assessment and support are an integral and beneficial part of treating pain in cancer patients (70-72).

There is evidence that highly emotional cancer patients, as detected through their own narratives, experience less pain than their less emotional counterparts (73). Cultural differences also play a role in pain perception (74).

Depression is the most prevalent psychiatric diagnosis in patients with cancer. Although there is no proof that psychotherapy is useful in non-cancer patients with depression, patients with incurable cancer can benefit from this type of treatment (75). In this setting, structured psychotherapy seems to be more effective than antidepressant medication (76). Interestingly, effective psychological management results in a reduction in depressive complaints, inflammatory markers, pain, and fatigue in cancer patients (77).

Cognitive behavioural therapy (CBT), such as relaxation and distraction, can provide pain relief (78-80). As expected, protocols tailored to individual patient characteristics can result in higher satisfaction in terms of pain relief, mood improvement and general well-being. The possibility of delivering CBT by home visits, telephone, or through the internet seems promising (81-83). Virtual consultation and automated symptom monitoring for cancer patients with depression can exceed all expectations (84). It has also been suggested that CBT may be particularly helpful for younger cancer patients (85).

More recently, the effects of dignity therapy on distress and end-of-life experience have been formally tested. Dignity therapy is based on a formal written narrative of the patient’s life. Its benefits in terms of end-of-life experiences might support its clinical application (86). Families can be dysfunctional (e.g., emotionally and organisationally) during palliative care and bereavement. Family-focused grief therapy based on communication, cohesiveness, conflict resolution, and shared grief is effective in protecting family members against the drama of disease and death (87). Other psychological interventions that aim to minimise caregiver emotional distress have not been effective (88). Overall, educational programmes that aim to maximise family and patient satisfaction with pain treatment seem promising (89).

The impact of early detection of psychological distress may improve health outcomes (90). There is also a real need for screening the patient’s desire for psychological support, as well as patient distress. This may include psychological interventions according to the patient’s needs and desires (91). Different tools are available to better assess patients’ needs, such as Palliative Care Needs Assessment Guidelines and Needs Assessment Tool (92) and the short form of the Supportive Care Needs Survey (SCNS-SF34) (93).

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Always offer psychological support to cancer patients and their loved ones.</td>
<td>1a</td>
<td>A</td>
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</table>

3.3.4.2 Adjunctive therapy
A number of therapeutic strategies have been proposed as non-pharmacological adjunctives to medical and surgical procedures. To date, there is no conclusive evidence on the effect of reflexology and massage therapy (94-96). Nevertheless, certain manipulations (e.g., sciatic nerve press) seem to be effective for immediate pain relief in many oncological conditions (97). The notion that acupuncture may be effective for cancer patients is
not supported by the currently available data (98,99). However, modest although significant improvements in depression and pain scales have been confirmed by well-conducted studies on acupuncture (100).

Evidence from robust studies is still lacking on the effect of traditional Chinese medicine and complementary alternative medicine (101,102). The effect of cupping therapy - an ancient form of medicine in which suction is created on the skin - on pain needs to be more rigorously tested (103). Physical exercise (short walks) can positively affect the pain experience of prostate cancer (PCa) patients (104). Similarly, moderate exercise positively affects cancer-related sleep disturbance (105). TENS might mitigate hyperalgesia in cancer patients. Unfortunately, reliable studies in this field are lacking (106).

Listening to music slightly reduces distress, pain intensity and opioid requirements in cancer patients (107,108). Music relaxation videos seem to positively affect pain severity, opioid consumption, and anxiety level in patients treated for some gynaecological tumours (109). It is likely that patients harbouring urological tumours could also benefit.

Strong evidence on the real potential of cannabis derivatives is lacking (110).

Evidence exists of the strong relationship between pain, anxiety and depression, and health-related QoL in cancer patients (111,112). Sexual dysfunction is a potential long-term complication of cancer treatment. Following treatment for PCa, transurethral alprostadil and vacuum constriction devices reduce sexual dysfunction, although negative effects are common. Vaginal lubricating creams are also effective, as are PDE5 inhibitors (PDE5Is) for sexual dysfunction secondary to prostate cancer treatment (113). Psychological interventions focused on sexual dysfunction following cancer can be considered as moderately effective (114).

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Moderate exercise can be an adjuvant and should be suggested in the treatment of cancer pain.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Acupuncture and traditional Chinese medicine have not been proven effective in the treatment of cancer pain.</td>
<td>1a</td>
<td>A</td>
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### 3.4 Pharmacotherapy

The successful treatment of cancer pain depends on the clinician’s ability to assess the presenting problems, identify and evaluate pain syndromes, and formulate a plan for comprehensive continuing care. This requires familiarity with a range of therapeutic options and responsiveness to the changing needs of the patient. The treatment of pain must be part of the broader therapeutic agenda, in which tumour control, symptom palliation (physical and psychological), and functional rehabilitation are addressed concurrently.

#### 3.4.1 Chemotherapy

A successful effect on pain is generally related to tumour response. There is a strong clinical impression that tumour shrinkage is generally associated with relief of pain, although there are some reports of analgesic benefit even in the absence of significant tumour shrinkage (115) (LE: 1a).

#### 3.4.2 Bisphosphonates

##### 3.4.2.1 Mechanisms of action

- Inhibition of bone resorption: beginning 24–48 h after administration. Target cells are the osteoclasts. There are three different mechanisms of inhibition of bone resorption corresponding to the three generations of bisphosphonates. There are four distinct effects on osteoclasts:
  - reduction of osteoclastic activity
  - inhibition of osteoclast adhesion
  - decrease in number of osteoclasts
  - induction of osteoclast apoptosis.
- Inhibition of crystallisation and mineralisation: clinically not relevant.
- Promotion of osteoblastic bone formation and production of osteoclast resorption inhibitor.
- Anti-angiogenic effect and effect on tumour cells.

##### 3.4.2.2 Effects and side effects

The main effects are:

- decrease of the risk of skeleton-related events (116) (LE: 1b);
- pain relief in 60-85% of patients (116-118) (LE: 1b).
The main side effects are:

- flu-like symptoms (20-40%), bone pain, fever, fatigue, arthralgia and myalgia (all < 10%);
- hypocalcaemia (rapid infusion in older patients with vitamin D deficiency);
- acute renal failure (rapid infusion); always check renal function (GFR);
- osteonecrosis of the jaw bones (only after iv therapy);
- gastrointestinal symptoms can occur after oral administration (2-10%).

### Recommendations

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<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Dehydration must be recognised and treated before administration.</td>
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<td>B</td>
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<tr>
<td>When using zoledronate, reduce the dose in the event of impaired renal function (119).</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Avoid simultaneous administration of aminoglycosides (120).</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Perform clinical examination of the patient’s mouth and jaws; avoid oral/dental surgery during administration of iv bisphosphonates (121-125).</td>
<td>2</td>
<td>B</td>
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#### 3.4.3 Denosumab

Histological findings and analysis of bone turnover markers support the view that bone metastases from PCa are characterised by an excess osteoclastic activity inducing bone destruction. This results in an increased risk of skeletal-related events (SREs), such as pathologic fractures, spinal cord compression, pain requiring radiotherapy or surgery, and hypercalcaemia. The receptor activator of nuclear factor-κB ligand (RANKL), mediates the formation, function, and survival of osteoclasts. Tumour cells induce osteoclast activation, which then mediates bone resorption and releases growth factors, resulting in a cycle of bone destruction and tumour proliferation.

Denosumab is a fully human monoclonal antibody that specifically binds and neutralises RANKL, inhibiting osteoclastogenesis and decreasing osteoclast-mediated bone destruction (126). Improvement in bone-metastases-free-survival (4.3 months) and increased time to first bone metastasis (3.7 months) has been reported with denosumab in a phase III randomised placebo controlled trial (127).

Another recently published phase III study, randomised men with CRPC and no previous exposure to iv bisphosphonate between 120 mg subcutaneous denosumab plus iv placebo, or 4 mg iv zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cut-off date. Denosumab significantly delayed the time to first onstudy skeletal-related event by 18% compared to zoledronic acid, with a between-group difference of 3-6 months (128). Occurrences of adverse events and serious adverse events were similar between groups. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 (6%); p<0.0001). Osteonecrosis of the jaw was infrequent in both groups. The authors concluded that denosumab was better than zoledronic acid for prevention of skeletal-related events, and potentially represents a novel treatment option in men with bone metastases from CRPC (128).

A large randomised study (1432 patients) showed that denosumab significantly increased bone-metastasis-free survival by a median of 4.3 months compared to placebo (median 29.5 (95% CI 25.4-33.3) vs 25.2 (22.2-29.5) months; hazard ratio (HR) 0.85, 95% CI 0.73-0.98, P=0.028). Denosumab also significantly delayed time to first bone metastasis (33.2 (95% CI 29.5-38.0) vs 29.5 (22.4-33.1) months; HR 0.84, 95% CI 0.71-0.98, P=0.032). Overall survival did not differ between groups (denosumab, 43.9 (95% CI 40.1-not estimable) months vs placebo, 44.8 (40.1-not estimable) months; HR 1.01, 95% CI 0.85-1.20, P=0.91). Rates of adverse events and serious adverse events were similar in both groups (127).

#### Recommendation

Denosumab use increases bone-metastasis-free survival and delays time to first bone metastasis in prostate cancer patients.

#### 3.4.4 Systemic analgesic pharmacotherapy - the analgesic ladder

Analgesic pharmacotherapy is the mainstay of cancer pain management (129-131). Although concurrent use of other interventions is valuable in many patients, and essential in some, analgesic drugs are needed in almost every case. Based on clinical convention, analgesic drugs can be separated into three groups:

- Non-opioid analgesics.
- Opioid analgesics.
- Adjunct analgesics.

Emphasising that pain intensity should be the prime consideration, the WHO has proposed a three-step approach to analgesic selection for cancer pain (129,131) (LE: 1a). Known as the analgesic adder, when
combined with appropriate dosing guidelines it can provide adequate relief in 70-90% of patients (132,133).

- **Step 1: non-opioid analgesic** Patients with mild to moderate cancer-related pain should be treated with a non-opioid analgesic.

- **Step 2: non-opioid analgesic + weak opioid** Patients who present with moderate to severe pain or who fail to achieve adequate relief after a trial of a non-opioid analgesia should be treated with a weak opioid (e.g. codeine or tramadol), typically by using a combination product containing a non-opioid (e.g. aspirin or paracetamol) and an opioid (e.g. codeine, tramadol or propoxyphene).

- **Step 3: non-opioid analgesic + strong opioid** Patients who present with severe pain or who fail to achieve adequate relief with step 2 drugs, should receive a strong opioid (e.g. morphine, fentanyl, oxycodone, methadon, buprenorphine, or hydromorphone).

### 3.4.4.1 Non-opioid analgesics

- Non-opioid analgesics are paracetamol, metamizole (dipyrone) and non-steroidal anti-inflammatory drugs (NSAIDs).
- Can be useful alone for mild to moderate pain (step 1 of the analgesic ladder).
- May be combined with opioids.
- Have a ceiling effect of analgesic efficacy.
- No tolerance or physical dependence.
- Inhibit the enzyme cyclo-oxygenase and block the synthesis of prostaglandins.
- Involvement of central mechanisms is also likely in paracetamol analgesia (134).
- Potential adverse effects: bleeding diathesis due to inhibition of platelet aggregation, gastroduodenopathy (including peptic ulcer disease) and renal impairment are the most common; less common adverse effects include confusion, precipitation of cardiac failure and exacerbation of hypertension. Particular caution must be used in elderly patients and those with blood-clotting disorders, predisposition to peptic ulceration, impaired renal function and concurrent corticosteroid therapy (135).
- Non-acetylated salicylates (choline magnesium trisalicylate and salsalate) are preferred in patients who have a predilection to bleeding; these drugs have less effect on platelet aggregation and no effect on bleeding time at the usual clinical doses.
- Paracetamol rarely produces gastrointestinal toxicity, but, if this occurs, with no adverse effect on platelet function. Hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses (136).

### 3.4.4.2 Opioid analgesics

Cancer pain of moderate or severe intensity should generally be treated with a systemically administered opioid analgesic (137). Classification is based on interaction with the various receptor subtypes:

- Agonist: most commonly used in clinical pain management, no ceiling effect.
- Agonist-antagonist (pentazocine, nalbuphine and butorphanol): ceiling effect for analgesia.

By convention, the relative potency of each of the commonly used opioids is based on a comparison with 10 mg parenteral morphine. Equianalgesic dose information provides guidelines for dose selection when the drug or route of administration is changed (138).

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain (138-141). Patients who present with severe pain should be treated with a strong opioid from the outset. Patients with moderate pain are commonly treated with a combination drug containing paracetamol or aspirin plus codeine, tramadol, or propoxyphene, the dose of which can be increased until the maximum dose of the non-opioid co-analgesia is attained (e.g. 4000 mg paracetamol).

Factors to consider when selecting an opioid include:

- pain intensity
- patient age
- response to previous trials of opioid therapy
- co-existing disease
- influence of underlying illness, characteristics of the opioid and concurrent medications.

### Routes of administration

Opioids should be administered by the least invasive and safest route that can provide adequate analgesia. In a survey of patients with advanced cancer, more than half required two or more routes of administration prior to death, and almost a quarter required three or more.
Non-invasive routes

- **Oral** routes are the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing, gastrointestinal dysfunction, require a very rapid onset of analgesia, or cannot tolerate the oral route.

- **Rectal** suppositories containing oxycodone, hydromorphone, oxycodone and morphine in combination are available, and controlled-release morphine tablets can also be administered per rectum. The potency of rectally administered opioids is believed to approximate to oral dosing (142).

- **Transdermal** routes: fentanyl and buprenorphine have been demonstrated to be effective in postoperative and cancer pain (143). There is some interindividual variability in fentanyl bioavailability by this route, which, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases (144). The efficacy of transdermal fentanyl is equal to morphine. The incidence of side effects such as sedation and constipation are lower than for morphine (145,146) (LE: 1b).
  - Transdermal patches able to deliver 12, 25, 50, 75 and 100 mg/h are available. Multiple patches can be used simultaneously for patients who require higher doses. Current limitations of the transdermal delivery system include costs, and the need for an alternative short-acting opioid for breakthrough pain.
  - Recently, buprenorphine has become available for transdermal administration. A high affinity partial μ-opioid agonist, it is in clinical use for the treatment of acute and chronic pain (147). Its analgesic effect is comparable with that of other opioids, and it shows no relevant analgesic ceiling effect throughout the therapeutic dose range (148). Unlike full μ-opioid agonists, buprenorphine’s physiological and subjective effects, including respiratory depression and euphoria, reach a plateau at higher doses. This ceiling may limit the abuse potential, and might result in a wider safety margin (149).

- **Sublingual** absorption of any opioid is potentially clinically beneficial, but bioavailability is very poor with drugs that are not highly lipophilic, so the chances of an adequate response are low (150). Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief for mild to moderate cancer pain. Overall, this route has limited value due to the lack of formulations, poor absorption of most drugs, and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl (incorporated into a sugar base) is useful for the rapid relief of breakthrough pain (151,152). Fentanyl delivered by this means is more effective than oral morphine at relieving pain (LE: 2).

<table>
<thead>
<tr>
<th>Recommendations</th>
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<th>GR</th>
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<tbody>
<tr>
<td>Transdermal fentanyl is equally effective to morphine. The incidence of side effects is lower than for morphine.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Oral transmucosal administration of fentanyl should be used to provide rapid relief of breakthrough pain. The starting dose is 400 μg, or 200 μg in the elderly and those with a history of opioid sensitivity or underlying pulmonary disease.</td>
<td>2a</td>
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Invasive routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is not available. Repeated parenteral bolus injections, which can be administered iv, intramuscularly (im) or subcutaneously (sc), may be useful in some patients, but are often compromised by the occurrence of prominent bolus effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repeated im injections are common, but are painful and offer no pharmacokinetic benefit; their use is not recommended (153).

- **Intravenous bolus** administration provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid, and ranges from 2-5 min for methadone, to 10-15 min for morphine (154). This approach is appropriate in two settings:
  - To provide parenteral opioids, usually transiently, to patients who already have venous access and are unable to tolerate oral opioids.
  - To treat very severe pain, for which iv doses can be repeated at an interval as brief as that determined by the time to peak effect until adequate relief is achieved.

- **Continuous parenteral infusions** is mainly used in patients who are unable to swallow, absorb opioids or otherwise tolerate the oral route, but is also employed in patients whose high opioid requirement renders oral treatment impractical (155). Long-term infusions can be administered iv or sc.
  - Ambulatory patients can easily receive a continuous sc infusion using a 27-gauge butterfly
needle, which can be left in place for up to a week. A recent study demonstrated that the bioavailability of hydromorphone by this route is 78% (156), and clinical experience suggests that dosing can be identical to that for continuous iv infusion. A range of pumps is available to provide patient-controlled rescue doses (supplemental doses offered on an as-needed basis to treat pain that breaks through the regular schedule) as an adjunct to continuous basal infusion.

- Opioids suitable for continuous sc infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with hydromorphone, oxycodone and morphine (157). Methadone appears to be relatively irritating and is not preferred (158). To maintain the comfort of an infusion site, the sc infusion rate should not exceed 5 mL/h.

- The infraclavicular and anterior chest sites provide the greatest freedom of movement for patients, but other sites can be used. A single infusion site can usually be maintained for 5-7 days.

**Opioid switching**

A systematic search was developed to include studies after 2004, with cancer patients switching between strong opioids and reporting pain control and adverse effects, usually from morphine or oxycodone to methadone. The search reviewed 288 papers, among which, only 11 (280 patients) met the inclusion criteria. Pain intensity was significantly reduced in the majority of studies, and there were fewer serious adverse effects (159).

**Changing the route of administration**

Switching between oral and parenteral routes should be guided by knowledge of relative potency to avoid subsequent over- or underdosing. In calculating the equi-analgesic dose, the potencies of the iv, sc and im routes are considered equivalent. Perform changes slowly in steps, e.g. gradually reducing the parenteral dose and increasing the oral dose over a 2-3 day period (LE: 3).

**Dosing**

- **A round-the-clock dosing.** Patients with continuous or frequent pain generally benefit from scheduled around-the-clock dosing, which provides continuous relief by preventing recurrence of the pain. This approach should be used only in patients with no previous opioid exposure. Patients should also be provided with a rescue dose. This combination offers gradual, safe and rational dose escalation that is applicable to all routes of opioid administration.

- **Controlled-release drug formulations.** These preparations of oral opioids can lessen the inconvenience of around-the-clock administration of drugs with a short duration of action. Numerous studies have demonstrated the safety and efficacy of these preparations in cancer patients with pain (160,161).

- **As-needed (prn) dosing.** This strategy is beneficial if rapid dose escalation is necessary or when beginning therapy with opioids with a long half-life (e.g., methadone or levorphanol). As-needed dosing may also be appropriate for patients who have rapidly decreasing analgesic requirements, or intermittent pains separated by pain-free intervals.

- **Patient-controlled analgesia (PCA).** This is a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug on demand according to parameters set by the physician. Long-term PCA in cancer patients is most commonly sc using an ambulatory infusion device. PCA is usually added to a basal infusion rate and acts, in effect, as a rescue dose.

**Adverse effects and their management**

- **Tolerance.** There is great variation in the opioid dose required to manage pain (400-2000 mg im morphine per 24 h) (162). The induction of true analgesic tolerance that could compromise the utility of treatment can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g., progressive disease) that would be capable of explaining the increase in pain. Extensive clinical experience suggests that most patients who require dose escalation to manage increasing pain do have demonstrable disease progression (163). This suggests that true pharmacological tolerance to the analgesic effects of opioids is not a common clinical problem, and has two important implications:
  - Concern about tolerance should not impede the use of opioids early in the course of the disease.
  - Worsening pain in patients receiving a stable dose of opioids should not be attributed to tolerance, but be assessed as evidence of disease progression or, less commonly, increasing psychological distress.
• **Adverse drug interactions.** There is potential for cumulative side effects and serious toxicity to arise from combinations of drugs. The sedative effect of an opioid may add to that of other centrally acting drugs, such as anxiolytics, neuroleptics and antidepressants. Likewise, constipation produced by opioids is probably worsened by anticholinergic drugs.

• **Respiratory depression.** This is the most serious adverse effect of opioid therapy, which can impair all phases of respiratory activity (rate, minute volume and tidal exchange). Clinically significant respiratory depression is always accompanied by other signs of central nervous system depression, including sedation and mental clouding. Repeated administration of opioid drugs appears to produce a rapid tolerance to their respiratory depressant effects, however, so these drugs can be used in the management of chronic cancer pain without significant risk of respiratory depression. When this does occur in patients on chronic opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation.

• **Sedation.** Tolerance to this effect usually develops within a period of days to weeks. Patients should be warned about it, to reduce anxiety and discouragement that could be dangerous if sedation occurs (e.g., driving). Some patients have a persistent problem with sedation, particularly if other sedating drugs are also being taken or if there is comorbidity such as dementia, metabolic encephalopathy, or brain metastases.

• **Confusion and delirium.** Confusion is a greatly feared effect of opioid drugs, and mild cognitive impairment is common (164). However, similar to sedation, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to 1-2 weeks. Although persistent confusion attributable to opioids alone does occur, it is usually related to the combined effect of the opioid and other factors, including electrolyte disorders, neoplastic involvement of the central nervous system, sepsis, vital organ failure and hypoxaemia (165). A stepwise approach to management often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5-1.0 mg orally or 0.25-0.5 mg iv or im) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.

• **Constipation.** This is the most common adverse effect of chronic opioid therapy (166-168), and laxative medication should be prescribed prophylactically. Combination therapy is frequently used, particularly co-administration of a softening agent (e.g., docusec) and a cathartic (e.g., senna, bisocodyl or phenolphthalein). The doses should be increased as necessary, and an osmotic laxative (e.g., magnesium sulphate) should be added if required. Chronic lactulose therapy is an alternative that some patients prefer, and the occasional patient is managed with intermittent colonic lavage using an oral bowel preparation.

• **Nausea and vomiting.** Opioids may produce nausea and vomiting via both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and affect the gastrointestinal tract (increased gastric antral tone, diminished motility, delayed gastric emptying). The incidence of nausea and vomiting in ambulatory patients is estimated to be 10-40% and 15-40%, respectively (169), with the effects greatest at the start of therapy. Metoclopramide is the most reasonable initial treatment. Tolerance typically develops within weeks. Routine prophylactic administration of an anti-emetic is not necessary. Serotonin antagonists (e.g., ondansetron) are not likely to be effective with opioid-induced symptoms as they do not eliminate apomorphine-induced vomiting and motion sickness, which appear to be appropriate models for opioid effects. Clinical trials are needed to confirm this.

• **Addiction and dependence.** Confusion about physical dependence and addiction augments the fear of opioids and contributes substantially to the undertreatment of pain (170). Patients with chronic cancer pain have a so-called therapeutic dependence on their analgesic pharmacotherapy, which may or may not be associated with the development of physical dependence, but is seldom associated with addiction. The medical use of opioids is rarely associated with the development of addiction (171). There are no prospective studies in patients with chronic cancer pain, but extensive clinical experience affirms the low risk of addiction in this population (LE: 3). Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is small.

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<th>Recommendation</th>
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<tr>
<td>Inform the patient that the use of morphine has a small risk of addiction.</td>
<td>3</td>
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**Adjuvant analgesics**

Defined as a drug that has a primary indication other than pain but is analgesic in some conditions. These drugs may be combined with primary analgesics on any of the three steps of the analgesic ladder to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. In
the management of cancer pain, adjuvant analgesics are conventionally categorised as follows.

- **Corticosteroids.** Widely used as adjuvant analgesics (172,173), this group has been demonstrated to have analgesic effects, to improve QoL significantly (174), and to have beneficial effects on appetite, nausea, mood and malaise in patients with cancer (175). The mechanism of analgesia may involve anti-oedemic and anti-inflammatory effects, plus a direct influence on the electrical activity in damaged nerves. (i.e., reduction of neuropathic pain). Patients with advanced cancer who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroids (e.g. dexamethasone 1-2 mg twice daily) (LE: 2a).

- **Benzodiazepines.** These drugs have a small analgesic effect (176), and must be balanced by the potential for side effects, including sedation and confusion. Benzodiazepines are generally used only if another indication exists, such as anxiety or insomnia (LE: 2b).

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<tr>
<td>Dexamethasone 1-2 mg twice daily can be a valuable adjuvant in the treatment of pain in advanced cancer.</td>
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</table>

### 3.4.5 Treatment of neuropathic pain

Numerous options are available for relieving neuropathic pain, including opioids, which give patients significant pain reduction with greater satisfaction than antidepressants (177,178). However, the potential complications of opioids mean that they are not always a satisfactory option (179). Besides opioids, effective therapies for managing neuropathic pain include antidepressants, anticonvulsants, topical treatments (lidocaine patch, capsaicin), N-methyl-D-aspartate (NMDA) receptor antagonists, baclofen, local anaesthetics, and clonidine (180,181).

#### 3.4.5.1 Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain (180). Antidepressants which work primarily via interaction with pathways running through the spinal cord from serotonergic and noradrenergic structures in the brain stem and mid-brain.

Tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine) are often the first drugs selected to alleviate neuropathic pain (182,183) (LE: 1a). The mechanism of action is predominantly by blocking the reuptake of norepinephrine and serotonin (dual acting), together with a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca2+ or Na+), and interaction with adenosine and NMDA receptors. However, treatment with these analgesics may be compromised (and outweighed) by their side effects. TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention. In addition, combination therapy with monoamine-oxidase inhibitors could result in the development of serotonin syndrome.

Duloxetine enhances both serotonin and norepinephrine function in descending modulatory pathways. It has weak affinity for the dopamine transporter and insignificant affinity for several neurotransmitters, including muscarinic, histamine, glutamate, and gamma-aminobutyric acid (GABA) receptors. Duloxetine has demonstrated a significant pain-relieving effect with a generally favourable side-effect profile in painful diabetic neuropathy (182) (LE: 1b).

Selective serotonin reuptake inhibitors (SSRIs) - sertraline, paroxetine, fluoxetine and citalopram - selectively inhibit the reuptake of serotonin. These antidepressants have a more favourable side effect profile than TCAs, but their effectiveness in neuropathic pain is disputed in the literature (second-line pharmacological treatment).

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Offer amitriptyline and nortriptyline as a first line treatment for neuropathic pain, with nortriptyline associated with fewer side effects.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention.</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>Duloxetine is first-line treatment for neuropathic pain due to diabetic polyneuropathy.</td>
<td>2a</td>
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<tr>
<td>Duloxetine may be tried as an analgesic in other neuropathic pain syndromes.</td>
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#### 3.4.5.2 Anticonvulsant medication

The rationale for the use of anticonvulsant drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain (184).
Different anticonvulsants have demonstrated pain relief by a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca²⁺ or Na⁺), and effects on neurotransmitters (enhancement of GABA, inhibition of glutamate release) and/or neuromodulation systems (blocking the NMDA receptor) (185,186). Carbamazepine and phenytoin were initially used for the treatment of trigeminus neuralgia. Although both drugs reduce neuropathic pain, their attendant side effects and complicated pharmacokinetic profile limit their use.

Despite the introduction of newer anticonvulsants with better side effect profiles, carbamazepine remains the drug of choice for treating trigeminus neuralgia (187) (LE: 1a). However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with a similar mechanism of action to that of carbamazepine but with a better side effect profile, may replace carbamazepine for this purpose (188).

Gabapentin and pregabalin are first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy (189-191) (LE: 1a). The combination of gabapentin with opioids seems to display synergistic effects in relieving neuropathic pain (192,193). Gabapentin has a favourable safety profile with minimal concern for drug interactions and no interference with hepatic enzymes. However, renal failure results in higher gabapentin concentrations and a longer elimination half-life, making dose adjustments necessary. Pregabalin (3-isobutyl GABA) is a structural analogue of gabapentin, but shows greater analgesic activity in rodent models of neuropathic pain than did gabapentin (194). Recent studies confirm the effectiveness of pregabalin in peripheral (including post-herpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain (195).

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<td>Offer gabapentin and pregabalin as first-line treatment for neuropathic pain, especially if tricyclic antidepressants are contraindicated.</td>
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3.4.5.3 Local analgesics
Neuropathic pain syndromes are typically associated with touch-evoked allodynia and hyperalgesia that impair patients’ QoL. As well as treatment with anticonvulsants and antidepressants, a topical drug can be effective in treating ongoing pain and allodynia, supporting the idea that peripheral actions are of key importance in the initiation and maintenance of neuropathic pain.

Local treatments for neuropathic pain include the 5% lidocaine patch, and capsaicin. The 5% lidocaine patch, a targeted peripheral analgesic, is effective in the treatment of post-herpetic neuralgia and a variety of other focal peripheral neuropathies (196,197) (first-line pharmacological treatment; LE: 1b). Once a day, up to three patches are applied to the painful skin, covering as much of the affected area as possible.

Capsaicin causes pain due to release of substance P from the nociceptive terminals, initiating nociceptive firing. An analgesic response follows because prolonged exposure to capsaicin desensitises the nociceptive terminals and elevates the pain threshold. Capsaicin (third-line pharmacological treatment) reduces pain in a variety of neuropathic pain conditions (including post-herpetic neuralgia, diabetic neuropathy and painful polyneuropathy). It is applied in a 0.075% concentration (198) (LE: 3).

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<th>Recommendations</th>
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<tr>
<td>Topical lidocaine 5% should be used as an adjuvant in patients suffering from post-herpetic neuralgia.</td>
<td>1b</td>
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<tr>
<td>Transdermal capsaicin may be used as an adjuvant in patients with neuropathic pain.</td>
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3.4.5.4 NMDA receptor antagonists
Within the dorsal horn, ionotropic glutamate receptors (NMDA, 2-amino-3-(3-hydroxy-5-methyl-4-isoxazole) propionate (AMPA), and kainate) and metabotropic glutamate receptors are all involved in neuropathic pain (170,199). However, the actions of excitatory amino acids (glutamate) on the NMDA receptor is considered a pivotal event in the phenomenon of wind-up and neuronal hyperexcitability (enhancement and prolongation of sensory transmission) that eventually leads to allostynia, and primary and secondary hyperalgesia.

Subanaesthetic doses of ketamine, and its active enantiomer S(+)ketamine, given parenterally, neuraxially, nasally, transdermally or orally, alleviate pain postoperatively and in a variety of neuropathic pain syndromes, including central pain (200) (LE: 2b). However, ketamine may result in unwanted changes in mood, conscious perception, and intellectual performance, as well as psychomimetic side effects (including visual and auditory hallucinations, dissociation and nightmares), limiting its use for neuropathic pain (199). It must therefore be
The primary role of low-dose systemic ketamine (bolus 0.25 mg/kg followed by continuous administration at 0.1-0.4 mg/kg/h) is as an anti-hyperalgesic, antiallodynic, or tolerance-protective compound in patients with severe acute pain, chronic or neuropathic pain, opioid tolerance, or those at risk for developing chronic postsurgical pain (following laparotomy, thoracotomy, breast surgery, and nephrectomy) (203,204). In the acute setting ketamine is effective as a rescue analgesic (0.25 mg/kg, iv) for acute pain that is not, or poorly, responsive to opioids (205).

Despite improved and prolonged analgesia following caudal administration of ketamine in paediatric anaesthesia, there remains a controversy in the preclinical (animal) and clinical literature as to the safety and justifiability of this compound for neuraxial administration. In a case report, as well as in an animal study, severe histological abnormalities indicating neurotoxicity were observed following neuraxial administration of ketamine (206,207).

**Recommendation**

Ketamine is effective as an analgesic in neuropathic pain, but may be responsible for severe life-threatening side effects and should be reserved for specialised pain clinics and as a last resort (third-line treatment).

### 3.4.5.5 Other drug treatments

Baclofen, a muscle relaxant, is analgesic due to its agonistic effect on the inhibitory GABAB receptors. Baclofen is efficacious in patients with trigeminal neuralgia, but not in those with other neuropathic pain conditions (208). However, this analgesic also has antispasticity properties and may induce analgesia by relieving muscle spasms, a frequent accompaniment of acute neuropathic pain. Baclofen can be considered a second-line agent for trigeminal neuralgia, or a third-line agent in neuropathic pain syndromes (LE: 3).

Clonidine, an α2-adrenoreceptor agonist, is available as a patch for transdermal administration and has been used in neuropathic pain states. When used locally, it seems to enhance the release of endogenous encephalin-like substances, but its use in the treatment of neuropathic pain is focused on intrathecal or epidural administration in combination with opioids and/or local anaesthetics. This delivery improves pain control because of a possible supra-additive effect during neuropathic pain treatment (209) (LE: 2b).

**Summary: treatment of neuropathic pain**

- **First-line agent:**
  - nortriptyline, pregabalin, gabapentin
  - duloxetine (first-line treatment in diabetic polyneuropathy only)
  - lidocaine 5% patch (first-line treatment in post-herpetic neuralgia only).
- **Second-line agent:**
  - opioids/tramadol (first-line treatment in patients with neuropathic cancer pain only).
- **Third-line agent:**
  - baclofen
  - transdermal capsaicin 0.075%
  - ketamine (an anaesthetic).

### 3.4.5.6 Invasive analgesic techniques

Studies suggest that 10-30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone without unacceptable drug toxicity (132,133). Anaesthetic and neurosurgical techniques may reduce the need for systemically administered opioids, while achieving relief.

**Peripheral nerve catheterisation in the management of cancer pain**

Tumour infiltration or compression of a peripheral nerve or plexus can result in severe neuropathic pain resistant to pharmacological treatment. In these patients invasive analgesic techniques may be emphasised (210,211).

**Recommendation**

Reversible regional anaesthetic techniques must be considered for the management of neuropathic pain.

GCP = good clinical practice
Neurolytic blocks to control visceral cancer pain

Visceral cancer pain is mainly treated with NSAIDs and opioids, but neurolytic blockade can be used to optimise palliative treatment for cancer in the viscera.

Different neurolytic blockades have been described (212,213). A coeliac plexus block is indicated to treat pain secondary to malignancies of the retroperitoneum or upper abdomen (distal part of the stomach, pancreas, liver, gall bladder) (214) (LE: 1b). A superior hypogastric plexus block has proven utility for pelvic pain (rectum, vaginal fundus, bladder, prostate, testes, seminal vesicles, uterus and ovaries) due to a neoplasm that is refractory to pharmacological treatment (215-217) (LE: 3).

Neuraxial administration of opioids

The delivery of low-dose opioids near the sites of action in the spinal cord may decrease supraspinally mediated adverse effects. Compared with neuroablative therapies, spinal opioids have the advantage of preserving sensation, strength and sympathetic function (218,219). Contraindications include bleeding diathesis, profound leukopenia and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter.

The addition of a low concentration of a local anaesthetic, such as 0.125-0.25% (levo)bupivacaine, to an epidural/intrathecal opioid increases the analgesic effect without increasing toxicity (220,221). The potential morbidity of these procedures requires well-trained clinicians and long-term monitoring (LE: 2).

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<thead>
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<th>Recommendation</th>
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<tr>
<td>Continuous intrathecal or epidural administration of morphine may be considered in patients with inadequate pain relief despite escalating doses with sequential strong opioids, or the development of side effects (nausea, vomiting, constipation, drowsiness, sedation) limiting further dose increase.</td>
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3.4.6 Breakthrough cancer pain

Breakthrough cancer pain (BTCP) is a common and debilitating problem (222). It has been defined as an increase in pain intensity in patients on regularly administered analgesia. Due to their slow onset of action, oral opioids are not considered to be an efficient treatment for BTCP. Transmucosal, buccal, sublingual and intranasal fentanyl preparations have shown adequate rapid analgesia. Evidence suggests that oral transmucosal fentanyl citrate is effective for BTCP, giving more rapid relief than morphine (223).

All the studies performed have shown that these drugs should be administered to opioid-tolerant patients receiving at least 60 mg/day morphine or its equivalent (224). Proper assessment and classification of BTCP could improve care and support of patients with this syndrome (225) (LE: 1a).
3.5 Quality of life (QoL)

Patients facing advanced stages of PCa frequently experience ‘total pain’, a mix of physical, psychological, spiritual and social suffering (226). Information about the illness and the process of care has proven to reduce distress (227,228). Treatment should include both psychological and somatic symptoms (226).

Physical activities adapted to the patient’s condition are beneficial in the treatment of fatigue (229-231). Family caregivers and support groups are crucial components of the patient support system. Members of PCa self-help groups provide each other with various types of assistance, usually non-professional and non-material, for a particular shared, usually burdensome, characteristic (228). Help may involve provision and evaluation of relevant information, relating personal experiences, listening to, and accepting the experiences of others, providing sympathetic understanding, and establishing social networks. A supportive self-help group may also inform the public or engage in advocacy. All efforts should be aimed at improvement of QoL (228).
3.6 Conclusions
The goal of analgesic therapy in cancer patients is to optimise analgesia with the minimum of side effects. Current techniques can provide adequate relief for the large majority of patients. Most will need ongoing analgesic therapy, and requirements often change as the disease progresses. Patients with refractory pain should have access to specialists in pain management or palliative medicine who can provide an integrated multidisciplinary approach.

3.7 References


190. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004 Jun;6(2);57-75.


4. PAIN MANAGEMENT IN UROLOGICAL CANCERS

The prevalence of cancer pain approaches 25% for newly diagnosed cases (1) and > 75% for advanced disease (2,3). This evidence will substantiate the next update on pain management in urological cancers.

4.1 Pain management in prostate cancer patients

For a complementary approach please refer to the EAU Guidelines on Prostate Cancer (4).

4.1.1 Clinical presentation

Pain in both early and advanced PCa can be caused directly by the cancer (77%), be related to the treatment (19%), or be unrelated to either (3%) (5). Management must focus on symptomatic patients with locally advanced disease or metastases.

The overall incidence of chronic pain in PCa patients is about 30-50%, but as patients enter the terminal phase this rises to 90% (6). Pain may be directly attributable to tumour infiltration of and growth in three main areas: bone, nerve or a hollow viscus.

4.1.2 Pain due to local impairment

4.1.2.1 Invasion of soft tissue or a hollow viscus

Pain caused by invasion of a hollow viscus is treated with surgery or minimally invasive procedures (e.g., catheter, stent or nephrostomy tube).
4.1.2.2  Bladder outlet obstruction
Continuous growth of the prostate can lead to an outlet obstruction. Lower urinary tract symptoms (LUTS) can occur, especially stranguria and an inability to void. Acute pain requires prompt relief. The best method is to insert a suprapubic catheter and treat the tumour according to the stage (4). If the outlet obstruction persists, palliative transurethral resection of the prostate (TURP) is an option if no curative therapy can be offered.

4.1.2.3  Ureteric obstruction
Ureteric obstruction is most frequently caused by tumour compression or infiltration within the true pelvis (7-10). Less commonly, obstruction can be more proximal, associated with retroperitoneal metastases. In most cases, obstruction is primarily asymmetrical. Untreated progressive ureteric obstruction results in bilateral hydronephrosis and subsequent renal failure. It is good practice to drain symptomatic hydronephrosis at once, and to drain only one kidney (the less dilated and better appearing kidney or the one with the better function, if known) in asymptomatic patients. A nephrostomy tube is superior to a double-J stent for drainage because the subsequent routine endoscopic replacement of the stent could be increasingly difficult in a continuously growing prostate gland, and a nephrostomy tube can be changed without anaesthesia. Anterograde ureteral stenting through the nephrostomy site can also be attempted when the patient desires an internal diversion.

4.1.2.4  Lymphoedema
Patients with a huge prostate mass and/or lymph node metastases in the pelvis frequently get lymphoedema of the legs. Physiatric techniques such as wraps, pressure stockings and pneumatic pumps can improve function and relieve pain and heaviness.

4.1.2.5  Ileus
Local obstruction of the rectum is a common occurrence in advanced PCa, and can lead to abdominal pain caused by obstructive ileus. Rarely, peritoneal involvement can also result in ileus. Surgery and/or rectal stenting must be performed for mechanical obstruction. Paralytic ileus due to tumour infiltration of a nerve plexus or secondary to analgesics may require laxatives for opioid-induced constipation to improve motility and reduce pain.

4.1.3  Pain due to metastases
4.1.3.1  Bone metastases
• Bone metastases are the most common cause of chronic pain in patients with PCa (11,12) as a result of:
  - endosteal or periosteal nociceptor activation (mechanical distortion or release of chemical mediators);
  - tumour growth into adjacent soft tissues or nerves;
  - other complex mechanisms (12).
• Widespread bony metastases frequently cause multifocal pain. Patients with multiple bony metastases typically report pain in only a few sites.
• More than 25% of patients with bony metastases are pain free (13).
• The factors that convert a painless lesion into a painful one are unknown.

The choice of treatment will depend on the site, histology and stage of the tumour, and on the patient’s physical and emotional condition. Although tumour-cell specific therapies are being developed, most commonly used techniques damage normal tissues, with consequent side effects. The pros and cons of the therapeutic options should be considered in each case; those with fewest side effects being administered first.

The treatment options are:
• hormone therapy
• radiotherapy
• orthopaedic surgery
• radioisotopes
• bisphosphonates
• denosumab
• calcitonin
• chemotherapy
• systemic analgesic pharmacotherapy (the analgesic ladder).

Other pain management tools such as nerve blocks are rarely used.
4.1.3.2 Hormone therapy

Huggins and Hodges (14) first noted the effect of exogenous oestrogen administration on prostatic carcinoma. A variety of additive or ablative hormone manipulations have been employed, including oestrogen, anti-androgen (cyproterone, flutamide), oestrogen-mustine complex (estramustine), progestogens, aminoglutethimide, gonadotrophin-releasing hormone (GnRH) analogues, orchidectomy, adrenalectomy and hypophysectomy. Corticosteroids are also used for the palliation of pain, particularly pain due to bone deposits.

For more information on hormone therapy, refer to EAU Guidelines on Prostate Cancer (4). Hormone therapy is generally much better tolerated than chemotherapy. It can cause a temporary exacerbation of pain (pain flare), which is generally predictive of a subsequent response (15). In a collected series of protocols, pain relief has been estimated at 35% (16) to 70% (17). This difference may have been due to patient selection and problems with pain measurement. Well-differentiated prostatic carcinoma is more likely to respond to hormones than are poorly differentiated tumours. Manipulations that include replacement corticosteroid therapy or have additional corticoid effects seem to give higher response rates. Corticosteroids are also used for the palliation of pain, particularly in bone metastases.

To date, most patients with adenocarcinoma of the prostate present with early-stage tumours and undergo treatment with curative intent. In cases of disease progression and symptoms, hormone therapy is indicated, with patients remaining asymptomatic for several years.

4.1.3.3 Radiotherapy

- The role of radiotherapy in the management of pain due to bone metastases is unquestionable (18).
- Radiotherapy techniques vary widely, from a large dose given as a single treatment to as many as 20 smaller treatments given over 4 weeks.
- The biological effect of the radiation depends not only on the total dose delivered, but also on the number of separate treatments and the total time over which the irradiation therapy is administered.
- Palliative doses are smaller than maximum tolerance doses.
- It should be noted that radiological evidence of a deposit may considerably underestimate the extent of disease.

In metastatic adenocarcinoma of the prostate, radiotherapy is associated with palliation of pain from bony metastases and improved QoL. Radiation therapy is effective at treating painful sites, and might also be effective at reducing the propensity for adjuvantly treated disease to become symptomatic in most patients (19). New organ limited approaches as the stereotactic ablative radiation therapy (SABR) of vertebral metastases can result in excellent local control (20). This effect does not appear to be significantly influenced by dose-time relationships or histology. The proportion of patients achieving complete pain relief approaches (70%) (21) (Section 3.3.3).

4.1.3.4 Orthopaedic surgery

If more than 50% of the thickness of the cortex of a long bone is eroded by metastasis, prophylactic fixation rather than radiotherapy alone should be considered. Internal fixation should be followed by postoperative radiotherapy because there is a real danger of continued tumour growth and further structural weakness (22,23). Radiotherapy should not be withheld for fear of inhibiting bone healing and regrowth. There is good evidence that palliative doses of radiotherapy are associated with recalcification (24). The sequential combination of radiofrequency and cementoplasty seems promising for the treatment of painful osseous metastases (25).

4.1.3.5 Radioisotopes

Widespread axial skeletal involvement in PCa has been successfully treated with systemically administered bone-seeking radioisotopes (see also Section 3.3.2). Commonly used radionuclides are 89Sr chloride and 153Sm-EDTMP. The addition of 89Sr as a single injection of 10.8 mCi (399.6 MBq) is an effective adjuvant therapy to local field radiotherapy, reducing disease progression, the requirement for further radiotherapy and analgesic support (26), and improving QoL.

Some evidence suggests that radioisotopes could give complete relief from pain over 1-6 months, with no increase in analgesia, although adverse effects, specifically leukocytopenia and thrombocytopenia, have been reported (26). \(\alpha\)-Particle therapy represents a new concept that has been successful in prolonging survival in phase III clinical trials (27). Unlike \(\beta\)-emitting radiopharmaceuticals, \(\alpha\)-pharmaceuticals, such as 223Ra, deliver an intense and highly localised radiation dose to bone surfaces (28). 223Ra thus has potentially better efficacy and tolerability when compared with \(\beta\)-emitters.
4.1.3.6 Bisphosphonates
Bisphosphonates can be part of the supportive care for patients with bone metastases and pain (29). Improvement in pain control has been demonstrated (29). They should be considered for the treatment of refractory bone pain in metastatic PCa (30). Zoledronic acid (4 mg intravenously over 15 min every 3-4 weeks) decreased the frequency of skeleton-related events, delayed the time to the first occurrence, and reduced pain (31). Studies are needed to determine the optimal timing, schedule and duration of treatment in men with bone metastases.

4.1.3.7 Denosumab
Denosumab reduces the risk of skeletal events in men with castration-resistant bone-metastatic PCa (32).

4.1.3.8 Calcitonin
Current evidence does not support the use of calcitonin to control pain arising from bone metastases (33).

4.1.3.9 Chemotherapy
In about 80% of men with metastatic PCa, primary androgen ablation leads to symptomatic improvement. The disease eventually becomes refractory to hormone treatment. Systemic chemotherapy should be reserved for this patient group. Recent data have shown encouraging signs in overall survival, palliation of symptoms and improvements in QoL (34), particularly with docetaxel.

Trials using single-agent chemotherapy in advanced disease have shown poor results, but newer studies confirmed that multiagent chemotherapies are more effective. Other studies have confirmed the symptomatic effect of mitoxantrone plus low-dose prednisone, but none found improved survival.

A PSA-response rate and a reduction of pain were also reported with other combined chemotherapies (Table 4). Individualised therapy was necessary as side effects were common and no regimen showed a survival benefit.

A major proportion of the morbidity and mortality related to chemotherapy can be traced to the burden of bone metastases (35). Any effective hormone therapy or chemotherapy is generally suited to relieve metastatic pain, or to limit, at least. Over the last decade, several new agents for metastatic castration-resistant prostate cancer (mCRPC) targeting different mechanisms of progression have been applied successfully: docetaxel, cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate, among others (36). Docetaxel is the standard first-line chemotherapeutic agent (37).

Despite a net survival benefit, the prognosis remains poor. Second-line therapeutic options are limited. Results from recently completed trials show a statistically and clinically significant improvement in pain relief and overall survival with cabazitaxel compared with mitoxantrone. Cabazitaxel has been shown to be well tolerated and has been approved as second-line chemotherapy for mCRPC (37,38). Also, a significant reduction of tumor associated pain and a survival advantage of 4.6 months compared to placebo following docetaxel-based chemotherapy has already been shown for abiraterone (phase III study) (38) (LE: 1b)

Cabozantinib is a potent inhibitor of tyrosine kinase c-Met and vascular endothelial growth factor receptor (VEGFR2) and seems to reduce pain and opioid consumption in patients with mCRPC (39). Denosumab is a human monoclonal anti-RANKL antibody but it does not reduce pain severity in patients with mCRPC (40). Although most of these regimens are associated with side effects such as fatigue, mild myelosuppression and gastrointestinal irritation, they are generally well tolerated by most patients (41). Pain management by chemotherapy could be effective, although it is much more cost-intensive than the administration of opioids, and the survival advantage is limited.

4.1.3.10 Systemic analgesic pharmacotherapy (the analgesic ladder)
If the treatments described above provide insufficient pain relief, systemic analgesic pharmacotherapy should be administered. In most cases, the drug selection scheme proposed by the WHO, the analgesic ladder, is recommended. Short-term studies have shown that NSAIDs alone are effective in managing cancer pain, with side effects similar to those with placebo. In about 50% of studies, increasing the dose of NSAIDs increased efficacy but not the incidence of side effects.

No large clinical difference has been demonstrated between combining an NSAID with an opioid vs either medication alone (42). Tramadol extended-release tablets and dihydrocodeine extended-release tablets were effective for the management of chronic tumour pain associated with PCa with bone metastasis on step 2 of the WHO ladder, with tramadol giving slightly better pain management and fewer side effects, particularly constipation (43).
The treatment of constipation in palliative care is based on experimental evidence, and uncertainty persists about its optimum management in this group of patients (44).

Oral morphine is an effective analgesic for cancer pain, with qualitative evidence showing that it compares well with other opioids. Morphine is the gold standard for moderate to severe cancer-related pain. Alternatives such as hydromorphone are available, but no clinically significant difference has been shown compared to other strong opioids such as morphine (45).

Patients with inadequate pain control and intolerable opioid related toxicity/adverse effects may have to switch to an alternative opioid for symptomatic relief, although the evidence to support opioid switching is largely anecdotal, observational or from uncontrolled studies (46).

4.1.4 **Spinal cord compression**

Spinal cord compression can occur due to the collapse of a vertebral body or to pressure from an extradural tumour within the spinal canal. Prodromal pain is a feature in 96% of these patients. The overall incidence in PCa patients is less than 10% (47). Thoracic cord compression is the most common area (70%), and the incidence of multiple extradural sites can be as high as 18% (48).

Definitive treatment with surgery (anterior decompression with spinal stabilisation) or radiotherapy should be considered. The symptom of local back pain sometimes disappears, despite an increase in motor deficits, because of the evolving sensory component of the paraplegia.

Corticosteroids (typically dexamethasone 16 mg daily) are of only temporary use in cord oedema. There is evidence that decompressive surgery benefits ambulant patients with poor prognostic factors for radiotherapy, and non-ambulant patients with a single area of compression, paraplegia of < 48 h duration, non-radiosensitive tumours and predicted survival of > 3 months. There is a significant risk of serious adverse effects from high-dose corticosteroids (49).

4.1.5 **Hepatic invasion**

Hepatic invasion by secondary tumour is a common cause of severe hypochondrial pain, often radiating to the back and shoulder blade. The mechanism may be the stretching of nerve endings in the liver capsule, diaphragmatic irritation, or haemorrhage into a necrotic area of tumour. Liver pain can often be controlled by conventional titration of appropriate analgesics or with corticosteroids.

Whole-liver palliative radiotherapy can also be useful in carefully selected patients with refractory pain, giving far fewer side effects than the alternatives of intra-arterial chemotherapy or hepatic artery embolisation. Hepatic irradiation can improve abdominal pain with little toxicity in more than half of patients (50). Doses should not exceed 30 Gy in 15 daily fractions or its equivalent if radiation hepatitis is to be avoided.

4.1.6 **Pain due to cancer treatment**

4.1.6.1 **Acute pain associated with hormonal therapy**

*Luteinising hormone-releasing hormone (LHRH) tumour flare in PCa*

Initiation of LHRH therapy for PCa produces a transient symptom flare in 5-25% of patients (51,52), presumably caused by an initial stimulation of LH release before suppression is achieved (53,54). The syndrome typically presents as an exacerbation of bone pain or urinary retention. Spinal cord compression and sudden death have also been reported (52). Symptom flare is usually observed within the first week of therapy, and lasts 1-3 weeks. Co-administration of an androgen antagonist at the start of LHRH agonist therapy can prevent this (55).

4.1.6.2 **Chronic pain associated with hormonal therapy**

*Gynaecomastia*

Chronic gynaecomastia and breast tenderness are common complications of anti-androgen therapies for PCa, the incidence varying between drugs. Frequently associated with diethylstilboestrol (56), it is less common with flutamide and cyproterone (57-59), and uncommon in patients receiving LHRH agonist therapy (7). In elderly patients, it must be distinguished from primary breast cancer or secondary cancer in the breast (7).
4.1.7 **Recommendations at a glance (stage M1) (60-65)**

<table>
<thead>
<tr>
<th>ANTICANCER TREATMENT</th>
<th>LE</th>
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<tbody>
<tr>
<td><strong>Recommendation</strong></td>
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<tr>
<td>Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)</td>
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</tr>
<tr>
<td>Total androgen blockade: flare prevention, second-line</td>
<td>2b</td>
<td></td>
</tr>
<tr>
<td>Intermittent androgen suppression experimental</td>
<td>3</td>
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</tr>
<tr>
<td>Monotherapy with anti-androgen is an option</td>
<td>2b</td>
<td></td>
</tr>
<tr>
<td>First-line treatment controls disease for 12-18 months, second-line individualised</td>
<td>1b</td>
<td></td>
</tr>
<tr>
<td><strong>Supportive care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose glucocorticoids</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone plus prednisolone</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Estramustine + vinblastine or etoposide or paclitaxel</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PAIN MANAGEMENT</th>
<th>LE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>LE</td>
<td></td>
</tr>
<tr>
<td>Pain assessment (localisation, type, severity, overall distress)</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Pain due to painful or unstable bony metastases (single lesions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External beam irradiation</td>
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</tr>
<tr>
<td><strong>Pain due to painful bony metastases (widespread)</strong></td>
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<tr>
<td>Radioisotopes (⁹⁰Sr or ¹⁵³Sm-EDTMP)</td>
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<td>B</td>
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<tr>
<td>Pain due to painful metastases (many spots)</td>
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</tr>
<tr>
<td>Bisphosphonates</td>
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</tr>
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<td>Denosumab</td>
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<tr>
<td><strong>Systemic pain management</strong></td>
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<td></td>
</tr>
<tr>
<td>WHO analgesic ladder step 1: NSAID or paracetamol</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td><strong>Opioid administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose titration</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Access to breakthrough analgesia</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

4.2 **Pain management in transitional cell carcinoma patients**

4.2.1 **Clinical presentation**

From the perspective of pain, there are no differences between transitional cell carcinoma (TCC) and other histotypes of urothelial malignant tumour. In bladder carcinoma, pain can be present at an early stage as a burning pain (dysuria), together with irritative symptoms (urgency and frequency), or late in advanced disease due to obstruction of the upper urinary tract, or local invasion of neighbouring tissues causing pelvic or metastatic organ invasion. In upper urinary tract TCC, pain is an initial symptom in 18-30% of cases (66,67).

4.2.2 **Origin of tumour-related pain**

4.2.2.1 **Bladder TCC**

The main causes of tumour-related pain in bladder TCC are:

- obstruction of the upper urinary tract due to growth of bladder tumour close to the ureteral orifices;
- invasion of the surrounding areas by a locally advanced tumour (pelvic wall, nerve roots, other organs such as bowel, or rectum);
- bone metastases;
- soft tissue metastases (seldom painful).

4.2.2.2 **Upper urinary tract TCC**

The main causes of tumour-related pain in the upper urinary tract TCC are:

- obstruction of the upper urinary tract (presenting symptom in around 30% of cases);
- acute obstruction due to blood clots;
- invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, or liver);
- bone metastases;
- soft tissue metastases (seldom painful).
4.2.3 Pain due to local impairment

4.2.3.1 Bladder TCC
Obstruction of the ureteral orifices by tumour infiltration may lead to hydronephrosis and consecutive flank pain due to ureteral distension (visceral pain). Transurethral resection of the tumour may be effective in eliminating ureteral obstruction, but in palliative situations, hydronephrosis is mainly treated by temporary or permanent ureteral stenting or percutaneous/open nephrostomy, similar to the treatment of obstruction caused by PCa (68).

In locally advanced disease, symptoms are comparable with those caused by T4 PCa. Infiltration of the contiguous soft tissue and neighbouring organs can cause acute burning pain by infiltration of the pelvic nerves (neuropathic pain), sometimes associated with paraesthesia radiating to the lower limb, or motor deficit. If the tumour invades adjacent organs (small bowel or rectum), there can be obstruction, and visceral pain due to distension of hollow organs. Growing bladder tumour can cause complete bladder outlet obstruction, with hypogastric abdominal pain from bladder distension. Obstruction of the lymphatic vessels by lymphadenopathy can cause lymphoedema of the lower limbs with pain due to distension of muscle fascia (somatic pain) (68).

In infiltrating and advanced bladder cancer, radical or debulking cystectomy and urinary diversion have a positive impact on pain, by removing the neoplastic mass invading the surrounding tissues (EAU Guidelines on Muscle Invasive Bladder Cancer, Chapter 8.1). Extended operations, including excision of involved bowel, are sometimes indicated. Palliative surgery may be necessary in occlusive intestinal syndromes (69). In a small retrospective study of patients with tumour infiltration of the rectum by locally recurrent PCa, total exenteration resulted in significant pain reduction in all patients, and 79% were completely pain free (70). In a mixed group of cancer patients (colorectal, urinary or gynaecological) with different symptoms such as bleeding, fistula, or pelvic pain or obstruction, palliative pelvic exenteration improved QoL in 88% (71).

First-line chemotherapy strategies that are mainly based on platinum-containing regimens have some effect in 12-75% of patients with advanced disease (EAU Guidelines on Muscle Invasive Bladder Cancer Guidelines, Chapter 12). It probably relieves pain by decreasing the neoplastic mass in respondent patients (72-76) (LE: 1a), but pain control was one of the study end points in only one small study (77).

In a phase III trial, vinflunine, as new second line chemotherapy agent, proved to be very effective in disease control with 76%, but pain control was not an end point. Quality of life stayed unchanged during chemotherapy despite drug toxicity (78).

Radiotherapy can be effective in controlling pelvic pain and other symptoms such as frequency and haematuria due to local disease progression. In a large randomised study with 500 participants, two radiotherapy schedules (35 Gy in 10 fractions and 21 Gy in three fractions) were compared for symptomatic improvement of bladder-related symptoms. Sixty-eight percent of the participants achieved symptomatic improvement, 71% with 35 Gy radiotherapy and 64% with 21Gy. Acute bowel toxicity was noticed in one third of the patients. There was no significant difference between the two study arms (79) (LE 1a). Some smaller studies have shown comparable results with respect to improvement of QoL by local radiotherapy (80,81).

4.2.3.2 Upper urinary tract TCC
Transitional cell carcinoma of the upper urinary tract often presents with microscopic or gross haematuria (70-80%), but flank pain also occurs in 20-40% of patients due to obstruction or lumbar mass (EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas, Chapter 3.4). A multi-institutional study with 654 patients has shown that local symptoms do not confer worse prognosis compared to patients with incidentally detected upper urinary tract TCC (82). Locally advanced primary tumours are usually managed by radical nephroureterectomy. Extended operations including excision of involved bowel, spleen or abdominal wall muscle are sometimes indicated.

With regard to chemotherapy, the same considerations are valid for upper urinary tract TCC as for bladder TCC (compare with EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas, Chapter 3.7.2). The standard chemotherapy regimens that moderately extend survival are MVAC (methotrexate, vinblastin, adriamycin, cisplatin) and gemcitabine/cisplatin as first-line drugs, as in bladder cancer (83). In a phase II study of 151 patients with locally advanced or metastatic urothelial cancer, 45 patients (29%) with upper urinary tract carcinoma were included, and vinflunine as second-line chemotherapy demonstrated moderate activity in these patients (84).

4.2.4 Pain due to metastases
Haematogenous metastases to the bone are often found in advanced bladder or upper urinary tract TCC. No
Radiotherapy has a palliative analgesic role in bone metastases (Chapter 3.3.3) and pain reduction > 50% can be achieved in 50% of patients (85) (LE: 1b). All the data concerning radiotherapy or radionuclide therapy of bone metastases have been taken from series including different carcinomas such as prostate, breast or kidney cancer. There are no specific trials studying the effect of radiotherapy on painful bone metastases in bladder cancer. Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (21,86) (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single fraction radiotherapy (21,86) (LE: 1a).

Radioisotope treatment (Chapter 3.3.2) or hemi-body irradiation can be used in patients with multiple bone metastases (85). There are no specific studies of radioisotope therapy for bone metastasis in TCC. Orthopaedic surgery can stabilise pathological fractures, as for those from PCa (Section 3.3.3.4 Pathological fractures).

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In locally advanced bladder cancer, palliative cystectomy or exenteration might be an option for symptom relief.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Use radiotherapy to reduce pain and symptoms of locally advanced bladder cancer.</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>Use radiotherapy to reduce pain due to bone metastases.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

#### 4.2.5 Conclusion for symptomatic locally advanced or metastatic urothelial cancer

- Chemotherapy in urothelial cell carcinoma is effective in terms of disease control (LE 1b).
- There is a correlation between pain control and quality of life (LE 2a).

#### 4.3. Pain management in renal cell carcinoma patients

##### 4.3.1 Clinical presentation

Renal cell carcinoma (RCC) is not painful unless the tumour invades adjacent areas or obstructs urine outflow due to haemorrhage and blood clot formation. Some 20-30% of patients present with metastases, and 30% of patients, primarily presenting with a localised kidney tumour, develop them during follow-up. Renal cell carcinoma metastasises mainly to lung, bone, brain, liver and ipsilateral or contralateral adrenergic glands. Such patients have a maximal 2-year survival rate of 20%. Overall, 50-60% of patients may need treatment for the symptoms of metastatic disease, mainly pain.

The main origins of tumour-related pain are:

- invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, liver);
- obstruction of the upper urinary tract due to haemorrhage and subsequent formation of blood clots;
- bone metastases;
- soft tissue metastases (seldom painful).

##### 4.3.2 Pain due to local impairment

Patients with invasion of surrounding areas (e.g. the posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, liver) by a locally advanced primary tumour without metastases usually present with pain. Surgical management is the only effective option for this type of tumour.

Extended operations that include excision of involved bowel, spleen or abdominal wall muscle are sometimes indicated.

Adjuvant immunotherapy or radiotherapy is without proven benefit with regard to recurrence. Even in cases of metastatic disease, palliative nephrectomy is indicated for the control of severe symptoms such as haemorrhage, pain or paraneoplastic syndromes (GCP). The frequency with which each of these symptoms is controlled, however, is unclear and there are no data in the literature comparing efficacy of nephrectomy in palliative situations with other therapies such as angioinfarction of the tumour.

Standard pre-operative (30 Gy) or postoperative radiotherapy offers no survival benefit, and its role in delaying local progression is questionable (87).

Low dose radiotherapy of soft tissue has no proven benefit for pain or tumour control. However, there are emerging data indicating that a complete palliative response is more likely when higher biologically effective doses of irradiation are delivered, especially to patients with a relatively high performance status (88).

In metastatic disease, the EORTC Genitourinary Group study 30947 demonstrated a significant increase in
survival with palliative nephrectomy plus immunotherapy compared with immunotherapy (interferon-α) alone (median survival of 17 compared with 7 months) (89) (LE: 2b). There is no special effect on pain relief from immunotherapy.

### Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th><strong>Recommendations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>GCP</td>
<td>Obstruction of the upper urinary tract due to haemorrhage and subsequent formation of blood clots is effectively treated by radical nephrectomy in non-metastatic tumour.</td>
</tr>
<tr>
<td>GCP</td>
<td>If the patient is physically fit for surgery, this should be done to increase the QoL, e.g., palliative nephrectomy in cases of metastatic tumour.</td>
</tr>
</tbody>
</table>

**GCP = good clinical practice**

There are no data in the literature about the efficacy of other therapies such as angioinfarction of the tumour with regard to haemorrhage and pain relief in palliative situations. WHO guidelines recommend analgesic therapy and/or palliative drainage of the urinary tract if patients are not fit for major surgery.

### 4.3.3 Pain due to metastases

Patients with bone metastases have a significantly better life expectancy (30 months) than those with visceral metastases (11.6 months) (90).

Surgery is indicated for solitary bone metastases that can be resected completely, intractable bone pain, and impending or demonstrable pathological fracture. In bone metastases with extensive soft tissue involvement and severe pain, amputation of a limb is sometimes required to maintain quality of life. Surgery for bone metastases achieves a significant decrease in pain in 89-91% of patients (91-93) (LE:3). Additionally, surgery prevents pathological fractures and spinal compression, and there is a significant impact on survival.

Preoperative embolisation of bone metastases or embolisation alone achieves good pain relief in hypervascular bone metastases (94,95) (LE: 3).

High-dose radiotherapy for palliation of painful bony metastases has been shown to be effective in 50-75% of all renal cancer patients (96-98) (LE: 3), and in 67% with general bone metastases (99) (LE: 2b). There is no impact on survival. Small studies of radionuclide therapy (e.g., 89Sr) have shown good pain relief in bony metastases from RCC (100) (LE: 3). Also, some minimally invasive attempts to control bone metastases seem promising (101).

Bone metastases show poor response to immunotherapy, and there is no proven benefit in pain relief. Hormonal therapy and chemotherapy are even less effective, and have no room in pain control.

Immunotherapy alone achieved an overall response in 15-27% of patients (102). Immunotherapy in combination with chemotherapy (interleukin-2 + interferon-α + 5-fluorouracil) is the most effective therapy, achieving partial tumour response in up to 46% of patients and complete response in a maximum of 15%, although these rates are mainly for lung/lymph node metastases (103).

Pain due to soft tissue metastases probably behaves analogous to tumour response, but there are no data on immunotherapy for pain control. Hormonal therapy has no proven benefit for survival or pain relief.

New inhibitors of the VEGF/VEGFR and mammalian target of rapamycin (mTOR) pathways (sorafenib, sunitinib, temsirolimus, bevacizumab, everolimus and pazopanib) are changing the second-line therapy to advanced renal cancer. Nevertheless, it is not clear yet what the ideal therapeutic schedule could be (104).

Renal cell carcinoma tends to spread to the brain. Radiosurgery seems to be an effective treatment modality for patients with brain metastases from RCC, and early significant tumour volume reduction after radiosurgery seems to result in long-term survival in RCC patients with brain metastases (105). Further randomised trials comparing whole brain radiation therapy (WBRT) alone versus WBRT plus stereotactic radiosurgery in treating patients with radioresistant brain metastases are needed.

### 4.4 Pain management in patients with adrenal carcinoma

Adrenal carcinoma is a rare disease and has a poor prognosis. Non-functional adrenal lesions of more than 5 cm in diameter should be removed because there is a high probability of malignancy (106).

#### 4.4.1 Malignant phaeochromocytoma

Phaeochromocytomas result from phaeochromocytes, which are the predominant cells of the adrenal medulla and are also found in the paraganglia near the aorta and in lesser numbers in the ganglia of the sympathetic nervous system (107). When correctly diagnosed and treated, the disease is curable, unless there are metastases.
Computed tomography (CT) and MRI have the highest sensitivity in detecting the tumour, achieving 94-100%. A $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) scan is positive in approximately 87% of cases (108).

Chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect on metastases (109) (LE: 2b), but therapeutic doses of $^{131}$I-MIBG (33 GBq = 900 mCi) may produce some results (110,111) (LE: 2b). The hormone response rate is 50%. There are no data on pain relief with $^{131}$I-MIBG in metastatic phaeochromocytoma, but a response rate that is at least the same as for hormone levels should be expected.

Malignant phaeochromocytomas are considered radioresistant, although there are some cases in which radiation therapy induced partial remission (112) (LE: 3). There is no information about the efficacy of radiation concerning pain relief in cases of bone or soft tissue metastases.

4.4.2 Treatment of pain
• Soft tissue and/or bone pain due to metastases are best treated by therapeutic doses of $^{131}$I-MIBG, if the phaeochromocytoma takes up this radionuclide (113) (LE: 2b). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic phaeochromocytoma.
  • Treat the pain symptomatically following the recommendations made in Section 3.4.

4.4.2.1 Adrenocortical carcinomas
Carcinoma of the adrenal cortex is highly malignant, with local and haematogenous metastasis, and 5-year survival rates of 25-43% for all treatments. Patients with distant metastases have a mean survival of only 4 months (114). An autopsy study showed metastasis to lung (60%), liver (50%), lymph nodes (48%), bone (24%) and pleura/heart (10%) (115). These tumours often extend directly into adjacent structures, especially the kidney.

Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic. The tumour-response rate is 25-35% (114,116) (LE: 2a). It remains to be proven whether chemotherapy prolongs survival. Radiotherapy has not been useful except for palliation and pain management (117) (LE: 2b).

4.4.2.2 Treatment of the pain depending on its origin
• Abdominal symptoms are typical on first presentation of the tumour. The treatment is surgical removal of the primary tumour, with attempts to remove the entire lesion even if resection of adjacent structures is necessary, as well as resection of local lymph nodes.
• Soft tissue and/or bone metastases causing local symptoms can be treated by radiotherapy (113,117). There are no data on chemotherapy or radiotherapy for pain relief in metastatic adrenocortical carcinomas.
  • Treat the pain symptomatically following the recommendations given in Section 3.4.

4.5 Pain management in penile cancer patients
4.5.1 Clinical presentation
Penile cancer is rare in Europe, with an annual incidence of 0.3-1.0 new cases per 100,000 men (118). It mostly affects men between the ages of 50 and 70 years, with only 19% of cases in those aged < 40 years and 7% in those < 30 years (119). The penile lesion itself usually alerts the patient to the presence of a penile cancer but there is often a delay in seeking medical attention.

Lymph node involvement is a critical component of treatment planning and prognosis. Up to 60% of the patients at the time of presentation have palpable inguinal lymphadenopathy, and up to 85% of men will be found to have metastatic disease (120). Pain can occur in both early and advanced penile cancer. In the early stages, acute pain is expressed mainly by voiding dysfunction (infravesical obstruction) due to invasion of the corpus spongiosum. In advanced disease, pain is also caused by enlarged inguinal or pelvic node metastases and lymphoedema of the scrotum and lower limbs. Azotemia can develop secondary to nodal obstruction of the ureters. Hypercalcemia was reported in 17-21% of patients in two series (121). This was attributed to the parathyroid-hormone-like substances secreted by bulky metastases that stimulate osteoclastic bone resorption.

4.5.2 Pain due to local impairment
Soft tissue and hollow-viscus invasion
Bladder outlet and ureteric obstruction is managed in the same manner as that described in Section 4.1.2.2.
4.5.3 **Lymphoedema**

Patients with a huge inguinal tumour mass, or scarred inguinal tissue after lymph node dissection, often show lymphoedema of the lower limbs. This is more frequent in cases involving both inguin al and iliac nodes.

Lymphoedema is treated with physiatric techniques (wraps, pressure stockings or pneumatic pumps), which can both improve function, and relieve pain and heaviness. Orthotics can immobilise and support painful or weakened structures, and assistive devices can benefit patients with pain on weight-bearing or ambulation.

4.5.4 **Pain due to metastases**

Pain management begins with antitumour treatment; usually surgery that includes partial/total penectomy, and inguinal and pelvic lymphadenectomy, depending on the clinical stage of the disease. Advanced penile cancer has a poor prognosis and must be approached with a multimodal treatment regimen that includes neoadjuvant chemotherapy, radiotherapy, followed by surgical resection (122).

The chemotherapy regimen that is so far most effective and well tolerated is paclitaxel, ifosfamide and cisplatin (TIP), although large randomised trials are lacking (123). The role of radiotherapy is mainly palliative because its use after chemotherapy might decrease the pain from fixed inguinal nodes, bone metastases, spinal cord compression and paraplegia (124). Treatment of hypercalcemia consists of administration of iv saline for volume expansion, furosemide to promote diuresis and bisphosphonates to prevent osteoclastic bone resorption. When tumour erosion into femoral vessels is suspected, emergency intervention with endoluminal vascular stents or transobturator bypass graft should be undertaken (125,126).

4.5.5 **Conclusions**

Pain management related to advanced penile carcinoma should include a multimodality regimen that consists of cisplatin-based chemotherapy, radiotherapy and surgical resection. The goals of palliative care should be: alleviation of pain using systemic analgesic pharmacotherapy (WHO Ladder) if multimodality therapy is unsuccessful, wound care, treatment of hypercalcemia and tumour erosion of the large groin vessels.

4.6 **Pain management in testicular cancer patients**

4.6.1 **Clinical presentation**

Testicular cancer generally affects men in the third or fourth decade of life. It is mainly diagnosed causally as an intrascrotal mass. Approximately 20% of patients present with scrotal or inguinal pain, which disappears after orchiectomy. Only 11% of patients complain of back or flank pain at first presentation (127). Primary advanced tumour with pain due to bone metastases is very rare, maximally 3% at first presentation. It should be treated causally by primary chemotherapy and adjuvant analgesics.

4.6.2 **Pain due to local impairment**

Orchiectomy is an effective treatment for local pain due to scrotal masses.

4.6.3 **Pain due to metastases**

- Back or flank pain due to retroperitoneal lymphadenopathy slowly disappears as chemotherapy causes the mass to decrease (128) (LE: 2b). Temporary analgesia is advisable (see Section 3.4.4).
- Retroperitoneal lymph node metastases can also cause obstruction of the ureter, leading to a symptomatic hydronephrosis with back or flank pain and perhaps additional fever. The therapy of choice is the immediate treatment of the hydronephrosis by ureteral stenting or the insertion of a percutaneous nephrostomy.
- Bone pain due to bony metastases is very rare and occurs mainly in patients with primary advanced disease and relapse after chemotherapy (129,130). Treatment with chemotherapy or second-line chemotherapy may be possible (128). There is no literature on radiotherapy in cases of relapse and limitation of further chemotherapy.
- Back pain and neurological symptoms due to spinal cord compression by vertebral metastases may require urgent surgery (131) (LE: 3).
### 4.7 Recommendations at a glance

#### Table 4: Efficacy of the therapeutic options in pain relief (expert opinion)

<table>
<thead>
<tr>
<th>Origin of pain/therapeutic options</th>
<th>RCC</th>
<th>TCC</th>
<th>PCa</th>
<th>Penile cancer</th>
<th>Adrenergic cancer</th>
<th>Testicular cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>Bone metastases</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Surgery</td>
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<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
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</tr>
<tr>
<td>Radiation</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>!</td>
<td>!</td>
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</tr>
<tr>
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<td>+++</td>
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<td><strong>Nerve compression/nerve infiltration</strong></td>
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<tr>
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<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Analgesics</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

? = no conclusive data on pain control; - = no pain control; + = low pain control; ++ = moderate pain control; +++ = good pain control.

! Although studies are lacking, patients presenting with bone metastases or soft tissue metastases should not be refused for radiotherapy as an antalgic effect can be expected.

### 4.8 References


39. Basch E, Bennett A, Scher H. Cabozantinib (XL184) reduces pain symptoms in patients (pts) with castration-resistant prostate cancer (CRPC) and bone metastases: Results from a phase 2 non randomized expansion cohort. Mol Cancer Ther, 2011. 10(11).


64. National Committee on Cancer Care Workgroup on Prostate Cancer. Treatment of metastatic prostate cancer (M1). In: Ministry of Health (Singapore): Prostate Cancer 2000, National Guideline Clearinghouse (withdrawn).


5. POSTOPERATIVE PAIN MANAGEMENT

5.1 Background

Postoperative pain is inevitable in surgical patients, and is associated with tissue damage, the presence of drains and tubes, or postoperative complications, or a combination of these (1,2). Approximately 70% of surgical patients experience a certain degree (moderate, severe or extreme) of postoperative pain (3,4) (LE: 1a). This is usually underestimated and undertreated (1,4), leading to increased morbidity and mortality, mostly due to respiratory and thromboembolic complications, increased hospital stay, impaired QoL, and development of chronic pain (1,4-7) (LE: 1a).

5.2 Importance of effective postoperative pain management

The physiological consequences of postoperative pain are shown in Table 5. All of these can delay or impair postoperative recovery and increase the economic cost of surgery (longer hospitalisation) (8,9) (LE: 3). Inadequate postoperative pain control may also lead to development of chronic pain (6,10) (LE: 2b).

Table 5: Physiological consequences of postoperative pain

<table>
<thead>
<tr>
<th>Condition</th>
<th>Consequences</th>
<th>Ref.</th>
<th>LE</th>
</tr>
</thead>
</table>
| Stress response to surgery     | Tissue trauma results in release of mediators of inflammation and stress hormones  
Activation of this stress response leads to:  
- retention of water and sodium  
- increase in metabolic rate | (11) | 2a  |
| Respiratory complications      | Shallow breathing  
Cough suppression  
Lobular collapse  
Retention of pulmonary secretions  
Infections | (12) | 2b  |
| Cardiovascular complications   | Hypertension  
Tachycardia  
Increased myocardial work,  
- myocardial ischaemia  
- angina  
- infarction | (13) | 2b  |
Thromboembolic complications | Reduced mobility due to inadequate pain management can lead to thromboembolic episodes | (14) | 2a
Gastrointestinal complications | Gastric stasis, Paralytic ileus mostly after open urological operations | (15) | 2b
Musculoskeletal complications | Prolonged confinement to bed: - reduced mobility - muscle atrophy | (9) | 3
Psychological complications | Perioperative pain may provoke fear and anxiety, which can lead to: - anger - resentment - hostility to medical and nursing personnel - insomnia | (8,9) | 3

5.2.1 **Aims of effective postoperative pain management**
- To improve patient comfort and satisfaction.
- To facilitate recovery and functional ability.
- To reduce morbidity.
- To promote rapid discharge from hospital (1,2,4) (LE: 1a).

5.3 **Pre- and postoperative pain management methods**

5.3.1 **Preoperative patient preparation**
- Patient evaluation.
- Adjustment or continuation of medication to avoid abstinence syndrome.
- Premedication as part of multimodal analgesia.
- Behavioural-cognitive interventions for patients and families to alleviate anxiety and fear of postoperative pain reduce postoperative analgesic requirements and result in better pain management (1) (LE: 1a).

5.3.2 **Pain assessment**
Careful pain assessment by the surgeon or the acute pain team before and after treatment can lead to more efficient pain control, and diminished morbidity and mortality (1,3) (LE: 2a). In the post-anaesthesia care unit, pain should be evaluated, treated and re-evaluated initially every 15 min and then every 1-2 h. After discharge to the surgical ward, pain should be assessed every 4-8 h before and after treatment (16,17).

Various rating scales have been described to measure postoperative pain, but their major disadvantage is that they are all subjective, making their results difficult to evaluate, especially in patients with communication difficulties (16).

5.3.3 **Pre-emptive analgesia**
Pre-emptive or preventive analgesia is defined as the administration of analgesia before surgical incision to prevent central sensitisation from incision or inflammatory injury, to achieve optimal postoperative pain control (18). The results of clinical trials on its efficacy are controversial (18,19) (LE: 2b).

5.3.4 **Systemic analgesic techniques**

5.3.4.1 **Non-steroidal anti-inflammatory drugs**
NSAIDs act by inhibiting cyclo-oxygenase (COX) and the subsequent production of prostaglandins. The main advantages of NSAIDs are that they do not produce respiratory depression or sedation, and seem to decrease the need for opioids (20). However, their analgesic effect is not strong enough for the management of severe postoperative pain (21). For NSAID dosage and administration, see Table 12, section 5.5.
Intravenous administration of NSAIDs should start 30-60 min before the estimated end of surgery, and oral administration should start as soon as possible. Intramuscular administration of analgesic drugs for postoperative pain control is generally avoided because of variability of serum drug concentrations (22).

Their main adverse effects are (21):
- gastric irritation, ulcer formation, bleeding;
- renal impairment;
- bronchospasm, deterioration of asthma;
- platelet dysfunction, inhibition of thromboxane A2;
- perioperative bleeding;
- inhibition of bone healing and osteogenesis.

COX-2 selective inhibitors are associated with fewer gastrointestinal complications and better bone healing. In addition, they cause minimal platelet inhibition compared with non-selective COX inhibitors (23). However, COX-2 inhibitors are contraindicated for long-term use in patients with cardiovascular problems (24). The use of COX-2 inhibitors is approved only for short-term postoperative pain therapy.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs are often effective after minor or moderate surgery.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>NSAIDs often decrease the need for opioids.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Avoid long-term use of COX inhibitors in patients with atherosclerotic cardiovascular disease.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

5.3.4.2 Paracetamol
Paracetamol (acetaminophen) is a relatively safe and effective antipyretic and analgesic for mild to moderate postoperative pain. In cases of severe postoperative pain, co-administration of paracetamol with strong opioids seems to reduce the consumption of opioids (25) (LE: 2). Its exact mode of action is unclear, although it may act by centrally inhibiting COX production (26).

**Dosage and routes of administration**
- 1 g four times daily (orally, iv or rectally). Dose should be reduced to 1 g three times daily in patients with hepatic impairment.
- iv administration of paracetamol should start 30 min before the end of surgery, and oral administration as soon as possible.

**Adverse effects**
No significant adverse effects have been observed in patients receiving paracetamol for acute postoperative pain. Caution should be taken when it is administered to patients with chronic alcoholism or hepatic failure. A dose > 6 g/day can cause acute renal failure.

**Combinations of paracetamol with opioids**
Paracetamol in combination with an opioid provides adequate postoperative analgesia for mild to moderate pain without the adverse effects of strong opioids. For dosage and administration of paracetamol/opioid combinations, see Table 11, Section 5.5.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of paracetamol is recommended for postoperative pain management because it reduces consumption of opioids.</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Administer paracetamol as a single therapy to alleviate mild postoperative pain without major adverse effects.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

5.3.4.3 Metamizole (dipyrone)
Metamizole is an effective antipyretic and analgesic drug used for mild to moderate postoperative pain and renal colic. Its use is prohibited in the USA and some European countries because of single reported cases of neutropenia and agranulocytosis. Elsewhere, it is considered to be a useful analgesic and antipyretic drug for moderate pain. Long-term use of metamizole is best avoided (27,28) (LE: 2b).

**Dosage and route of administration**
The dose is 500-1000 mg qds (orally, iv or rectally).
Adverse effects
Apart from single sporadic cases of neutropenia and agranulocytosis, metamizole can cause minor side effects such as nausea, mild hypotension, and allergic reactions. Allergic reactions and the rare complication of agranulocytosis have been described only after direct iv administration, therefore, iv metamizole should be administered as a drip (1 g in 100 mL normal saline).

5.3.4.4 Opioids
Opioids are the first-line treatment for severe acute postoperative pain. Correct dose titration can minimise their unwanted effects (29). Opioid dosage and administration can be found in Tables 12 and 13, section 5.5.

5.3.4.5 Patient-controlled analgesia
Systemic administration of opioids may follow the “as needed” schedule or “around-the-clock” dosing. The most effective mode is PCA (30,31) (LE: 1a) (Table 6).

### Table 6: Typical PCA dosing schedule

<table>
<thead>
<tr>
<th>Drug (concentration)</th>
<th>Bolus size</th>
<th>Lockout interval (min)</th>
<th>Continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (1 mg/mL)</td>
<td>0.5-2.5 mg</td>
<td>5-10</td>
<td>0.01-0.03 mg/kg/h</td>
</tr>
<tr>
<td>Fentanyl (0.01 mg/mL)</td>
<td>10-20 μg</td>
<td>5-10</td>
<td>0.5-0.1 μg/kg/h</td>
</tr>
<tr>
<td>Pethidine (10 mg/mL)</td>
<td>5-25 mg</td>
<td>5-10</td>
<td>-</td>
</tr>
</tbody>
</table>

The use of intravenous patient controlled analgesia is recommended because it provides superior postoperative analgesia, improving patient satisfaction and decreasing risk of respiratory complications.

Opioids adverse effects are:
- respiratory depression, apnoea;
- sedation;
- nausea, vomiting;
- pruritus;
- constipation;
- hypotension.

5.3.4.6 Adjuncts to postoperative analgesia
Adjuncts to postoperative analgesia in low doses, such as ketamine, α2 agonists (clonidine or dexmedetomidine), or gabapentinoids (gabapentin or pregabalin), in appropriate doses and monitored care are beneficial in improving analgesic efficacy and reducing opioid-related side effects, with good safety and tolerability (32,33).

Low-dose ketamine is defined as a bolus dose < 2 mg/kg when given im or < 1 mg/kg when administered via the iv or epidural route. For continuous iv administration, low-dose ketamine is defined as a rate of ≤ 20 g/kg/min (34). Its use is contraindicated in patients with coronary disease, uncontrolled hypertension, congestive heart failure and arterial aneurysms. There are insufficient data to confirm the neurotoxicity of ketamine, even though some animal studies have shown some degree of neurodegeneration after continuous use (35) (LE: 2b).

Clonidine when given preoperatively, or epidurally postoperatively (1 μg/kg) can reduce opioid requirements (36).

More clinical evidence on dexmedetomidine is necessary to confirm its definite role in acute postoperative pain control (37).

In 17 studies up to 2007, patients received a single preoperative dose of 300-1200 mg gabapentin, 30 min-2 h before surgery in the remaining studies, the drug was administered at a dose of 1200-1800 mg/day at 1-24 h before the procedure and continued for 10 days. Gabapentin, used before as well as after surgery, decreases pain severity and the need for analgesic supplementation (38).

Perioperative pregabalin (300 mg/day) reduces opioid consumption and opioid-related adverse effects after surgery, however postoperative pain intensity is not reduced by pregabalin (39).

Single-injection caudal blocks with clonidine or ketamine are beneficial in paediatric patients (40).
Recommendations

Administer adjuncts in appropriate doses and monitored care to improve analgesic efficacy and reduce opioid-related side effects.  

Administer clonidine preoperatively or epidurally postoperatively to reduce opioid requirements.  

Gabapentin can be administered before as well as after surgery to decrease pain severity and need for analgesic supplementation.

5.3.5 Regional analgesic techniques

5.3.5.1 Local anaesthetic agents

The most commonly used local anaesthetics are:

- bupivacaine;
- I-bupivacaine;
- ropivacaine.

Bupivacaine is considered to be cardiotoxic in high doses. I-Bupivacaine and ropivacaine appear to be safer, but the degree of motor blockage they provide is not as good as that of bupivacaine. Ropivacaine has the longest duration of action.

5.3.5.2 Epidural analgesia

Epidural analgesia provides excellent postoperative pain relief for extended periods after major surgery, and reduces postoperative complications and consumption of opioids (1,2) (LE: 1a) (Table 7).

Table 7: Typical epidural dosing schemes*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single dose</th>
<th>Continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1-5 mg</td>
<td>0.1-1 mg/h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50-100 μg</td>
<td>25-100 μg/h</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10-50 μg</td>
<td>10-20 μg/h</td>
</tr>
<tr>
<td>Pethidine</td>
<td>10-30 mg</td>
<td>10-60 mg/h</td>
</tr>
<tr>
<td>Bupivacaine 0.125% or ropivacaine 0.2% + fentanyl 2 μg/mL</td>
<td>10-15 mL</td>
<td>2-6 mL/h</td>
</tr>
</tbody>
</table>

*I-bupivacaine doses are equivalent to those of bupivacaine.

5.3.5.3 Patient-controlled epidural analgesia

Patient-controlled epidural analgesia (PCEA) has become very common because it allows individualisation of dosage, decreased drug use, and greater patient satisfaction. It also seems to provide better analgesia than intravenous PCA (41,42) (LE: 1a) (Table 8).

Table 8: Typical PCEA dosing schemes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Demand dose</th>
<th>Lockout interval (min)</th>
<th>Continuous rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>100-200 μg</td>
<td>10-15</td>
<td>300-600 μg/h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10-15 μg</td>
<td>6</td>
<td>80-120 μg/h</td>
</tr>
<tr>
<td>Pethidine</td>
<td>30 mg</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Bupivacaine 0.125% + fentanyl 4 g/mL</td>
<td>2 mL</td>
<td>10</td>
<td>4 mL/h</td>
</tr>
<tr>
<td>Ropivacaine 0.2% + fentanyl 5 μg/mL</td>
<td>2 mL</td>
<td>20</td>
<td>5 mL/h</td>
</tr>
</tbody>
</table>

Recommendation on epidural analgesia

Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques (41).

5.3.5.4 Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement postoperative analgesia (43) (LE: 2a) (Table 9).
Table 9: Examples of neural blocks

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Drug/dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliohypogastric or ilioinguinal nerve infiltration after hernia repair</td>
<td>10-20 mL bupivacaine or 0.25-0.5% ropivacaine</td>
</tr>
<tr>
<td>Intercostal nerve infiltration</td>
<td>5-10 mL bupivacaine or 0.25-0.5% ropivacaine</td>
</tr>
<tr>
<td>Continuous intrapleural infusion</td>
<td>10 mL/h bupivacaine or 0.1-0.2% ropivacaine</td>
</tr>
</tbody>
</table>

5.3.5.5  **Wound infiltration**
Intraoperative wound infiltration with local anaesthetic (usually 10-20 mL ropivacaine or 0.25-0.5% bupivacaine) can provide some postoperative analgesia and may reduce the requirement for systemic analgesia (44) (LE: 2b).

5.3.5.6  **Continuous wound instillation**
Continuous postoperative wound instillation of a local anaesthetic via a multi-hole catheter placed intraoperatively by the surgeon has been shown to provide satisfactory analgesia for moderate to severe postoperative pain, reducing consumption of systemic analgesics (45-47) (LE: 2b).

5.3.6  **Multimodal analgesia**
The concept of multimodal (balanced) analgesia is that combining different doses and routes of administration of analgesics improves the effectiveness of pain relief after surgery and reduces the maximal dosage and adverse effects (48) (LE: 2b). It seems to be more effective when different drugs are administered via different routes than when different drugs are administered via a single route (1) (LE: 2b).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimodal pain management should be used whenever possible because it helps to increase efficacy while minimising adverse effects.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

5.3.7  **Special populations**

5.3.7.1  **Ambulatory surgical patients**
A multimodal analgesic plan uses a combination of NSAIDs or paracetamol plus local anaesthetics used as peripheral nerve blocks, tissue infiltration, or wound instillation so as to avoid the use of opioids, which can prolong hospital stay ([49,50], LE: 2a; [51], LE: 2b).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For postoperative pain control in outpatients, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>If possible, avoid opioids.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

5.3.7.2  **Geriatric patients**
Pain perception appears to be reduced in geriatric patients, and requirement for analgesia generally decreases with increasing age (52,53). Geriatric patients can also suffer from emotional and cognitive impairment such as depression and dementia, which could affect adequate pain management (54). Postoperative delirium in elderly patients is a common complication and is often multifactorial. It may be associated with administration of pethidine (55). Multimodal postoperative analgesia may be the pain management technique of choice in elderly patients, as the drug doses required are lower. However, it is important to be vigilant for adverse reactions, because they tend to increase in number in the geriatric population (56) (LE: 2b). Epidural analgesia might diminish the risk of postoperative delirium and respiratory complications in elderly patients (57) (LE: 2b).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimodal and epidural analgesia are preferable for postoperative pain management in elderly patients because these techniques are associated with fewer complications.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

5.3.7.3  **Obese patients**
Obese patients appear to be at higher risk for certain postoperative complications, including respiratory, cardiovascular and thromboembolic episodes, and wound infections (58,59). Administration of opioids to obese patients is associated with sudden respiratory arrest, therefore, a combination of NSAIDs or paracetamol with an epidural local anaesthetic might be the safest analgesic solution (60,61) (LE: 2b).
If absolutely necessary, opioids should be used with caution under careful titration to avoid depression of the respiratory drive (61). Oxygen therapy should also be applied postoperatively to increase oxygen saturation (62).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative use of opioids should be avoided in obese patients unless absolutely necessary.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

5.3.7.4 Drug- or alcohol-dependent patients
It has been proved that regional anaesthesia and analgesia are preferable to opioids in drug addicts. Moreover, clonidine is beneficial in those with withdrawal syndrome due to opioid or alcohol abstinence and postoperative delirium tremens (63) (LE:1a).

5.3.7.5 Other groups
Critically ill or cognitively impaired patients present special difficulties. Regional or multimodal analgesia might be more effective in such patients because drug doses are reduced and behavioural interventions and patient-controlled methods are unsuitable (LE: 3).

5.3.8 Postoperative pain management teams
The importance of efficient postoperative pain management has led to the development of acute postoperative pain management teams, which generally consist of nursing and pharmacy personnel led by an anaesthesiologist. They have been shown to improve pain relief, decrease analgesic side effects, improve patient satisfaction, and decrease overall costs and morbidity rates (64-66) (LE: 2b). Improved pain control can lead to shorter hospitalisation and fewer unscheduled readmissions after day surgery (67) (LE: 3).

5.4 Specific pain treatment after different urological operations
5.4.1 Extracorporeal shock wave lithotripsy
Extracorporeal shock wave lithotripsy (SWL) is a minimally invasive treatment, during and after which 33-59% of patients do not need any analgesia (68-70) (LE: 2b). Post-treatment pain is unlikely to be severe and oral analgesics are usually sufficient.

Analgesic plan
- Preoperative assessment (see Section 5.3.2).
- Intraoperatively: experience exists for alfentanil (0.5-1.0 mg/70 kg iv), given on demand during SWL.

NSAIDs or midazolam given 30-45 min before treatment reduces the need for opioids during the procedure (LE: 2b). With diclofenac premedication (100 mg rectally), only 18% of patients needed pethidine during lithotripsy (71). After premedication with 5 mg midazolam orally, 70% of patients were completely free of pain during treatment, and if buprenorphine was added, this proportion rose to 87% (72). After premedication with midazolam (2 mg iv, 5 min before treatment), diclofenac or tramadol was safe and effective, with fewer side effects than fentanyl (73) (LE: 1b). Other effective regimes for intraoperative pain treatment are fentanyl (1 μg/kg iv [74]), sufentanil or remifentanil. These drugs are usually given by the anaesthesiologist because of the risk of respiratory depression, which was significantly lower (20% vs 53%) after the procedure if remifentanil was used instead of sufentanil (75,76) (LE: 1b).
- Postoperative: NSAIDs, metamizole, paracetamol, codeine and paracetamol combination or tramadol can all be used on an as needed or time-contingent basis. If pain is more severe or persistent, examination is generally necessary to exclude hydronephrosis or renal haematoma.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics should be given on demand during and after SWL because not all patients need pain relief.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Premedication with NSAIDs or midazolam often decreases the need for opioids during the procedure.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>iv opioids and sedation can be used in combination during SWL; dosage is limited by respiratory depression.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Post-SWL, analgesics with a spasmolytic effect are preferable.</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

SWL = extracorporeal shock wave lithotripsy.
5.4.2 Endoscopic procedures

5.4.2.1 Transurethral procedures
Transurethral operations are usually performed under spinal anaesthesia (epidural or subarachnoid block) with the patient awake or mildly sedated, and usually with analgesia for 4-6 h after surgery. Pain is generally caused by the indwelling catheter or the double-J (ureteral stent following ureterorenoscopy), which mimics overactive bladder syndrome. Drugs with an antimuscarinic effect have been proven to be useful in addition to the opioids (77) (LE: 1b).

Analgesic plan
- Preoperative assessment: see Section 5.3.
- Intraoperative: spinal (intrathecal or epidural) anaesthesia provides intraoperative analgesia and last for 4-6 h postoperatively.
- Postoperative: after 4-6 h, mild oral analgesics such as NSAIDs or paracetamol ± codeine, or stronger opioids; also orally. In the case of bladder discomfort from the indwelling catheter, metamizole (orally or iv), pethidine (iv) or piritramide (iv) is also effective. Antimuscarinic drugs such as oxybutynin (5 mg orally three times daily) are useful and reduce the need for opioids (77) (LE: 1b).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative analgesics with spasmolytic effect or mild opioids are preferable.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Antimuscarinic drugs could be helpful in reducing discomfort resulting from the indwelling catheter.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Antimuscarinic drugs may reduce the need for opioids.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

5.4.2.2 Percutaneous endoscopic procedures
The analgesic plan is nearly the same as that for transurethral procedures. Local anaesthetic (e.g., 10 mL 0.5% bupivacaine) can be infiltrated locally into the skin incision. General anaesthesia is required for the procedure because of the uncomfortable decubitus (prone position) and the prolonged duration of the operation.

5.4.2.3 Laparoscopic procedures
These procedures are performed under general anaesthesia, therefore, patients cannot take oral medication for at least 4-6 h postoperatively, so parenteral analgesia should be used. Then, oral or systemic analgesia can be given, depending on bowel motility.

A particular problem after laparoscopic cholecystectomy is the development of shoulder pain as a result of diaphragmatic irritation following pneumoperitoneum. This seems to be dependent on the intra-abdominal pressure used during the procedure, because reduced CO2 insufflation reduces postoperative shoulder pain (78-80) (LE: 1b). The same could apply for some transabdominal urological laparoscopic interventions.

Analgesic plan
- Preoperative assessment: Section 5.3.
- Intraoperative: iv opioids ± NSAIDs, paracetamol or metamizole administered by an anaesthesiologist. The infiltration of local anaesthetic into the port incisions reduces pain after laparoscopy (81).
- Postoperative: administration of systemic opioids iv (im or sc), is very effective in the immediate postoperative period. NSAIDs (e.g., paracetamol and/or metamizole) and incisional local anaesthetics (multimodal concept) can be given to reduce the need for opioids (81,82).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intra-abdominal pressure and good desufflation at the end of the procedure reduces postoperative pain.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>NSAIDs are often sufficient for postoperative pain control.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>NSAIDs decrease the need for opioids.</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

5.4.3 Open surgery
5.4.3.1 Minor operations of the scrotum/penis and the inguinal approach
These two types of operations are relatively minor and nearly all patients can take oral analgesics afterwards. The operation is often performed as an ambulatory procedure under local anaesthesia, or with the aid of an ilioinguinal or iliohypogastric nerve block.
Recommendations  | LE  | GR  
---|---|---
For postoperative pain control, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used. | 3 | B 
If possible, avoid opioids for outpatients. | 3 | C 

5.4.3.2  Transvaginal surgery
General, local or regional anaesthesia can be used for these operations.

Recommendations  | LE  | GR  
---|---|---
NSAIDs are often sufficiently effective after minor or moderate surgery. | 2A | B 
NSAIDs decrease the need for opioids. | 1b | B 

5.4.3.3  Perineal open surgery
Analgesic plan
- Preoperative assessment: Section 5.3.
- Intraoperative: general anaesthesia is usually used, particularly for perineal radical prostatectomy, because of the uncomfortable exaggerated lithotomy position. Sometimes an intrathecal catheter (epidural) can be sited for intra- and postoperative pain control.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic or PCA is usually used. When systemic opioids are required, it is advisable to use them in combination with NSAIDs so as to reduce their dose and side effects. When the patient is able to take oral analgesics, metamizole or paracetamol ± codeine can be used.

5.4.3.4  Transperitoneal laparotomy
Analgesic plan
- Preoperative assessment: see Section 5.3.
- Intraoperative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be sited.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics (depending on bowel motility) metamizole, paracetamol ± codeine or tramadol can be used. Multimodal concepts (combining NSAIDs with opioids, fast-track strategies, keeping abdominal and urinary drainage as short as possible) are useful in reducing the need for analgesia (48).

Recommendations  | LE  | GR  
---|---|---
The most effective method for systemic administration of opioids is PCA (see Section 5.3.4.5), which improves patient satisfaction and decreases the risk of respiratory complications. | 1b | A 
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3). | 1b | A 

PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia.

5.4.3.5  Suprapubic/retropubic extraperitoneal laparotomy
Postoperatively, it is possible to use the oral route for analgesia earlier than after a transperitoneal procedure. Oral opioids, metamizole and/or paracetamol ± NSAIDs can be used.

Analgesic plan
- Preoperative assessment: see Section 5.3.
- Intraoperative: general anaesthetic and regional technique.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics metamizole, paracetamol ± codeine, ± NSAIDs can be used.

5.4.3.6  Retroperitoneal approach - flank incision - thoracoabdominal approach
Analgesic plan
- Preoperative assessment: see Section 5.3.
- Intraoperative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be inserted.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic gives significantly better pain control compared with iv analgesics (83,84). If epidural analgesia is
not possible or refused, PCA should be provided. Once the patient is able to take oral analgesics (depending on bowel motility) paracetamol ± codeine or metamizole can be associated (to reduce the need for opioids) or used alone.

**Recommendation**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction and is therefore preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3).</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

*PCEA = patient-controlled epidural analgesia.*

## 5.5 Dosage and method of delivery of some important analgesics

### 5.5.1 NSAIDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional NSAIDs</strong>&lt;br&gt;(non-selective COX inhibitors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>10-30 mg four times daily</td>
<td>Orally or iv</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg three times daily</td>
<td>Orally</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>50 mg four times daily</td>
<td>Orally or iv</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>75 mg twice daily</td>
<td>Orally or iv</td>
</tr>
<tr>
<td></td>
<td>50 mg three times daily</td>
<td>Orally or iv</td>
</tr>
<tr>
<td></td>
<td>100 mg twice daily</td>
<td>Rectally</td>
</tr>
<tr>
<td><strong>COX-2 selective inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>15 mg once per day</td>
<td>Orally</td>
</tr>
<tr>
<td>Lornoxicam</td>
<td>4-8 mg twice daily</td>
<td>Orally or iv</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>200 mg once per day</td>
<td>Orally</td>
</tr>
<tr>
<td>Parecoxib</td>
<td>40 mg once or twice daily</td>
<td>iv form only</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>90-120 mg once daily</td>
<td>Orally</td>
</tr>
</tbody>
</table>

### 5.5.2 Opioids

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>Method of administration</th>
<th>Single dose (mg)</th>
<th>Maximal dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Orally</td>
<td>500-1000</td>
<td>4000 (50 mg/kg)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>iv</td>
<td>1000</td>
<td>4000 (50 mg/kg)</td>
</tr>
<tr>
<td>Metamizole</td>
<td>Orally</td>
<td>500-1000</td>
<td>4000</td>
</tr>
<tr>
<td>Metamizole</td>
<td>iv</td>
<td>1000-2500</td>
<td>5000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>Opioid</th>
<th>Times per day</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol 1 g</td>
<td>Codeine 60 mg</td>
<td>Four</td>
<td>Orally or rectally</td>
</tr>
<tr>
<td>Paracetamol 600-650 mg</td>
<td>Codeine 60 mg</td>
<td>Four</td>
<td>Orally or rectally</td>
</tr>
<tr>
<td>Paracetamol 500 mg</td>
<td>Codeine 30 mg</td>
<td>Four</td>
<td>Orally or rectally</td>
</tr>
<tr>
<td>Paracetamol 300 mg</td>
<td>Codeine 30 mg</td>
<td>Four</td>
<td>Orally or rectally</td>
</tr>
<tr>
<td>Paracetamol 650 mg</td>
<td>Dextropropoxyphene 65 mg</td>
<td>Four</td>
<td>Orally</td>
</tr>
<tr>
<td>Paracetamol 600-650 mg</td>
<td>Tramadol 75-100 mg</td>
<td>Four</td>
<td>Orally</td>
</tr>
<tr>
<td>Paracetamol 325 mg</td>
<td>Oxycodone 5 mg</td>
<td>Four</td>
<td>Orally</td>
</tr>
</tbody>
</table>
Table 12: Dose and delivery of opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Method of administration</th>
<th>Common single dose (mg)</th>
<th>Maximal dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>Orally</td>
<td>50</td>
<td>400-600</td>
</tr>
<tr>
<td>Tramadol</td>
<td>iv</td>
<td>50-100</td>
<td>400-600</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Orally</td>
<td>60-120</td>
<td>240</td>
</tr>
<tr>
<td>Piralamid</td>
<td>sc/im</td>
<td>15-30</td>
<td>120</td>
</tr>
<tr>
<td>Pethidine</td>
<td>Orally</td>
<td>25-150</td>
<td>500</td>
</tr>
<tr>
<td>Pethidine</td>
<td>Rectally</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>Pethidine</td>
<td>sc/im</td>
<td>25-150</td>
<td>500</td>
</tr>
<tr>
<td>Pethidine</td>
<td>iv</td>
<td>25-100</td>
<td>500</td>
</tr>
<tr>
<td>Morphine*</td>
<td>Orally</td>
<td>Starting with 10</td>
<td>No maximal dose</td>
</tr>
<tr>
<td>Morphine*</td>
<td>Rectally</td>
<td>Starting with 10</td>
<td>No maximal dose</td>
</tr>
<tr>
<td>Morphine*</td>
<td>sc/im</td>
<td>Starting with 5</td>
<td>No maximal dose</td>
</tr>
<tr>
<td>Morphine*</td>
<td>iv</td>
<td>Starting with 2</td>
<td>No maximal dose</td>
</tr>
<tr>
<td>Morphine*</td>
<td>iv (PCA)</td>
<td>0.5-2.5 mg bolus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-15 min lockout</td>
<td></td>
</tr>
</tbody>
</table>

*Strong opioids have no real upper dose limit (except buprenorphine). The dose must be titrated in correlation with pain relief and depending on the individual strength of unwanted effects such as respiratory depression (Section 5.3.4.4).

*A simple way of calculating the daily dose of morphine for adults (20-75 years) is: 100 - patient’s age = morphine per day in mg.

Table 13: Common equi-analgesic doses for parenteral and oral administration of opioids*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral (mg)</th>
<th>Oral (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>-</td>
</tr>
<tr>
<td>Pethidine</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15</td>
<td>20-30</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Tramadol</td>
<td>37.5</td>
<td>150</td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
</tr>
</tbody>
</table>

*All listed opioid doses are equivalent to parenteral morphine 10 mg. The intrathecal opioid dose is 1/100, and the epidural dose 1/10 of the dose required systemically.

5.6 Perioperative pain management in children

5.6.1 Perioperative problems

The main preoperative problems in children are fear of surgery, anxiety about separation from their parents, and the pain of procedures such as venipuncture. Contrary to the popular belief, the presence of parents during anaesthesia induction does not alleviate children’s anxiety (85) (LE: 1a). The preoperative use of oral morphine sulphate, 0.1 mg/kg, can help to prevent crying in children and thereby reduce oxygen consumption and pulmonary vasoconstriction (Table 16). The prior application of EMLA (2.5% lidocaine and 2.5% prilocaine) cream helps to reduce the pain of venipuncture (86) (LE: 1a). Atropine, 0.01-0.02 mg/kg iv, im, orally or rectally, prevents bradycardia during anaesthesia induction.

Table 14: Premedication drugs in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Route of administration</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>6 mg/kg</td>
<td>Oral, intranasal, im</td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.5 mg/kg</td>
<td>Oral, intranasal, rectally</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>Dexametomidine</td>
<td>4 μg/kg</td>
<td>Oral, intranasal</td>
<td>α2-receptor agonist</td>
</tr>
<tr>
<td>Clonidine</td>
<td>4 μg/kg</td>
<td>Oral</td>
<td>α2-receptor agonist</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>4-6 mg/kg</td>
<td>im</td>
<td>Barbiturate</td>
</tr>
<tr>
<td>Chlora hydrate</td>
<td>50-100 mg/kg</td>
<td>Oral</td>
<td>Barbiturate</td>
</tr>
<tr>
<td>Methohexital</td>
<td>25-30 mg/kg</td>
<td>Rectally</td>
<td>Barbiturate</td>
</tr>
</tbody>
</table>
5.6.2 **Postoperative analgesia**

Postoperatively, paracetamol, NSAIDs, opioids and their combinations are used according to the severity of the surgical procedure (Table 15).

Table 15: Dosage of analgesics in children for postoperative analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Severity of surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>10-15 mg/kg every 4 h</td>
<td>Oral, rectally</td>
<td>Minor</td>
</tr>
<tr>
<td></td>
<td>20-30 mg/kg every 6 h</td>
<td></td>
<td>Minor</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>10-15 mg/kg every 6 h</td>
<td>Oral, iv, rectally</td>
<td>Minor, medium</td>
</tr>
<tr>
<td>Naproxen</td>
<td>6-8 mg/kg every 8-12 h</td>
<td>Oral, iv, rectally</td>
<td>Minor, medium</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.5-1 mg/kg every 3-4 h</td>
<td>Oral</td>
<td>Minor, medium</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1 mg/kg every 2-4 h Infusion: 0.03 mg/kg/h 0.3 mg/kg every 3-4 h</td>
<td>Oral, iv, sc</td>
<td>Medium, major</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>0.1-0.2 mg/kg every 3-4 h</td>
<td>Oral</td>
<td>Medium</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.04-0.08 mg/kg every 3-4 h</td>
<td>Oral</td>
<td>Medium</td>
</tr>
<tr>
<td>Tramadol</td>
<td>1 mg/kg every 4-6 h</td>
<td>iv</td>
<td>Medium, major</td>
</tr>
<tr>
<td>Pethidine</td>
<td>2-3 mg/kg every 3-4 h</td>
<td>iv</td>
<td>Medium, major</td>
</tr>
</tbody>
</table>

The postoperative use of COX-2 inhibitors in children is still controversial. PCA can be used safely in children older than 6 years. Nurse-controlled analgesia is effective in infants and children unable to use PCA (87).

Locoregional techniques such as wound infiltration, nerve blocks, and caudal and epidural analgesia are also successful (88,89). The most commonly drugs used are bupivacaine and ropivacaine (Table 16). Higher volumes of lower drug concentrations appear to be more effective than lower volumes of higher concentrations (90) (LE: 1a). The addition of opioids, ketamine or clonidine increases the duration of pain relief and reduces the need for rescue analgesia, thus providing more effective pain relief than local anaesthesia alone in caudal analgesia (91-93) (LE: 1a).

Table 16: Epidural dose of local anaesthesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bolus 0-12 months</th>
<th>Bolus &gt; 1 year</th>
<th>Infusion for 0-12 months</th>
<th>Infusion &gt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>2 mg/kg</td>
<td>2.5 mg/kg</td>
<td>0.2 mg/kg/h</td>
<td>0.4 mg/kg/h</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>2.5 mg/kg</td>
<td>3.5 mg/kg</td>
<td>0.3 mg/kg/h</td>
<td>0.6 mg/kg/h</td>
</tr>
</tbody>
</table>
5.7 References


6. **NON-TRAUMATIC ACUTE FLANK PAIN**

6.1 **Background**
Acute flank pain is a frequently occurring and complex medical problem. Ureterolithiasis is the most common non-traumatic cause. However, half of all renal colics are not caused by urolithiasis (1-3) (Table 17).

<table>
<thead>
<tr>
<th>Urological causes</th>
<th>Non-urological causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal or ureteral stones</td>
<td>Aortic aneurysm</td>
</tr>
<tr>
<td>Urinary tract infection (pyelonephritis, pyonephrosis, renal abscess)</td>
<td>Gallbladder disorder</td>
</tr>
<tr>
<td>Uretero-pelvic junction obstruction</td>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Renal vascular disorders (renal infarction, renal vein thrombosis)</td>
<td>Pancreatic disease</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td>Gynaecological disorders</td>
</tr>
<tr>
<td>Intra- or peri-renal bleeding</td>
<td>Musculoskeletal disease</td>
</tr>
<tr>
<td>Testicular cord torsion</td>
<td></td>
</tr>
</tbody>
</table>

6.2 **Initial diagnostic approach**

6.2.1 **Symptomatology**
History and physical examination, including body temperature, can be very helpful in the differential diagnosis.
of acute flank pain (4).

- Acute renal colic is indicated by pain of short duration (< 12 h), nausea, vomiting, loin tenderness and haematuria (erythrocytes > 10,000/mm³) (4).
- Because the signs and symptoms can be very similar, acute uncomplicated pyelonephritis should be immediately differentiated from complicated renal colic:
  - Concomitant fever (> 38°C) makes imaging obligatory (5). A radiological evaluation of the upper urinary tract should be offered to every patient presenting with flank pain and fever to rule out urinary tract obstruction irrespective of the accompanying symptoms, duration of the episode and urine macroscopic or microscopic findings.
  - Imaging is also imperative in patients with acute flank pain and a solitary kidney (5) (LE: 4).
- Acute flank pain in patients with an increased risk for thromboembolic events should raise the suspicion of renal infarction (6).
- Careful abdominal examination can reveal an abdominal aortic aneurysm (misdiagnosed in 30% of patients).
- Renal vein thrombosis (RVT) may often present with symptoms of acute flank pain, proteinuria, haematuria, hypotension and renal insufficiency.
- Obstruction of the ureteropelvic junction can result in acute flank or abdominal pain after a high fluid volume intake, especially in paediatric patients.
- Renal papillary necrosis is not uncommon in the course of systemic diseases such as diabetes mellitus or analgesic nephropathy; the passage of sloughed papillae down the ureter may cause flank pain and haematuria.
- Testicular torsion should always be excluded in children with acute abdominal/flank pain.
- Torsion of the appendix testis can also result in abdominal pain or radiate to the flank.
- Spontaneous bleeding either within the kidney or to the retroperitoneum can be caused by kidney tumours (including angiomyolipomas), bleeding disorders or anticoagulation; acute flank pain is sometimes the presenting symptom.

### Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile patients (&gt; 38°C) with acute flank pain and/or with a solitary kidney need urgent imaging.</td>
<td>4</td>
<td>B*</td>
</tr>
</tbody>
</table>

*Recommendation based on expert opinion.

### 6.2.2 Laboratory evaluation

All patients with acute flank pain require a urine test (red and white cells, bacteria or urine nitrite), blood cell count, and serum creatinine measurement. In addition, febrile patients with flank pain require C-reactive protein and urine culture. Pyelonephritis ± obstructive uropathy should be suspected when the white blood count exceeds 15,000/mm³.

### 6.2.3 Diagnostic imaging

#### 6.2.3.1 Ultrasonography

Unenhanced helical computed tomography has high sensitivity and specificity for the evaluation of acute flank pain (7,8) (LE: 1a). Unenhanced helical computed tomography (UHCT) is superior because it detects ureteral stones with a sensitivity and specificity of 94-100%, regardless of stone size, location and chemical composition, and identifies extraurinary causes of flank pain in about one-third of all patients presenting with it. In addition, it does not need contrast agent, and is a time-saving technique (8,9) (LE: 1a).

#### 6.2.3.2 Intravenous urography

The use of US in the management of acute flank pain has been increasing. If the findings of pelvic and/or ureteral dilatation, stone visualisation and the absence of ureteral ejaculation are combined, sensitivity to ureteral dilatation can be 96% (7,10,11) (LE: 2a). Together with a plain abdominal radiograph, US can be accepted when computed tomography (CT) is not available (7,12-16) (LE: 1b).The disadvantages of US include inability to differentiate dilatation from true obstruction and the need for highly specialised personnel (12). Sensitivity varies from 58 to 96% in untrained staff in emergency rooms (14), but evidence suggests that, with even short training, non-specialists can be highly effective at excluding disorders such as abdominal aortic aneurysm, free abdominal fluids, gallstones and obstructive uropathy (14) (LE: 2b). US is the diagnostic imaging modality of choice during pregnancy.

#### 6.2.3.3 Unenhanced helical CT

Intravenous urography (IVU) reliably provides information on the anatomy of the urinary collecting system (ureteral and renal pelvic dilatation) in 80-90% of cases and can identify ureteral calculi in 40-60% of cases.
Direct identification of ureteral calculi can be achieved in 40-60% of cases, whereas indirect signs (e.g. ureteral and renal pelvic dilatation) allow detection in 80-90% of cases. Drawback is that IVU results can be hampered by poor quality related to suboptimal bowel preparation, toxicity of contrast agents, allergic and anaphylactic reactions, and by significant radiation exposure. In emergency cases, IVU should be avoided due to the risk of fornix rupture.

Unenhanced helical CT or IVU should be considered in patients initially evaluated by other means who are still febrile after 72 h of treatment to rule out further complicating factors (renal, perinephric or prostatic abscesses) (8,9).

Table 18 shows comparative results of UHCT US and IVU in assessing acute flank pain and suspicion of ureterolithiasis (17-19). Figure 4 summarises the diagnostic approach to non-traumatic acute flank pain.
Figure 4: Diagnostic approach to non-traumatic acute flank pain

Acute flank pain

History, physical examination, temperature, urinalysis → pain treatment

If not conclusive

Ultrasonography and/or unenhanced CT scan

Normal + normal urinalysis

Non-urological flank pain

Refer patient

Normal + abnormal urinalysis (leucocyturia, haematuria or bacteriuria)

Further investigation and appropriate treatment

Genitourinary abnormality

Non-genitourinary abnormality

Refer patient

Abnormal

Normal + abnormal urinalysis

Refer patient

Hydronephrosis

No hydronephrosis

No stone

Check for:
- renal infarct
- renal abscess
- renal vein thrombosis
- tumour
- cyst
- haematoma
- urinoma
- extrarenal mass

Stone

Treat infection

No UTI

Stone management

UTI

Ureteral obstruction

Check for:
- ureteral tumour
- papillary necrosis
- upj obstruction
- retroperitoneal fibrosis

Management to relieve pain or obstruction

No UTI

Stone management

UTI

Urinary drainage and infection treatment

CT = computed tomography; UTI = urinary tract infection.
Unenhanced helical computed tomography is the diagnostic imaging modality with the highest sensitivity and specificity for evaluation of non-traumatic acute flank pain.

Ultrasound can be an alternative to unenhanced helical computed tomography in the initial approach to non-traumatic acute flank pain.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Performance</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHCT</td>
<td>Sensitivity 100%, specificity 96%, accuracy 98%</td>
<td>17</td>
</tr>
<tr>
<td>Abdominal radiograph + US versus UHCT</td>
<td>UHCT: sensitivity and specificity of 100% US: sensitivity 100%, specificity 90%</td>
<td>18</td>
</tr>
<tr>
<td>Low-dose UHCT versus IVU</td>
<td>UHCT: sensitivity 97%, specificity 96% Low-dose UHCT is superior to IVU</td>
<td>19</td>
</tr>
</tbody>
</table>

6.3 Initial emergency treatment

6.3.1 Systemic analgesia

Pain relief is usually the first, most urgent, therapeutic step (20, 21):

- Intravenous NSAIDs are very effective in most cases, e.g., a bolus of diclofenac sodium, 75 mg (20) (LE: 1a); a slow iv injection of ketorolac, 30 mg, four times daily, is equivalent to diclofenac in the treatment of renal colic (22).
- Tests have shown a single dose of dipyridamol to be less effective than diclofenac, 75 mg (23) (LE: 1a), but a slow iv infusion of dipyridamol, 1 or 2 g, is just as effective as dicyclofenac (24).
- In cases of unresponsiveness to diclofenac (25) (LE: 1b), or contraindication of NSAIDs (24) (LE: 1b), iv papaverine hydrochloride (120 mg) is a safe and effective alternative.
- Large-scale studies have shown that NSAIDs and opioids are both effective analgesics, but vomiting is more prevalent with opioids (particularly pethidine) (20).
- The combination of iv morphine + ketorolac seems superior to either drug alone, and appears to be associated with a decrease in the need for rescue doses of analgesia (26).
- Antimuscarinics are often used in acute renal colic; there is no evidence that hyoscine butylbromide reduces opioid requirements in this condition (26) (LE: 1b).

The origin of the pain should be immediately clarified in febrile patients and those with a solitary kidney.

6.3.2 Local analgesia

A number of manipulations have been tested in the field of acute renal colic.

- Local warming of the abdomen and lower back region seems to decrease pain in patients with acute renal colic (27) (LE: 1a).
- Trigger-point injection of lidocaine can provide effective pain relief in 50% of patients with renal colic; it is significantly better than iv butylscopolamine bromide + sulpyrine (28) (LE: 1a). There are no comparative studies with NSAIDs.

6.3.3 Supportive therapy

Patients with acute flank pain often present with moderate to severe dehydration. Fever, vomiting and anorexia produce serious discomfort and should be treated from the outset. If possible, iv fluids should be generous (60 mL/h normal saline and 60 mL/h 5% glucose solution), but maintenance iv fluids (20 mL/h normal saline) can be as effective as forced hydration with regard to pain perception and analgesic use (29) (LE: 1b). No clear evidence supports using diuretics to treat acute ureteral colic (30). Metoclopramide chloride (0.5 mg/kg/24 h in three divided doses) can be effective in controlling nausea and vomiting irrespective of aetiology (infectious, obstructive, oncological).
6.3.4 **Upper urinary tract decompression**

If pain relief cannot be achieved using medical therapy and there are signs of infection and impaired renal function, upper urinary tract drainage should be undertaken. The main indications for stenting for urgent relief of obstruction include (31):

- urine infection with urinary tract obstruction;
- urosepsis;
- intractable pain and/or vomiting;
- obstruction of a solitary or transplanted kidney;
- bilateral obstructing stones;
- ureteral calculus obstruction in pregnancy.

Catheter-derived symptoms such as flank pain, pain during voiding, frequency, nocturia and urgency can be effectively treated with terazosin and tamsulosin (32-34).

New technological advances such as the antireflux JJ ureteral stents seem to minimise catheter-related pain (35,36) (LE: 1b).

6.4 **Aetiological treatment**

6.4.1 **Urolithiasis**

Treatment of urolithiasis is discussed in the EAU Guidelines on Urolithiasis (37).

6.4.2 **Infectious conditions**

Infectious uncomplicated conditions (i.e. acute pyelonephritis in otherwise healthy individuals) should be treated with appropriate antibiotics and analgesics according to the EAU Guidelines on Urological Infections (38).

The first-line treatment of mild cases should be an oral fluoroquinolone (twice daily for 7 days) in areas with low rates of fluoroquinolone-resistant Escherichia coli. In areas with raised resistance rates, or in pregnancy, lactation or adolescence, a second- or third-generation oral cephalosporin is recommended. Pain can usually be controlled with oral NSAIDs (diclofenac 75 mg, three times daily, or dipyrone 500 mg three times daily) except in pregnant or lactating women.

6.4.3 **Other conditions**

6.4.3.1 **Ureteropelvic junction obstruction**

Ureteropelvic junction obstruction can result in intermittent flank or abdominal pain. Symptoms may worsen during brisk diuresis (after consumption of caffeine or alcohol). Dismembered or non-dismembered pyeloplasty is standard. A ureteral stent can help to relieve pain in very symptomatic patients prior to definitive surgery. Outcomes are excellent, with resolution of the obstruction in 90-95% of cases, including newborns (39).

6.4.3.2 **Papillary necrosis**

Papillary necrosis commonly presents as painless macroscopic haematuria, but can be complicated by ureteral obstruction. As well as symptomatic treatment, treatment should be given for the underlying cause of papillary necrosis, such as interstitial nephritis, acute pyelonephritis, diabetes mellitus, analgesic abuse or sickle cell disease. Ureteral obstruction due to sloughed papillae can be successfully treated with ureteroscopy or temporary ureteral stenting (40).

6.4.3.3 **Renal infarction**

There is no specific treatment for acute renal infarction, but the underlying disease (atrial fibrillation, left ventricular thrombus or a hypercoagulable state) may require anticoagulation with iv heparin followed by warfarin to prevent future events (41).

6.4.3.4 **Renal vein thrombosis**

Renal vein thrombosis is often clinically silent, but can present with acute flank pain. Systemic anticoagulation with heparin to prevent further propagation of thrombus or other thromboembolic phenomena (42) is standard, but the successful use of fibrinolytic agents in selected patients without clinical contraindications has been reported (43). Thrombectomy or nephrectomy is reserved for cases refractory to medical therapy.

6.4.3.5 **Intra- or perirenal bleeding**

Acute spontaneous intra- or perirenal bleeding often results in acute flank pain. Spontaneous renal haemorrhage (Wunderlich’s syndrome), is an unusual and life-threatening cause of acute abdomen. Nephrectomy is usually the only therapeutic alternative (44,45).
6.4.3.6 Testicular cord torsion

Testicular cord torsion can produce lower abdomen and flank pain; it should be treated surgically at once.

6.5 References


7. PALLIATIVE CARE

7.1 Background

The inevitable progression of certain diseases frequently results in unbearable suffering. When cure is no longer possible, palliation and compassion are mandatory. In the following section the reader will find a straightforward approach to the treatment of many psychological and physical symptoms. Unfortunately, the level of evidence for the proposed interventions is poor. Nevertheless, a well-structured map should be applied to provide the most effective and compassionate care for patients and their loved ones. Also, healthcare providers deserve particular care because the extent of professional anxiety and frustration can be significant in this clinical scenario.

7.2 Definition and aim of palliative care

According to the WHO definition (1), palliative care is “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.” The goal of palliative care is to obtain the highest QoL for patients and their loved ones.

Palliative care:

• provides relief from pain and other distressing symptoms;
• affirms life and regards dying as a normal process;
• intends neither to hasten nor postpone death;
• integrates the psychological and spiritual aspects of patient care;
• offers a support system to help patients live as actively as possible until death;
• offers a support system to help the family cope during the patient’s illness and in their own bereavement;
• uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
• enhances QoL, and may also positively influence the course of illness;
• is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiotherapy, and includes investigations needed to understand and manage better distressing clinical complications (1).

The readiness of patients to accept palliative care and a vision of palliative care shared by the patient and all caregivers involved are potentially important elements in this definition (2).

7.3 General principles
The panel assumes that the ethics of disease palliation are beyond doubt. Hence, a discussion on ethical principles is omitted from this document. Legislation on palliative and end-of-life care across Europe is variable. This panel considered it pointless to address that particular topic in depth. The panel also decided not to address physician-assisted suicide. Details about this and euthanasia can be found elsewhere (3,4). The current document focuses on interventions that can be applied in institutions. Home palliation is not addressed because few patients require this type of care are in the urological setting.

Palliation involves:
• communication;
• placing the patient at the centre of treatment;
• cultural and spiritual approaches;
• multidisciplinary approach.

7.3.1 Communication
Communication is one of the cornerstones in palliative care. Good communication skills are relevant not only in the relationship between caregivers and patient and families, but also with all professionals inside and outside the hospital. Specific communication skills allow a better assessment of patients’ needs and improve patient wellbeing and adherence to treatment. Communication skills include making eye contact with the patients, asking open-ended questions, responding to a patient’s emotions, and showing empathy (5). Figure 5 illustrates the principles for communicating with patients about major topics in palliative care.
Communication skills are important at every stage of the disease. Terminal patients deserve specific information about their condition. This kind of information increases the quality of terminal care (6,7). Several guidelines have been established to help physicians and nurses improve their communication skills (5,8).

Moreover, it seems important to tailor information to the needs of the individual patient. Difficult discussions should be personalised to the individual patient. These can vary dramatically both in the area of disclosure of bad news about prognosis and end-of-life decision making. This also requires proper advanced care planning at an early stage in the management of patients with terminal cancer (9).

Communication is also part of the relationship between partners, when one member of the couple has a chronic illness such as cancer. When communication between the couple fails, it is more difficult to address the patient’s needs. The Couples’ Illness Communication Scale (CICS) is a simple tool for the clinical setting and can provide a springboard for addressing difficulties with illness-related communication between couples. It can be an aid for decision making in couple counselling. Relationship intimacy and how patients and partners communicate to achieve this intimacy is important for the psychological adjustment of early-stage PCa survivors and their partners (10,11).

Many initiatives provide patient guidance and education, from assessment to diagnosis and treatment planning. For example, at the Prostate Cancer Assessment Clinic, Ottawa Hospital, Canada, a nurse-led initiative has shown that effective communication between physicians, nurses, patients and families, and the interdisciplinary team and community partners is the key to improving the experience of PCa patients (12).

Adapted from the Education on Palliative and End-of-life Care Project.
7.3.2 **Patient-centred treatment**

Patient-centred treatment is another aspect of palliative care. There is evidence about the benefit of involving the patient in making any decisions. The patient must be at the heart of every decision and be provided with greater choice and control (13).

7.3.3 **Cultural and spiritual approach**

The profound influence of personal circumstances on patients’ experiences of illness, expectations of medical interventions, communication styles, and ways of coping should be considered, because it can lead to misunderstanding, conflict, anger, resentment, and lower quality of care (14).

Spirituality is also an important aspect that should be taken into account. Cancer patients do not expect spiritual solutions from oncology team members, but they wish to feel comfortable enough to raise spiritual issues and not be met with fear, judgmental attitudes, or dismissive comments. Spirituality can be a major resource for both patients and physicians, yet it can never be imposed but only shared (15).

In addition, it may be of interest to assess spiritual outcomes in palliative care. Nine tools have been identified in a review that has been validated in cross-cultural palliative care populations, and subject to appraisal of their psychometric properties, they may be suitable for cross-cultural research (16).

7.3.4 **Multidisciplinary approach**

One of the main principles of palliative care is a multidisciplinary approach. All professions are concerned and the treatment decision (either palliation or terminal disease management) should be taken on a multidisciplinary basis (physicians, nurses, social workers, dieticians and psychologists). This is not always easy but it is effective (17). Multidisciplinary care is based on strong collaboration between acute, hospice and home care. It has been shown that the problems of many palliative cancer patients would be more appropriately addressed by advanced home care instead of acute hospital care (18).

7.3.5 **Can anyone provide palliative care? Health care staff and advanced urological diseases**

Palliative care is practised everywhere and not only in palliative care units or hospices. For various reasons, people tend to delay facing questions associated with the end of life, and fear of the unknown often creates an environment of avoidance and an atmosphere of taboo (19). Healthcare professionals who are not used to working in palliative care often feel helpless. Often, there is a lack of communication with, and active listening to, patients and their families. This is not well received by patients who need communication with doctors and nurses (20).

Healthcare professionals caring for patients with advanced cancer are often exposed to burnout syndrome. It is important to detect signs of this condition at an early stage in order to prevent it from progressing (21,22). The tool mostly used is the Maslach Burnout Inventory (23).

The way that services are managed influences the occupational wellbeing of healthcare professionals. Also, services organised around an effective social support system enhance the quality of work life among caregivers, influencing their perceived stress and their coping strategies. Quality of life of the caregivers affects the quality of care (24).

Irrespective of the reasons for embarking on palliative care, once it has been decided upon, the professionals involved should commit themselves to respect the agreed interventions and implement them in every clinical situation. Clear policies on place of care (hospital, hospice or home), urinary diversions, and resuscitation are needed. Before assuming professional responsibility for terminal care, practices for parenteral hydration and antibiotic use should be clarified.

7.4 Treatment of physical symptoms

7.4.1 **Pain**

All the details concerning pain treatment have been previously addressed in Chapters 3 and 4.

7.4.2 **Dyspnoea and respiratory symptoms**

Breathlessness is common and very disturbing for patients with many types of advanced cancer. In this setting, the use of morphine and other opioids is not supported by research studies. Breathing training, walking, chest wall vibration, and electrical muscle stimulation, are effective non-pharmacological measures for relieving breathlessness (25).

When compared with placebo, benzodiazepines can cause more adverse effects (such as drowsiness), but fewer adverse effects are expected when compared to morphine. Despite the lack of evidence from well-conducted RCTs, benzodiazepines can be considered when opioids and non-pharmacological support measures fail to control breathlessness (26). Oxygen provides no symptomatic relief of dyspnoea compared with room air (27) (LE:1b).

Noisy breathing (death rattles) occurs in most people who are dying. The cause of death rattle
remains unclear but is presumed to be due to air passing over upper airways secretions. It can be treated physically or pharmacologically. Although distressing for some professionals and most families, there is no evidence to suggest that any pharmacological (anticholinergic drugs) or non-pharmacological intervention is superior to placebo. Nevertheless, atropine 0.5 mg, hyoscine butylbromide 20 mg, and scopolamine 0.25 mg (subcutaneous, followed by continuous administration) can be moderately effective for treatment of death rattles (28,29).

**Recommendation**

Benzodiazepines can be considered when opioids and non-pharmacological measures fail to control breathlessness.

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### 7.4.3 Cancer anorexia-cachexia syndrome

Cancer anorexia-cachexia syndrome (CACS) is frequent in patients with advanced cancer. Nutritional support in this setting seems to be ineffective (30) (LE: 1b), as does drug therapy. In a few selected cases, dexamethasone (4 mg/day) or progesterone analogues (megestrol acetate, 480-800 mg/day) can be considered, because it is thought that they have a significant effect on appetite and weight gain. A patient-doctor shared decision seems necessary before opting for treatment, considering that no gain in survival or QoL can be expected (31,32). The effect of orally administered cannabis extract (CE) on appetite and QoL in patients with CACS has been rigorously tested. Although CE is well tolerated, its effect on appetite did not clearly differ from that with placebo (33).

More recently, a phase II RCT has shown that thalidomide (50 mg/day, orally, for 2 weeks) is effective against cancer-related anorexia (34).

### 7.4.4 Vomiting

Chronic nausea occurs in most patients with advanced cancer, and in many cases, it is refractory to metoclopramide. In this setting, dexamethasone does not seem superior to placebo (32).

Droperidol is an antipsychotic drug that has been used as an antiemetic in the management of postoperative and chemotherapy-induced nausea and vomiting. Unfortunately, there is insufficient evidence to advise its use in the management of nausea and vomiting in palliative care (35).

Patients with a high incidence of emesis - usually post-chemotherapy - should receive a serotonin 5-hydroxytryptamine (5-HT3) receptor antagonist (ondansetron, tropisetron, granisetron, dolasetron or palosetron), dexamethasone, and a neurokinin 1 receptor antagonist such as aprepitant or fosaprepitant. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. Patients undergoing high emetic risk radiotherapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 h after treatment, and may receive a 5-day course of dexamethasone during fractions 1 to 5 (36).

Electroacupuncture is beneficial for chemotherapy-induced acute vomiting, but studies combining electroacupuncture with state-of-the-art antiemetics, and in patients with refractory symptoms, are needed to determine clinical relevance. Self-administered acupressure appears to be protective against acute nausea and can readily be taught to patients, although this has not been subjected to placebo-controlled studies. Non-invasive electrostimulation appears unlikely to have a clinically relevant impact when patients are given state-of-the-art antiemetic drug therapy (37).

**Recommendations**

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### 7.4.5 Other symptoms

#### 7.4.5.1 Fatigue

Asthenia is an overwhelming, persistent feeling of tiredness in which normal activity becomes an effort. Cancer-related fatigue (CRF) can be a significant problem with a serious impact on QoL. There are several tools to measure fatigue such as the Brief Fatigue Inventory (BFI), Numeric Rating Scale (NRS), and Revised Piper Fatigue Scale (PFS). The BFI includes nine items that measure the severity and impact of fatigue. It has adequate reliability with an established validity (38). The NRS has only one item: fatigue intensity. It is easy and
quick to use but less reliable (38). The Revised PFS has 22 items plus five additional open-ended items that measure four dimensions of subjective fatigue: behaviour/severity, affective meaning (mental aspect of fatigue), sensory, cognition/mood. It is an adequate and reliable measuring tool with established validity (39).

Trials of erythropoietin and darbopoetin (for anaemic patients) and psychostimulants have provided evidence for improvement in CRF. There are no data to support the use of paroxetine or progestational steroids for treatment of CRF. The amphetamine methylphenidate (standard treatment for attention deficit hyperactivity disorder) has been proposed for treatment of asthenia in patients with advanced cancer (40). There is evidence suggesting reduction in fatigue and depression when compared with placebo. Its effect on fatigue seems dose-dependent and sustained over time. Standard oral doses are 10-40 mg/day (41). Data from a phase III RCT suggest that modafinil - another psychostimulant - can be effective for the treatment of anorexia and depression in patients with advanced cancer (42).

Exercise is an effective intervention for patients with CRF (43). Like exercise, psychoeducational activity is a promising therapy for ameliorating CRF (44).

7.4.5.2 Restlessness
Most patients in the final stages of their lives experience restlessness. Although neuroleptics have been widely used in this setting, there is insufficient evidence to suggest that a single drug or class of medication is appropriate for terminal restlessness (45).

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<tr>
<th>Recommendation</th>
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<tr>
<td>Neuroleptics cannot be recommended for treatment of terminal restlessness.</td>
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7.4.5.3 Agitated delirium
There is limited high quality evidence on the role of drug therapy for delirium in terminal patients. Although benzodiazepines have been widely used, it has not been possible to assess the effectiveness of treatment options (46,47). However, haloperidol (5-10 mg, intravenous) remains a useful drug for the treatment of many forms of delirium (48).

7.4.5.4 Constipation
Chronic constipation can be a serious problem for cancer patients taking opioids. Oral lactulose seems more effective than polyethylene glycol (49). Nevertheless, evidence on laxatives for management of constipation remains limited due to insufficient RCTs (49).

Interestingly, subcutaneous methylnaltrexone seems effective in inducing laxation in patients with opioid-induced constipation when standard laxatives fail (50,51). Its safety, however, has to be proven in properly organised RCTs. No clear recommendations as to the use of a particular laxative can be made (LE: 1a).

7.4.5.5 Anxiety
Anxiety is a common symptom in patients near the end of life. A myriad of drugs has been used to calm anxiety in terminally ill patients (including anxiolytics, antidepressants, antipsychotics, benzodiazepines, butyrophenones, phenothiazines and thienobenzodiazepines). There is currently insufficient evidence on the role of this type of drug in patients with terminal illness, and it is therefore not possible to draw any conclusions about the effectiveness of pharmacotherapy in this setting (52).

7.5 Terminal care
For medical practitioners who are trained to save lives, the end of life represents a completely different professional scenario in which personal skills give way to multidisciplinary, compassionate intervention. Relieving suffering requires well-trained teams and clearly established goals. It seems clear that early identification of patients needing palliative care can effectively improve QoL (53).

Recognition of intolerable refractory symptoms, standardised monitoring of disease progress, and availability of terminal care pathways are crucial for supporting patients and families with terminal disease. In addition to the above-mentioned interventions, palliative sedation is one of the alternatives to keep in mind when dealing with terminally ill patients. Patients experiencing refractory symptoms (e.g., pain, vomiting, delirium and dyspnoea) can be considered for palliative sedation. It consists of the deliberate administration of drugs in minimum doses and combinations required not only to reduce the consciousness of the patients but also to achieve adequate alleviation of one or more refractory symptoms, and with the prior consent given by the patient explicitly, or implicitly, or delegated (54). The aim of palliative sedation is never to hasten death and there is evidence that it does not jeopardise survival (55,56). Figure 6 is an aid for the recognition of refractory symptoms.
Although physicians are responsible for the objective evaluation of symptoms, fully competent patients have the right to prompt interventions or to refuse any kind of treatment. When the patient is mentally incapable, the nearest relative can make decisions. For certain complicated cases, physicians might seek the help of their ethics committee or ask for a legal consultation. Nevertheless, it should always be kept in mind that doubt should not be expressed in front of a suffering patient.

The ethics of palliative treatment at the end of life seem beyond question. Nevertheless, a few countries in Europe (Netherlands, Belgium and Switzerland) and some of the United States (Oregon and Washington) have clear regulations on the right to terminal sedation. Cultural and ethnic differences in the approach to the end of life are also prominent (57-64), thus making the approach to the final stages of life not always equitable.

### 7.5.1 When and how to withdraw specific treatment

With every single intervention, the ethical principles of beneficence, non-maleficence, autonomy and justice should be considered. Relieving suffering - rather than sustaining life at any cost - might be sensible in patients with advanced disease. Patients (or relatives when they are incompetent) have the right to ask for treatment cessation at any time. It will always be taken into account that proxies are supposed to interpret the patient's wishes and not their own. Artificial ventilation, haemodialysis, parenteral nutrition, blood transfusion and chemotherapy can all be stopped at the patient’s request (65).

**Recommendation**

<table>
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<td>The patient (or relatives if incompetent) should be able to decide on every single intervention.</td>
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*Recommendation based on expert opinion.

### 7.5.2 Parenteral hydration: should it be discontinued in the terminal phases?

There is an interesting controversy about forced hydration in terminally ill patients. At present, good quality studies on this topic are lacking, making recommendations for practice pointless (66). There is scientific evidence to show that artificial hydration provides no clear benefit in relation to normalising renal function and electrolyte levels compared with non-hydrated patients (67). Nevertheless, it seems that parenteral hydration can improve many of the symptoms experienced by terminally ill, dehydrated cancer patients (68).

The decision should be taken on an individual basis, but it is suggested that patients who cease drinking are close to death and will gain little from artificial hydration (3).
7.5.3 **Palliative sedation**

Considering the lack of randomised trials on palliative sedation, the panel decided to stick to the principles of the Royal Dutch Medical Association (KNMG) in this respect (3).

As mentioned earlier, palliative sedation is the deliberate lowering of the level of consciousness in the last stages of life. As such, it can only be considered in the context of a palliative care plan. The object of palliative sedation is to relieve suffering, and lowering consciousness is the means to that end. Palliative sedation never aims to hasten death. Deciding whether the indications for palliative sedation are met is always a medical task, but not necessarily a matter for specialised physicians. The untreatable nature of the symptoms must be demonstrated beyond reasonable doubt. Besides the presence of medical indications in the form of one or more refractory symptoms, another precondition is the expectation that death will ensue in the reasonably near future – that is, within 1-2 weeks (3,69).

It is generally agreed that physicians and nurses should be present the moment palliative sedation begins (69). Subcutaneous administration is the preferred route and midazolam the drug of choice (1,70). Table 19 provides a suggestion for palliative sedation (3).

Table 19: Three steps approach to palliative sedation. In the hospital setting, Phase 3 can follow Phase 1 (1)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug</th>
<th>Bolus</th>
<th>Continuous administration</th>
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<tbody>
<tr>
<td>Phase 1</td>
<td>Midazolam</td>
<td>Start with 10 mg s.c. If necessary, 5 mg every 2 h s.c.</td>
<td>Initial dose 1.5-2.5 mg/h sc/iv. If the desired effect is not achieved, increase the dose by 50% after a minimum of 4 h, always in combination with a bolus of 5 mg sc. If risk factors are present (age &gt; 60 years, weight &lt; 60 kg, severe kidney or liver dysfunction, very low serum albumin, and/or co-medication that could exacerbate the effect of sedation): - lower initial dose (0.5-1.5 mg/h), and - lengthen interval (6-8 h) before increasing maintenance dose. In the case of doses &gt; 20 mg/h, see Phase 2.</td>
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<tr>
<td>Phase 2</td>
<td>Levomepromazine</td>
<td>25 mg sc/iv, possibly 50 mg after 2 h</td>
<td>0.5-8 mg/h sc/iv in combination with midazolam. After 3 days, halve the dose to prevent drug accumulation. If the desired effect is not achieved, stop administering midazolam and levomepromazine; see Phase 3.</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Propofol</td>
<td>20-50 mg iv</td>
<td>20 mg/h iv, increase by 10 mg/h every 15 min. Administration under supervision of an anaesthesiologist is advisable. In hospital, this may be considered for Phase 2.</td>
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7.6 **Treatment of psychological aspects**

7.6.1 **Fear**

While improvements in screening, prevention and treatment are encouraging, cancer is still related to very intensive treatment, and finally to death in many patients. It may cause deep fear and depression. The role of the healthcare giver is important in this process (71). Measuring distress should be a major part of assessing patient emotional disturbance. Different tools are available such as the Hospital Anxiety and Depression Scale and the Distress Thermometer. Successful implementation of a screening procedure depends on its acceptability to patients and clinicians, as well as the clinicians’ perception of the added value. Distress is often related to the physical complications of cancer and its treatment, therefore, the approach should include psychological and physical well-being (72).

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<td>Distress must be recognised, measured, treated and monitored at all stages of the disease.</td>
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7.6.2 Depression

There is a strong correlation between physical disease and depression but there is no evidence that depression may cause cancer. Depression is associated with adverse outcomes such as increased pain, disability and poor prognosis (73).

The effectiveness of pharmacological agents for anxiety has not yet been proved. Nevertheless, both psychosocial and pharmacological interventions have been shown to be efficacious in treating depression in cancer patients (74,75).

One study has shown that prescription prevalence among cancer patients in the last year of life is almost four times higher than in the general population. One out of 10 patients is prescribed with antidepressants so close to death that the clinical effects can be questioned (76).

Moreover, behavioural therapy, counselling, psychotherapy, education/information, relaxation and social support alleviate depression and anxiety (77). Centralised telecare management coupled with automated symptom monitoring can improve pain and depression outcomes in cancer patients receiving care in geographically dispersed urban and rural oncology practices (78).

Screening for depression in terminally ill patients can optimise their physical comfort at the end of life and provide them with the opportunity to confront and prepare for death (79).

**Recommendation**

Efforts should be made to detect hidden depression.

*Recommendation based on expert opinion.*

7.6.3 Family care

Family and relatives have an important role to play in the care of patients with advanced disease and they should be involved in decision-making about where the patient should be cared for (e.g., home or hospice). Nevertheless, the patient’s views should always be kept in mind. In addition, the family is emotionally affected by the disease, and their emotional distress may influence the patient’s mood. It is important to screen for depressive symptoms and predictors of depression among family caregivers, especially in the dying process and after death (80).

Patients and families need to be prepared for death. The process can then take place under good, serene conditions (81,82). Otherwise, it can lead to dysfunctional family dynamics that can be disturbing to the staff members in their efforts to provide optimal palliative care, and to the patient (81). Family-focused grief therapy based on communication, cohesiveness, conflict resolution, and shared grief is effective in protecting family members against the drama of disease and death (83).

Table 20: Arresødal Hospice principles of management of intrafamilial conflicts (81)

| Maintain the palliative perspective | Consider the possibility and implementation of palliative management perspective strategies in certain subtypes of family dysfunction and to extend beyond this (if favourable circumstances allow), incorporate a more long-term outlook for future rehabilitation of the surviving relatives. |
| Maintain flexibility | Take into account the strengths, psychological resources, level of intellect and emotional state of conflicting family members before deciding whether to use interpretive or supportive techniques. Be prepared to reflect over strategies that have not been optimal, and modify as necessary. |
| Maintain neutrality | Current information for all staff members involved through mono- or multidisciplinary meetings is essential. It is important to handle conflicting family dynamics in an open, transparent and professional way, not to be unexpectedly absorbed as an active part of the conflict, and to avoid covert behaviour. The principle of neutrality applies to this strategy in that involvement in long-term prior conflicts is to be avoided. |
| Avoid splitting | Avoid, or at least identify and understand splitting between members of staff by recognizing that dysfunctional families with conflicting dynamics may display completely opposing attitudes within short periods of time, which can be challenging to staff. In the worst case scenarios, relatives in conflict may project their issues onto others as a way to control fragmented or distressed parts of themselves. |
| Avoid demonising | Encourage and enable staff to share awkward, challenging and/or negative feelings brought on by sudden or inadvertent involvement in conflicting family dynamics. |
Set necessary limits | Limits need to be identified and maintained consistently if behaviour of a family member threatens the integrity or safety of the patient, other relatives, staff or the palliative-therapeutic relationship.

Intervention | Encourage staff members to maintain the professional/personal balance through multidisciplinary discussions, counselling and prompt debriefing.

7.6.4 Communication of bad news

Informing patients of bad news about malignancies is a difficult task; bad prognosis for some cancers and severe symptoms and treatment side effects make it painful for health professionals. It may be easier not to inform the patient. Nevertheless, disclosure will emphasise uncertainty and anxiety. In addition, patients have the right to be informed and the right to choose non-disclosure (84). Specific, patient-targeted information increases the quality of terminal care (7).

Patients’ families often experience anticipatory grief when learning of a diagnosis of advanced or terminal cancer. Anticipatory grief can be a response to threats of loss of ability to function independently, loss of identity, and changes in role definition, which underlie fear of death. When an oncologist delivers bad news, the patient and family members often hear the same discussion through different filters, which can lead to conflict and dysfunction. It is then important to provide a supportive and safe environment, and to help the patients reframe “hope” realistically so that they may have the opportunity for personal growth as well as reconciliation of primary relationships toward the end of life (85).

In such situations, good communication skills are needed. There are methods to help health care professionals deliver information about bad news, such as using sociograms and psychodrama (86).

7.7 References

   http://www.ncbi.nlm.nih.gov/pubmed/21532350


8. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AMPA  α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ATC  around-the-clock
CBT  cognitive behavioural therapy
CNS  central nervous system
COX  cyclo-oxygenase
CRPC  castration-resistant prostate cancer
CT  computed tomography
EDTMP  ethylenediaminetetramethylenephosphonate
EORTC  European Organisation for Research and Treatment of Cancer
GABA  gamma-aminobutyric acid
GFR  glomerular filtration rate
GCP  good clinical practice
IASP  International Association for the Study of Pain
im  intramuscular
iv  intravenous
IVU  intravenous urography
131J-MIBG  131J-metaiodobenzylguanidine
mCRPC  metastatic castration-resistant prostate cancer
MRI  magnetic resonance imaging
MSCC  metastatic epidural spinal cord compression
NMDA  N-methyl-D-aspartate
NRS  numerical rating scale
NSAIDs  non-steroidal anti-inflammatory drugs
PACU  post-anaesthesia care unit
PCa  prostate cancer
PCA  patient-controlled analgesia
PCEA  patient-controlled epidural analgesia
prn  as needed
PRPE  perineal radical prostatectomy
QoL  quality of life
RCC  renal cell carcinoma
RLND  retroperitoneal lymph node dissection
RVT  renal vein thrombosis
sc  subcutaneous
153Sm  samarium-153
89Sr  strontium-89
SRI  selective serotonin reuptake inhibitors
SPECT  single photon emission computed tomography
SWL  extracorporeal shock wave lithotripsy
TCA  tricyclic antidepressants
TCC  transitional cell carcinoma
TENS  transcutaneous electrical nerve stimulation
TURB  transurethral resection of bladder tumour
TURP  transurethral resection of prostate
UHCT  unenhanced helical CT
VAS  visual analogue scale
VRS  verbal rating scale
WHO  World Health Organization

Conflict of interest
All members of the General Pain and Palliative Care Guidelines expert panel have provided disclosure
statements on all relationships that they have and that might be perceived to be a potential source of conflict
of interest. This information is publically accessible through the European Association of Urology website. This
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have been provided.
Guidelines on Chronic Pelvic Pain

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1. INTRODUCTION

1.1 The Guideline
Chronic pelvic pain (CPP) is a prevalent condition which can present a major challenge to health care providers due to its complex aetiology and poor response to therapy. Chronic pelvic pain is a multifactorial condition and therefore, quite often, poorly managed. Management requires knowledge of all pelvic organ systems and their association with other systems and conditions, including musculoskeletal, neurologic, urologic, gynaecologic and psychological aspects, promoting a multidisciplinary approach.

The European Association of Urology (EAU) Guidelines Working Group for Chronic Pelvic Pain prepared this guidelines document to assist urologists and medical professionals from associated specialties, such as gynaecologists, psychologists, gastroenterologists and sexologists, in assessing the evidence-based management of CPP and to incorporate evidence-based recommendations into their every-day clinical practice.

1.1.1 Panel composition
The panel of experts responsible for this document include urologists, a neuro-urologist, consultants in pain medicine, a gynaecologist, a psychologist, a gastroenterologist and a sexologist.

1.1.2 Publication history
The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 (1) which formed the basis of a scientific publication in European Urology in 2004 (2). Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”.

Partial updates of the CPP guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 (3,4).

For the update in 2012 the panel focussed on:
1. restructuring the text to emphasise the significance of holistic management of CPP;
2. addressing the changes in the management of CPPS based on the concept of pain as a disease process.

A complete update of the guidelines is foreseen in 2014.

As a result, two new chapters were added; Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain.

A quick reference document presenting the main findings of these CPP guidelines (pocket guidelines) is also available and has been updated. All texts, alongside scientific publications, can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.2 Methodology
The full text update is based on a systematic review of literature using the Embase and Medline databases, the Cochrane Central Register of controlled trials and the PsycInfo and Bandolier databases to identify the best evidence from RCTs, Level of Evidence 1 (LE: 1), according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (Table 1) (5). Where no (LE: 1) literature could be identified the search was moved down to the next lower level on the rating scale. Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 and May 2011 and were restricted to English language publications.
1.2.1 Level of evidence and grade of guideline recommendations*

References used in the text have been assessed according to their level of evidence (Table 1), and recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (5). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence (LE)*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (5)

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and
burdens, values and preferences and cost when a grade is assigned (6-8).

The EAU Guidelines Office, do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

Table 2: Grade of recommendation (gR)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (5)

1.2.2 Formal review

A formal review was carried out prior to publication by a multidisciplinary team of international experts, covering the different fields of expertise described in these guidelines.

1.3 Acknowledgements

The expert panel should like to express their gratitude to professor Magnus Fall, former chairman and patriarch of the CPP panel who established the foundation of these guidelines, the current expert panel can now build on.

The support provided by research scientist Drs. J. Krabshuis has proved to be highly valuable in enhancing the methodological quality of this publication.

1.4 References


2. CHRONIC PELVIC PAIN

2.1 Introduction to chronic urogenital pain syndromes
Over the years much of the focus for CPP has been on peripheral-end-organ mechanisms, such as inflammatory or infective conditions. However, both animal and clinical research have indicated that many of the mechanisms for the CPP syndromes are based within the central nervous system (CNS). Although a peripheral stimulus such as infection may initiate the start of a CPP condition, the condition may become self-perpetuating as a result of CNS modulation, independent of the original cause. As well as pain, these central mechanisms are associated with several other sensory, functional, behavioural and psychological phenomena. It is this collection of phenomena that forms the basis of the pain syndrome diagnosis and individual phenomena need to be addressed in their own right through multispecialty and multidisciplinary care.

Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPP syndromes in which no peripheral ongoing pathology (such as infection or neoplastic disease) is detected. The main exception is when pain is due to peripheral nerve damage, which will be discussed in chapter 6.

2.2 Pain mechanisms - pain as a disease process
Chronic pelvic pain mechanisms may involve:
1. Ongoing acute pain mechanisms (1) (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS (2).
3. Emotional, cognitive, behavioural and sexual responses and mechanisms (3-6). These are covered in chapter 7 and 8.

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. They underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 3: Comparison between visceral and somatic pain

<table>
<thead>
<tr>
<th></th>
<th>Visceral pain</th>
<th>Somatic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective painful stimuli</td>
<td>Stretching and distension, producing poorly localised pain.</td>
<td>Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.</td>
</tr>
<tr>
<td>Summation</td>
<td>Widespread stimulation produces significantly magnified pain.</td>
<td>Widespread stimulation produces a modest increase in pain.</td>
</tr>
<tr>
<td>Autonomic involvement</td>
<td>Autonomic features (e.g., nausea and sweating) frequently present.</td>
<td>Autonomic features less frequent.</td>
</tr>
<tr>
<td>Referred pain</td>
<td>Pain perceived at a site distant to the cause of the pain is common.</td>
<td>Pain is relatively well localised but well recognised.</td>
</tr>
<tr>
<td>Referred hyperalgesia</td>
<td>Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.</td>
<td>Hyperalgesia tends to be localised.</td>
</tr>
<tr>
<td>Innervation</td>
<td>Low density, unmyelinated C fibres and thinly myelinated A\d fibres.</td>
<td>Dense innervation with a wide range of nerve fibres.</td>
</tr>
<tr>
<td>Primary afferent physiology</td>
<td>Intensity coding. As stimulation increases afferent firing increases with an increase in sensation and ultimately pain.</td>
<td>Two fibre coding. Separate fibres for pain and normal sensation.</td>
</tr>
<tr>
<td>Silent afferents</td>
<td>50-90% of visceral afferents are silent until the time they are switched on. These fibres are very important in the central sensitisation process.</td>
<td>Silent afferents present, but form a lower percentage.</td>
</tr>
</tbody>
</table>
Central mechanisms: Play an important part in the hyperalgesia, viscero-visceral, viscero-muscular and musculo-visceral hyperalgesia. Sensations not normally perceived become perceived and non-noxious sensations become painful. Responsible for the allodynia and hyperalgesia of chronic somatic pain.

Abnormalities of function: Central mechanisms associated with visceral pain may be responsible for organ dysfunction. Somatic pain associated with somatic dysfunction, e.g., muscle spasm.

Central pathways and representation: As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation. Classical pain pathways.

2.2.1 Ongoing peripheral visceral pain mechanisms as a cause of CPP

In most cases of CPP, ongoing tissue trauma, inflammation or infection is not present (7-10). However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in CPP in a small proportion of cases. It is for this reason that the early stages of assessment include looking for these pathologies (11). Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur, thus magnifying the afferent signalling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) (12,13).

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility.

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulates the receptors of the transducers (14).
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 is to lower the threshold and the effect of 3 is to increase responsiveness to external stimuli.

Some of the chemicals responsible for the above changes may be released from those cells associated with inflammation, but the peripheral nervous system may also release chemicals in the form of positive and inhibitory loops (Table 4) (15).

Table 4: Mechanisms in the periphery that affect nociceptor response to a nociceptive stimulus

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve growth factor (NGF)</td>
<td>May activate primary afferents directly, but also indirectly such as through bradykinin (16). The result is an increase in response of the primary afferents, with multiple action potentials being generated in response to a stimulus, as opposed to just one or two. The TrkA-NGF complex formed on the afferent neurons may also be transmitted centrally where it may alter gene expression. Such long-term gene modification may underlie some of the mechanisms of chronic NGF-induced hypersensitivity.</td>
</tr>
<tr>
<td>Adenosinetriphosphate (ATP)</td>
<td>Is thought to be released in increased amounts from certain viscera when stimulated by noxious stimuli. As well as this increased ATP producing an increased stimulation of its receptors, when inflammation is present, the ATP receptors have their properties changed so that there is an increased response per unit of ATP contributing to the nociceptor activation. ATP is thought to act on P2X3 purine receptors, which are found on visceral afferents and small-diameter dorsal root ganglion (DRG) neurons.</td>
</tr>
<tr>
<td>Substance P and other neurokinins (17)</td>
<td>Act on afferent tachykinin receptors, such as TRPV1, which is a transducer for noxious heat and protons, and are thought to play a primary role in inflammatory hyperalgesia.</td>
</tr>
</tbody>
</table>
Voltage-gated ion channels
E.g., tetrodotoxin-resistant sodium channel, NaV1.8 are also implicated in peripheral sensitisation. These channels open or close in response to changes in membrane potential. Changes in potassium and calcium voltage-gated channels may also underlie a part of the mechanism responsible for peripheral sensitisation.

Second messenger pathways
Within the primary afferents enable amplification of peripheral messages that they receive. In general, these pathways are balanced by others that are responsible for reducing any activation. During chronic pain, these mechanisms may become imbalanced.

2.2.2 Central sensitisation - spinal and higher mechanisms of visceral pain
There are essentially three processes at the spinal cord level that are involved in central sensitisation (17). Changes in existing protein activity (post-translational processing) are the earliest (within minutes); however, changes in genetic transcription of proteins and even structural changes in neuron connectivity may also have roles to play. These latter changes may occur within days (18).

The chemicals involved in the early phase include several neurotransmitters such as glutamate, substance P, calcitonin gene-related peptide (CGRP), prostaglandin E2 and brain-derived neurotrophic factor (BDNF) (15).

Increased levels of glutamate, due to recurrent afferent nociceptive fibre activity, remove the magnesium ion block of N-methyl-D-aspartate (NMDA). This allows calcium ions to enter the secondary afferents with enhanced depolarisation. Glutamate also binds to amino-methylene-phosphonic acid (AMPA), which may be another pathway by which it increases intracellular calcium. Other transmitters/modulators released centrally include: substance P, which acts on neural kinin receptors; PGE2, which binds to endogenous prostanoid receptors; and BDNF, which acts on tyrosine kinase B receptors and all of these may also increase intracellular calcium.

The calcium ions act to lower the threshold for second-order neuron firing, with increased signalling being transmitted to the higher centres. The second important feature of this increase in calcium ions is post-translational processing; this usually involves the addition of phosphate groups to amino acids by kinases. Phosphorylation can dramatically alter the properties of a protein, typically lowering the threshold at which channels open, but also, the channels remain open for longer. The result is that a stimulus produces a magnified evoked response in these neurons.

2.2.3 Spinal mechanisms and visceral hyperalgesia
Central sensitisation (18) is responsible for a decrease in threshold and increase in response duration and magnitude of dorsal horn neurons. It is associated with an expansion of the receptive field. As a result, sensitisation increases signalling to the CNS and amplifies what we perceive from a peripheral stimulus. As an example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally subthreshold and not usually perceived may be perceived. For instance, with central sensitisation, stimuli that are normally subthreshold may result in a sensation of fullness and a need to void the bladder or to defecate. Stimuli normally perceived may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of the bladder pain syndrome (BPS) (formally known as interstitial cystitis (IC) and irritable bowel syndrome (IBS)) may be explained by central sensitisation. A similar explanation exists for the muscle pain of fibromyalgia.

2.2.4 Supraspinal modulation of pain perception
It is important to appreciate that nociception is the process of transmitting to centres involved in perception information about a stimulus that has the potential to cause tissue damage. Pain is far more complex and involves activation of the nociceptive pathways but also the emotional response. Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (19). The brain may affect the modulation of pain pathways at the spinal cord level.

2.2.5 Higher centre modulation of spinal nociceptive pathways
It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain (20).
The midbrain periaqueductal grey (PAG) plays an important part in spinal modulation. It receives inputs from centres associated with thought and emotion. Projections from the PAG (via several relay systems) to the dorsal horn can inhibit nociceptive messages from reaching conscious perception by spinal mechanisms. The PAG and its associated centres may also be involved in diffuse noxious inhibitory control (DNIC). DNIC is when a nociceptive stimulus, in an area far from the receptive fields of a second nociceptive stimulus, can prevent or reduce pain from that second area. This is thought to be the mechanism for the paradigm of counter-irritation.

Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main contenders are the opioids, 5-hydroxytryptamine and noradrenaline.

The pathways and chemicals for the facilitatory modulation are even less well understood, but the mechanisms are well accepted.

2.2.6 Neuro modulation and psychology
Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres. Some of these processes are sophisticated and others fundamental in evolutionary terms, and their interaction with pain processing is complex. As indicated above, many of the areas involved in relevant psychological processes interact with the PAG, and this is therefore one mechanism by which they may influence pain transmission at the spinal level.

At the spinal level, visceral nociception is dependent upon a system of intensity coding. In the viscera, primary afferents for normal sensations and nociception appear to be the same small fibres arriving at the spinal cord, and the difference between a normal and a noxious message depends upon the number of afferent signals transmitted to the dorsal horn (as opposed to the dual fibre, A/C fibre for nociception and A for light touch, seen in somatic tissue). It is thought that psychological modulation can alter intensity coding more easily than dual-fibre coding, and hence, pain perception.

Various psychological processes affect pain neuromodulation at the higher level. Inhibiting or facilitating both the nociceptive signal reaching the consciousness and appraisal and interpretation of that signal; they will also modulate the response to the nociceptive message and hence the pain experience. Further, descending pathways represent cognitive, emotional and behavioural states at spinal and peripheral levels.

Functional Magnetic Resonance Imaging (fMRI) has indicated that the psychological modulation of visceral pain probably involves multiple pathways. For instance, mood and attentional focus probably act through different areas of the brain when involved in reducing pain (21).

This psychological modulation may act to reduce nociception within a rapid time frame but may also result in long-term vulnerability to chronic visceral pain, through long-term potentiation. This involvement of higher centre learning may be at both a conscious and subconscious level, and is clearly significant in the supratentorial neuroprocessing of nociception and pain. Long-term potentiation (22) may also occur at any level within the nervous system, so that pathways for specific or combinations of stimuli may become established, resulting in an individual being vulnerable to perceiving sensations that would not normally be experienced as painful.

Stress is an intrinsic or extrinsic force that threatens the homeostasis of an organism and can be physical or psychological. Stress induces an adaptive response that involves the endocrine, autonomic nervous and immune systems, and these systems in turn appear to have feedback loops. Stress can modify the nervous system by long-term potentiation so that there are long-term actual or potential changes within these systems. It is this process that may be responsible for the effect of early life and significant adverse life events associated with chronic pain syndromes. It is through all of these factors that stress can play a significant role in nociceptive and pain neuromodulation, with the increased experience of pain as well as the more general effect that stress may have on coping resources (23). Significant adverse life events include, rape, sexual abuse, sexual trauma and sexual threat, such as during internment or torture. These events may produce long-term physical changes in the CNS (biological response), as well as having an effect on a patient’s, emotional, cognitive, behavioural and sexual responses (24-26).

2.2.7 Autonomic nervous system
The role of the autonomic nervous system in chronic pain is poorly understood, however, there is good evidence that damaged afferent fibres may develop a sensitivity to sympathetic stimulation, both at the site of injury and more centrally, particularly the dorsal horns. In visceral pain, the efferent output of the CNS may be
influenced by central changes (again, those changes may be throughout the neuraxis), and such modification of the efferent message may produce significant end-organ dysfunction. These functional abnormalities can have a significant effect on quality of life (QoL) and must be managed as appropriate.

2.2.8 Endocrine system
The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress may occur following such events and is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Upregulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells.

A range of stress-related illnesses have been suggested, with IBS and BPS being examples. There is also evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception.

2.2.9 Genetics and chronic pain
An individual who has had one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred that are more prone to an apparent chronic pain state. A whole range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes in transmitters and their receptors. However, the picture is more complicated in that development, environment and social factors also influence the situation.

2.3 Clinical paradigms and CPP

2.3.1 Referred pain
Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, as an example, afferent fibres from the viscera and the somatic site of referred pain converge onto the same second order projection neurons. The higher centres receiving messages from these projection neurons are unable to separate the two possible sites from the origin of the nociceptive signal (9,13,27).

2.3.2 Referred pain to somatic tissues with hyperalgesia in the somatic tissues
Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and biliary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infection. Vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscero-somatic neurones. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

2.3.3 Muscles and pelvic pain
In the urogenital pain syndromes muscle tenderness and trigger points may be implicated as a source of pain. Central mechanisms are of great importance in the pathogenesis of this muscle hyperalgesia. The muscles involved may be a part of the spinal, abdominal or pelvic complex of muscles. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but is more often associated with classical referral patterns. As well as trigger points, inflammation of the attachments to the bones (enthesisitis) and of the bursa (bursitis) may be found (28-30).

Certain postures affect the different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect (23).

2.3.4 Visceral hyperalgesia
The increased perception of stimuli in the viscera is known as visceral hyperalgesia, and the underlying mechanisms are thought to be responsible for IBS, BPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g., due to infection) followed by long-term central sensitisation.
2.3.5 **Viscero-visceral hyperalgesia**

Viscero-visceral hyperalgesia is thought to be due to two or more organs with converging sensory projections and central sensitisation. For instance, overlap of bladder and uterine afferents or uterine and colon afferents.

Figure 1: Predisposing factors, cause, central en peripheral mechanisms

<table>
<thead>
<tr>
<th>Predisposing factors</th>
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<tbody>
<tr>
<td>genetics</td>
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<tr>
<td>psychological state</td>
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<tr>
<td>recurrent somatic trauma</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Causes</th>
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<tbody>
<tr>
<td>surgery</td>
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<tr>
<td>trauma</td>
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<tr>
<td>infection</td>
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<table>
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<tr>
<th>Peripheral nerve injury</th>
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<tbody>
<tr>
<td>Abnormal peripheral afferent signalling</td>
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</table>

<table>
<thead>
<tr>
<th>Peripheral sensitisation</th>
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<tbody>
<tr>
<td>Increased peripheral afferent signalling</td>
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<table>
<thead>
<tr>
<th>Central sensitisation</th>
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<tbody>
<tr>
<td>Abnormal central afferent signalling</td>
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<table>
<thead>
<tr>
<th>Consequences include:</th>
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<tbody>
<tr>
<td>sensory problems</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consequences include:</th>
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<tbody>
<tr>
<td>changes in organ function</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological, behavioural and sexual consequences</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Regional and systemic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred pain, viscero-visceral hyperalgesia, viscero-somatic hyperalgesia. Trophic, autonomic, endocrine and immunological responses</td>
</tr>
</tbody>
</table>

2.4 **Definitions of CPP terminology**

2.4.1 **Classification**

Much debate over the classification of CPP has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition, phenotyping, terminology and taxonomy.

2.4.2 **Phenotyping**

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner’s ulcers and glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for IBS, which may be subdivided into that with primarily diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, autoimmune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome - a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint.

2.4.3 **Terminology**

Terminology is the words that are used within classification, both to name the phenotype and within the definition of the phenotype. Examples of names for phenotypes associated with the bladder include interstitial cystitis, painful bladder syndrome or BPS. The EAU, the International Society for the study of BPS (ESSIC), the International Association for the Study of Pain (IASP) and several other groups now prefer the term bladder pain syndrome. In the pain syndromes, the role of the nervous system in generating the sensations is thought to be pivotal, but the term syndrome is also holistic and takes into account the emotional, cognitive, behavioural, sexual and functional consequences of the chronic pain.

When defining the phenotype, the terminology used in that definition must also be clear and if necessary defined. One of the most important guiding principles is that spurious terminology should be avoided. Terms that end in “itis” in particular should be avoided unless infection and or inflammation is proven and considered
to be the cause of the pain (7). It must be appreciated that end-organ inflammation may be secondary and
neurogenic in origin and not a primary cause of the pain.

2.4.4 **Taxonomy**

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach subdivides CPP into
conditions that are pain syndromes and those that are non-pain syndromes. The latter are conditions that have
well-recognised pathology (e.g., infection, neuropathy or inflammation), whereas the former syndromes do not
and pain as a disease process is the mechanism. Other terms for the non-pain syndromes include “classical
conditions”, “well-defined conditions” and “confusable diseases”. Although the EAU approach deals primarily
with urological conditions, this approach to classification can be applied to all conditions associated with pain
perception within the pelvis; the classification has been developed to include non-urological pain and was
accepted by the IASP for publication in January 2012.

2.5 **Classification of CPP syndromes**

2.5.1 **Importance of classification**

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for
classifying CPP go far beyond that.

**Clues to the mechanism**

As a result of systematic phenotypic and taxonomic classification, similarities and differences between
conditions become clear. Drawing comparisons between the phenotypes of different disorders allows one to
compare disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

**Guidelines for best treatment options**

As conditions become better defined, more specific treatment approaches can be adopted. In particular, there
will be a move away from treatments based upon spurious terms (e.g., antibiotics and non-steroidal anti-
inflammatory drugs for the “-itis” conditions). Generic treatments aimed at groups of conditions will be more
commonplace and based upon research evidence.

**Research platform**

Only by clearly defining the phenotype being investigated can research be valued or applied in the clinical
situation.

**Patient needs**

A diagnosis, or name, for a set of symptoms can provide patients with a sense of being understood, as well
as hope for relief. It may therefore help in acceptance of the problem as chronic, resolution of unfounded
fears about its implications (if not life-threatening), and engagement in therapeutic endeavours, as well as in
self-management. However, it may also lead to accessing information of variable quality associated with the
diagnosis or name, and the possibility of generating new concerns about long-term consequences or about
appropriateness of treatment.

**Remuneration**

In certain countries, having a defined condition is necessary for the patient to receive treatment for their
condition.

2.5.2 **IASP definitions**

**Subdividing pain syndromes**

There is much debate on the subdivisions of the pain syndromes within the hierarchical taxonomy. The EAU
has led the way in this regard and the guiding principles are as follows (31):

1. The pain syndromes are defined by a process of exclusion. In particular, there should be no evidence
   of infection or inflammation. Investigations by end-organ specialists should thus be aimed at obtaining
   a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of
   chronic pain syndromes.

2. A subdivision phenotype should only be used if there is adequate evidence to support its use. For
   instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic
   pelvic pain syndrome (CPPS) should be used. If the pain can be localised to an organ, then a more
   specific term, such as rectal pain syndrome, may be used. If the pain is localised to multiple organs,
   then the syndrome is a regional pain syndrome and the term CPPS should once again be considered.
   As well as defining the patient by a specific end-organ phenotype, there are several other more
general descriptors that need to be considered. These are primarily psychological (e.g., cognitive
or emotional), sexual, behavioural and functional. Psychological and behavioural factors are well established to relate to QoL issues and prognosis. In North America a research programme, the MAPP program (Multi-disciplinary Approach to the study of Chronic Pelvic Pain research) has been devised to investigate the importance of these factors and looks at all types of pelvic pain irrespective of the end-organ where the pain is perceived. It also looks at systemic disorder associations, such as the co-occurrence of fibromyalgia, facial pain, or autoimmune disorders.

3. In 2004 this expert panel introduced the concept of managing the polysymptomatic nature of CPP, since then others have developed their own schemes, such as Nickel’s UPOINT (32), modified by Magri et al. (33). In the light of these and other publications, the symptom classification table has been updated (Table 5).

The debate in relation to subdividing the pain syndromes remains ongoing. As more information is collected suggesting that the CNS is involved, and indeed may be the main cause of many CPP conditions (e.g., bladder, genitalia, colorectal or myofascial), there is a general tendency to move away from end-organ nomenclature. Whether this is appropriate, only time and good research will tell. To enable such research, it is essential to have a framework of classification within which to work. Any hierarchical taxonomy must be flexible to allow change.

In table 5 the classification has been set up according to the axis system used by IASP. The panel used this table from their first edition and found it very useful for clinical purpose.
Table 5: EAU classification of chronic urogenital pain syndromes

<table>
<thead>
<tr>
<th>Axis IV</th>
<th>End-organ as identified from Ia, II, and III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axis V</td>
<td>Temporal characteristics</td>
</tr>
<tr>
<td>Axis VI</td>
<td>Character</td>
</tr>
<tr>
<td>Axis VII</td>
<td>Associated symptoms</td>
</tr>
<tr>
<td>Axis VIII</td>
<td>Psychological symptoms</td>
</tr>
<tr>
<td>Axis IX</td>
<td>Referral characteristics</td>
</tr>
<tr>
<td>Axis X</td>
<td>System</td>
</tr>
<tr>
<td>Axis XI</td>
<td>Region</td>
</tr>
</tbody>
</table>

### Axis I: Region
- Chronic pelvic pain
- Specific disease associated pelvic pain
- OR
- Public pain syndrome

### Axis II: System
- Urological
- Gynaecological
- Neurological
- Sexological
- Psychological
- Musculo-skeletal
- Cutaneous

### Axis III: Syndrome
- End-organ as identified from Ia, II, and III
- Urethral
- Testicular
- Epididymal
- Penile
- Scrotal
- Testicular
- Epididymal
- Penile
- Vulvar
- Vestibular
- Clitoral

### Axis IV: Referral characteristics
- Proximal
- Distal
- Perineal
- Buttocks
- Thighs

### Axis V: Temporal characteristics
- Acute
- Chronic
- Sporadic
- Cyclic
- Continuous

### Axis VI: Character
- Aching
- Burning
- Stabbing
- Electric

### Axis VII: Associated symptoms
- Urological
  - Frequency
  - Nocturia
  - Hesitance
  - Dysfunctional flow
  - Urge
  - Incontinence
- Gynaecological
  - Menstrual
  - Menopause
- Gastrointestinal
  - Constipation
  - Diarrhoea
  - Bloatedness
  - Urge
  - Incontinence
- Neurological
  - Dysaesthesia
  - Hyperaesthesia
  - Allodynia
  - Hyperalgesia
- Sexological
  - Dyspareunia
  - Sexual avoidance
  - Erectile dysfunction
- Psychological
  - Anxiety
  - Depression
  - PTSD

### Axis VIII: Psychological symptoms
- Anxiety
  - About pain or putative cause of pain
  - Catastrophic thinking about pain
- Depression
  - Attributed to pain or impact of pain
  - Attributed to other causes
  - Unattributed
- PTSD

### Axis IX: Referral characteristics
- DOI
  - Acute
  - Chronic
- ONG
  - Acute
  - Chronic
  - Sporadic
  - Cyclic
  - Continuous
- Pain
  - Filling
  - Emptying
  - Immediate post
  - Late post
  - Trigger
  - Provoked
  - Spontaneous

### Axis X: System
- Urological
- Gynaecological
- Neurological
- Sexological
- Psychological
- Musculo-skeletal
- Cutaneous

### Axis XI: Region
- Pelvic floor muscle
- Abdominal muscle
- Spinal
- Coccyx

### Table Data
- Table 5: EAU classification of chronic urogenital pain syndromes includes various categories such as region, system, end-organ as pain syndrome, and associated symptoms with specific examples for each category.
2.5.3  **Pain syndromes**

The original EAU classification (31) was inspired by the IASP classification (19) and much work around what has become known as “pain as a disease” and its associated psychological, behavioural, sexual and functional correlates. After 10 years work developing the initial ideas, an updated version was accepted by IASP Council for publication in January 2012.

2.5.3.1  **Definition of chronic pelvic pain (CPP)**

Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction.

[*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localised the pain as being perceived in the specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least 6 months. That is, it can be cyclical over a 6-month period, such as the cyclical pain of dysmenorrhoea. Six months is arbitrary, however, it was chosen because 3 months was not considered long enough if we include cyclical pain conditions. If non-acute and central sensitisation pain mechanisms are well documented, then the pain may be regarded as chronic, irrespective of the time period.

Cyclical pain is included in the classification and hence dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be subdivided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology. For the purpose of this classification, the term “specific disease-associated pelvic pain” is proposed for the former, and “chronic pelvic pain syndrome” for the latter. The following classification only deals with CPPS.

2.5.3.2  **Definition of chronic pelvic pain syndrome**

Chronic pelvic pain syndrome (CPPS) is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. CPPS is a subdivision of CPP.

2.5.3.2.1 Further subdivision of CPPS

Pain perception in CPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome, fibromyalgia or Sjögren’s syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an end-organ term such as BPS (Table 6). The use of such a phrase with the terminology “syndrome” indicates that, although peripheral mechanisms may exist, CNS neuromodulation may be more important and systemic associations may occur. When the pain is localised to more than one organ site, the term CPPS should be used. Many, including some of the authors of this text, never subordinate by anatomy and prefer to refer to patients with pain perceived within the pelvis and no specific disease process as suffering from CPPS, subdivided by psychological and functional symptoms.

2.5.3.2.2 Psychological considerations for classification

Many CPPSs are associated with a range of concurrent negative psychological, behavioural and sexual consequences that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships. Both anxiety and depression can be significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients’ report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. It is suggested that CPPS sometimes creates a sense of helplessness that can be reported as overwhelming, and may be associated with the refractory nature of the patients’ symptoms. It is important to note that many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of salience for any one individual suffering from CPPS. In all patients with CPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable...
characteristics of the syndrome).

2.5.3.2.3 Functional considerations for classification

Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and hence the bowel control is abnormal. The term is not used in the sense of a psychiatric functional disorder. Many CPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype.

Functional pain disorders may not express significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

2.5.3.2.4 Multisystem subdivision

It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multisystemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the authors have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS.

2.5.3.2.5 Dyspareunia

Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically subdivided into superficial and deep.

2.5.3.2.6 Perineal pain syndrome

Perineal pain syndrome is a neuropathic-type pain that is perceived in the distribution area of the pudendal nerve, and may be associated with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Perineal pain syndrome should be distinguished from pudendal neuralgia, which is a specific disease associated with pelvic pain that is caused by nerve damage.
## Table 6: Urological pain syndromes

<table>
<thead>
<tr>
<th>Urological Pain Syndromes - Chapter 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Bladder pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Scrotal pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Testicular pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Epididymal pain syndrome</strong></td>
</tr>
<tr>
<td>Syndrome</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td><strong>Penile pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Urethral pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Postvasectomy scrotal pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Gynaecological Pain Syndromes: external genitalia - Chapter 4</strong></td>
</tr>
<tr>
<td><strong>Vulvar pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Generalised vulvar pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Localised vulvar pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Vestibular pain syndrome</strong></td>
</tr>
<tr>
<td><strong>Clitoral pain syndrome</strong></td>
</tr>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Endometriosis-associated pain syndrome</td>
</tr>
<tr>
<td>CPPS with cyclical exacerbations</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
</tr>
<tr>
<td>Pelvic floor muscle pain syndrome</td>
</tr>
<tr>
<td>Coccyx pain syndrome</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
</tr>
</tbody>
</table>
2.6 Conclusions and recommendations: CPP and mechanisms

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPPS mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.</td>
<td>2</td>
</tr>
<tr>
<td>The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.</td>
<td>1</td>
</tr>
<tr>
<td>End-organ function can also be altered by the mechanisms of neuroplasticity and neuropathic pain, so that symptoms of function can also occur.</td>
<td>1</td>
</tr>
<tr>
<td>CPP is associated with a high impact on QoL.</td>
<td>1</td>
</tr>
<tr>
<td>The diagnosis of a CPPS as a pain syndrome is essential as it encourages a holistic approach to management with multispecialty and multidisciplinary care.</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of those involved in the management of CPP should have an understanding and training in CPPS pain mechanisms.</td>
<td>A</td>
</tr>
<tr>
<td>The early assessment of patients should involve not only investigations aimed at specific disease-associated pelvic pain but also assessment of functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation.*</td>
<td>A</td>
</tr>
<tr>
<td>CPPS patients should be managed in a multispecialty and multidisciplinary environment with consideration of all their symptoms.</td>
<td>A</td>
</tr>
<tr>
<td>Future classification should involve consideration of all three recommendations above.</td>
<td>A</td>
</tr>
</tbody>
</table>

CPP = chronic pelvic pain; CPPS = chronic pelvic pain syndrome.
* Instruments for assessment see Chapter 8.

2.7 An algorithm for CPP diagnosis and treatment

The algorithm for diagnosing and treating CPP (Figure 2) has been developed to guide a physician through the process from diagnosis to management. A physician should follow the lines by answering the appropriate questions with yes or no. By doing this the clinician will end up at a box that refers to the chapter in this guideline that contains all the information needed.

Because CPP is pain perceived in structures related to the pelvis, it is necessary to approach a patient diagnosed with CPP as a chronic pain patient. Confining the diagnosis to a specific organ may overlook multisystem functional abnormalities requiring individual treatment and general aspects of pain in planning investigation and treatment. This idea is easily recognised in the algorithm where the division in specific disease associated pain is made on one hand and pelvic pain syndrome on the other.

The algorithm also illustrates that the authors advocate early involvement of a multidisciplinary pain team. In practice, this should mean that well-known diseases, e.g. ‘true’ cystitis and endometriosis, will be diagnosed and treated early. If treating such conditions does not reduce symptoms, or such well-defined conditions are not found, then further investigation may be necessary, depending on where the pain is localised.

Every chapter of this guideline shows specific algorithms that assist the clinician in decision making. It should be noted, however, that over-investigation may be as harmful as not performing appropriate investigations. The EAU algorithms introduce the concept of the ‘minimum investigations’ required to exclude a well-defined condition.
Figure 2: An algorithm for diagnosing and managing CPP

Chronic Pelvic Pain

History

Physical examination

Symptom of a well known disease

Specific disease associated pelvic pain

Treat according to specific disease guidelines

Pelvic pain syndrome

Organ specific symptoms present

no

Go to: Pain management (Fig. 3)

yes

urology

see chapter 3

gynaecology

see chapter 4

gastro-enterology

see chapter 5

neurology

see chapter 6

sexology

see chapter 7

pelvic floor

see chapter 9

Figure 3: An algorithm for pain management

Multidisciplinary team

Holistic approach

Psychology

Physiotherapy

Pain medicine

see chapter 8

see chapter 9

see chapter 10
Figure 4: Phenotyping and assessment algorithm for CPP

<table>
<thead>
<tr>
<th>Phenotyping</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urology</td>
<td>Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry</td>
</tr>
<tr>
<td>Psychology</td>
<td>History of negative experiences, important loss, coping mechanism, depression</td>
</tr>
<tr>
<td>Organ specific</td>
<td>Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints</td>
</tr>
<tr>
<td></td>
<td>Gynaecological examination, rectal examination</td>
</tr>
<tr>
<td>Infection</td>
<td>Semen culture and urine culture, vaginal swab, stool culture</td>
</tr>
<tr>
<td>Neurological</td>
<td>Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function</td>
</tr>
<tr>
<td>Tender muscle</td>
<td>Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles</td>
</tr>
</tbody>
</table>

2.8 References


3. UROLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

3.1 Prostate pain syndrome

3.1.1 Introduction

Chronic pain in the region of the prostate has been linked to the term “prostatitis” in the past, although there is a proven bacterial infection in only 10% of the cases (1). The remaining 90% should be classified as prostate pain syndrome (PPS), based on the fact that there is no proven infection or other obvious pathology. If CPP cannot be clearly ascribed to the prostate or another organ of the pelvis, the condition is defined more generally as CPPS, as outlined in Chapter 2.

3.1.2 Definition

Prostate pain syndrome is the occurrence of persistent or recurrent episodic pain in the region of the prostate over at least 3 out of the past 6 months, which is convincingly reproduced by prostate palpation. There is no proven infection or other obvious local pathology. PPS is often associated with negative cognitive, behavioural, sexual, or emotional consequences (2), as well as with symptoms suggestive of lower urinary tract and sexual dysfunction (3,4). According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) classification, this correlates to CP/CPPS (Cat. III). Laboratory diagnosis goes along with sterile specimen cultures and either significant, or insignificant, white blood cell counts in prostate-specific specimens (i.e. semen, expressed prostatic secretions and urine collected after prostate massage) (5). At present, there are no clinically relevant diagnostic or therapeutic consequences arising from differentiating inflammatory from non-inflammatory PPS (according to NIH definition), therefore, they are considered here as one entity.

3.1.3 Pathogenesis

Pain is the main symptom in PPS. As a common feature of chronic pain syndromes, no single aetiological explanation has been found. One explanation (6) is that the condition probably occurs in susceptible men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological inflammatory state and/or neurogenic injury, creating acute and then chronic pain. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state (see Chapter 2) (6). This could also explain why tissue damage is not usually found in PPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPS. As outlined earlier, PPS patients have been shown to report higher visual analogue scale scores than controls to short bursts of noxious stimuli to the perineum but not to the anterior thigh (7). This implies an altered sensation in the perineum compared with healthy controls similar to other chronic pain syndromes.

3.1.4 Epidemiology

There is only limited information on the true prevalence of PPS in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostate syndrome and BPS), purely symptom-based case definitions may not reflect the true prevalence of PPS (8,9). Prostatitis was diagnosed in 8% of all visits.
to urologists and 1% of all primary care physicians annually in the USA (10). In a systematic review of the literature, the population-based prevalence of prostatitis symptoms was found to be 8.2% (range: 2.2-9.7%) (11). In two recent studies not included in this review, prevalence was found to be 2.7% (4) and 2% (12). A prospective Italian survey of visits to a urologist for a physician-assigned diagnosis of prostatitis revealed a prevalence of 12.8%. Among these, ~40% had clinical features of PPS (13). In a self-reported, population-based, cross-sectional study of Finnish men aged 20-59 years, the overall lifetime prevalence of prostatitis was as high as 14.2% (14). The risk of prostatitis increased with age (men aged 50-59 years had a 3.1-fold greater risk than those aged 20-39 years). Usual clinical treatment in North American populations has been studied in two studies of sufficient quality. In the follow-up of a cohort of men with PPS-like symptoms based on the NIH Prostatitis Symptom Index (NIH-CPSI) pain and voiding domains, 63% still suffered from persistent symptoms, in contrast to 3% of controls with newly developing symptoms (15). Patients with more severe symptoms were more likely to report symptoms 1 year later. In addition, symptoms substantially improved for up to 6 months follow-up, but then remained unchanged (16).

3.1.5 Diagnosis

Prostate pain syndrome is a symptomatic diagnosis, which is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other lower urinary tract pathology, for a minimum of 3 out of the past 6 months. This implies that specific disease-associated pelvic pain caused by bacterial infection, urogenital cancer, urinary tract disease, urethral stricture, and neurogenic disease of the bladder must be ruled out. A thorough history is an important first step in the evaluation of PPS. It should include type of pain and localisation. Pain is often reported in other pelvic areas outside the prostate such as perineum, rectum, penis, testicles and abdomen (17). In addition, associated lower urinary tract symptoms (LUTS), sexual function, psychological, social and economic factors should be addressed. Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument. Quality of life should also be measured because it can be as poor as in acute myocardial infarction, unstable angina pectoris or Crohn’s disease (19,20). In a study by Tripp et al. (2) more pain, pain-contingent rest, and urinary symptoms were associated with greater disability (also measured by self-report), and pain was predicted by depression and by catastrophising (helplessness subscale).

Demographic and social support variables were not associated with either pain or adjustment. Reliable, valid indexes of symptoms and QoL are the NIH-CPSI (17) and the International Prostate Symptom Score (I-PSS) (18). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice and have been translated and validated for many European languages.

There is no single “gold standard” diagnostic test for PPS, therefore, procedures are on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Physical examination including digital rectal examination should be carried out. Muscle tenderness and trigger points in the pelvic floor may be palpated. Measurement of resting urine by ultrasound should exclude incomplete voiding. Prostate-specific antigen testing does not help to diagnose PPS but can exclude prostate cancer in patients at risk.

Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation (21). Besides sterile pre-massage urine (voided bladder urine-2), PPS shows < 10,000 cfu of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) (22). In an extensive analysis of both tests, PPMT was able to indicate the correct diagnosis in > 96% of patients (23). Overall, these tests help only a little in the diagnosis of PPS, because 8% of patients with suggested PPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic (24).

In PPS, urodynamic studies should be considered in patients with significant LUTS. They may demonstrate decreased urinary flow rates, incomplete relaxation of the bladder neck and prostatic urethra, as well as abnormally high urethral closure pressure at rest. The external urethral sphincter may be dysfunctional (non-relaxing) during voiding (25). As for non-PPS cases, cystoscopy may be considered for further evaluation of micturition symptoms to exclude bladder outlet or urethral pathology, or if haematuria or infection has been found to exclude intravesical pathology.

A general algorithm for assessment and treatment of PPS is shown in Figure 5.
3.1.6  **Conclusions and recommendations: assessment/diagnosis PPS**

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPS is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.</td>
<td>2b</td>
</tr>
<tr>
<td>PPS has no known single aetiology.</td>
<td>3</td>
</tr>
<tr>
<td>Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.</td>
<td>2a</td>
</tr>
<tr>
<td>PPS has a high impact on QoL.</td>
<td>2b</td>
</tr>
<tr>
<td>Depression and catastrophic thinking are associated with more pain and poorer adjustment.</td>
<td>3</td>
</tr>
<tr>
<td>The prevalence of PPS-like symptoms is high in population-based studies (&gt; 2%).</td>
<td>2b</td>
</tr>
<tr>
<td>There is significant overlap of symptoms with other conditions.</td>
<td>2b</td>
</tr>
<tr>
<td>Reliable instruments assessing symptom severity as well as phenotypic differences exist.</td>
<td>2b</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific diseases with similar symptoms must be excluded. It is therefore recommended to adapt diagnostic procedures to the patient and to aim at identifying them.</td>
<td>A</td>
</tr>
<tr>
<td>After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with prostate pain syndrome.</td>
<td>A</td>
</tr>
<tr>
<td>A validated symptom and quality of life scoring instrument, such as the NIH-CPSI, should be considered for initial assessment as well as for follow-up.</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to assess prostate pain syndrome associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.</td>
<td>B</td>
</tr>
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</table>

3.1.7  **Treatment**

There is a large discrepancy in the treatment effects reported in case series and controlled trials that results from a large placebo effect or publication bias. As a result of the multifactorial origin of PPS, one reason for treatment failure in some large randomised placebo-controlled trials may be the heterogeneity of the patient population. Thus, one strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for PPS has shown significant improvement of symptoms and QoL (26). Monotherapeutic strategies for the treatment of PPS may fail (27), therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past 10 years, results from RCTs have led to advances in standard and novel treatment options.

3.1.7.1  **Alpha-blockers**

Positive results from RCTs of alpha-blockers, i.e. terazosin (28,29), alfuzosin (30) doxazosin (31,32) and tamsulosin (33) have led to widespread use of alpha-antagonists in the treatment of PPS in recent years. The effects of alpha-antagonists may include improved outflow performance by blocking the alpha-receptors of the bladder neck and prostate and by direct action on alpha1A/1D receptors in the CNS (33). In contrast, an earlier meta-analysis of nine trials (n = 734) did not show a beneficial effect on pain (34). Moreover, in accordance with an earlier negative report on tamsulosin (35), one adequately powered large placebo-controlled randomised trial of 12 weeks treatment with alfuzosin failed to show any significant difference in the outcome measures, with the exception of the score for ejaculation of the Male Sexual Health Questionnaire scores (showing significant improvement in the alfuzosin group compared to the placebo group, P = 0.04) (36). Regarding safety, this large trial reported similar adverse event rates in the treatment and placebo groups. The most recent in-depth systematic review and network meta-analysis of alpha-blockers (37) has shown significant improvement in symptoms, with standardised mean differences in total symptom, pain, voiding, and QoL scores of -1.7 [95% confidence interval (CI): -1.8 to -0.3], -1.1 (95% CI: -1.8 to -0.3), 1.4 (95% CI: -2.3 to -0.5), and -1.0 (95% CI: -1.8 to 0.2), respectively. In addition, they had a higher rate of favourable response compared to placebo (pooled relative risk of 1.6 (95% CI: 1.1-2.3). However, this finding was associated with publication bias for smaller studies. Overall, alpha-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPS patients (36). Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g. patients with PPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.
3.1.7.2 Antibiotic therapy
Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for 4-6 weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS (38), and prostate biopsy culture findings do not differ from those of healthy controls (39). The only randomised placebo-controlled trials of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (6 weeks) (35), levofloxacin (6 weeks) (40), and tetracycline hydrochloride (12 weeks) (41). These have been analysed in a recently published meta-analysis (37). Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom scores (-9.8; 95% CI: -15.1 to -4.6), pain scores (-4.4; 95% CI: -7.0 to -1.9), voiding scores (-2.8; 95% CI: -4.1 to -1.6), and QoL scores (-1.9; 95% CI: -3.6 to -0.2) compared with placebo. Overall, antibiotic treatment of PPS is based only on weak evidence. Combination therapy of antibiotics with alpha-blockers has shown even better outcomes in network meta-analysis. However, sample sizes of the studies were relatively small and treatment effects were only modest and most of the time below clinical significance. It may be speculated that patients profiting from treatment have had some unrecognised uropathogens. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over 6 weeks.

3.1.7.3 Anti-inflammatory drugs
For non-steroidal anti-inflammatory drugs, only two RCTs have been published. The first was for rofecoxib, which is no longer on the market; statistical significance over placebo was achieved in some of the outcome measures (42). In the second trial with celecoxib, pain subscore, QoL subscore, and total NIH-CPSI score were in favour of the treatment arm versus placebo, but effects were limited to the duration of therapy (43). A leukotriene antagonist, zafirlukast, has been evaluated in a small randomised placebo-controlled study of patients treated with concomitant doxycycline (44). This study was negative but had a lack of power. For corticosteroids, no significant benefits were shown in a low-power, placebo-controlled, randomised pilot study of a short course of oral prednisolone (45). In a recent meta-analysis, two studies of NSAIDs (40,43) and one with prednisolone (45) were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo (total n = 190, RR: 1.8; 95% CI: 1.2-2.6). Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies should be done for final confirmation, and long-term side effects have to be taken into account.

3.1.7.4 Opioids
Opioids produce modest pain relief in some patients with refractory PPS, although there are limited data on the long-term efficacy of opioids in non-cancer pain. Opioid treatment carries the risks of side effects, reduced QoL, addiction, opioid tolerance and opioid-induced hyperalgesia (46). Urologists should use opioids for PPS only in collaboration with pain clinics and with other treatments.

3.1.7.5 5-alpha-reductase inhibitors
Although a few small pilot studies with 5-alpha-reductase inhibitors supported the view that finasteride may improve voiding and pain, the first placebo-controlled randomised trial published in a peer-reviewed journal did not support this, but the study did lack power (47). In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a 1-year period, but lacked a placebo-control arm (48). A 6-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power (49). Based on these data, 5-alpha-reductase inhibitors cannot be recommended for use in PPS.

3.1.7.6 Allopurinol
An RCT of allopurinol was conducted based on the hypothesis that urine reflux intoprostatic ducts causes prostatic inflammation via high concentrations of purine and pyrimidine base-containing metabolites in prostatic secretions (50). However, positive results have not been considered sufficient for recommendation by reviewers of the Cochrane Database (51). In addition, a recent randomised placebo-controlled trial of allopurinol as an adjunct to ofloxacin has not shown any benefit (52).

3.1.7.7 Phytotherapy
Positive effects of phytotherapy have been documented. Although a validated symptom score was not used, an RCT of a pollen extract (Prostat/Poltit) showed significant symptom improvement (53). An adequately powered randomised placebo-controlled study of Cernilton, another pollen extract, showed clinically significant symptom improvement over a 12-week period in inflammatory PPS patients (NIH Cat. IIIA) (54). The effect was mainly based on a significant effect on pain. Quercetin, a polyphenolic bioflavonoid with documented
antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT (55).
In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not
improve symptoms over a 1-year period (48). In a systematic review and meta-analysis, patients treated
with phytotherapy were found to have significantly lower pain scores than those treated with placebo (37). In
addition, overall response rate in network analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

3.1.7.8 Pentosan polysulphate
High-dose oral pentosan polysulphate (3 300 mg/day), as for BPS, is able to improve clinical global assessment
and QoL significantly over placebo in men with PPS, suggesting a possible common aetiology (56).

3.1.7.9 Muscle relaxants
Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal
muscle spasm, but there have been only a few prospective clinical trials to support these claims. In a recent
RCT, a triple combination of a muscle relaxant (tiocolchicoside), an anti-inflammatory drug (ibuprofen) and an
alpha-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an alpha-blocker alone
(32).

3.1.7.10 Pregabalin
Pregabalin is an antiepileptic drug that has been approved for use in chronic postherpetic neuralgia,
fibromyalgia, and diabetic neuropathy. In an adequately powered randomised placebo-controlled study, a
6-week course of pregabalin (n = 218) compared to placebo (n = 106) did not result in a significant reduction of
NIH-CPSI total score by at least 6 points (57).

3.1.7.11 Botulinum toxin A
Botulinum toxin A (BTX-A) may have pain-alleviating effects through non-neuromuscular action on afferent
nociceptive pathways. Local treatment with perirethral injection of BTX-A (200 U) has been tested in a small
pilot study with improvement in pain and changes in urethral pressure profile (58). A small randomised placebo-
controlled study of perineal skeletal muscle injection (100 U) has been published recently (59). Some effect
was found in the global response assessment and the NIH-CPSI pain subdomain score. However, patient
number was too low (13 in the BTX-A group and 16 in the placebo group), and follow-up was too short to draw
definitive conclusions.

3.1.7.12 Physical treatments
- Electromagnetic therapy. In a small, sham-controlled, double-blind study, 4 weeks electromagnetic
  therapy showed a significant, sustained effect over a 1-year period (60).
- Microwave thermotherapy. Significant symptomatic improvement has been reported from heat
  therapy, for example, transrectal and transurethral thermotherapy (61,62), but there was no sham-
  control.
- Extracorporeal shock wave therapy. A recent sham-controlled double-blind study of four times weekly
  perineal extracorporeal shock wave therapy (n = 30) showed significant improvement in pain, QoL,
  and voiding compared to the control group (n = 30) over 12 weeks (63). Confirmatory studies are
  awaited because of an absent placebo-effect, which is very unusual in PPS trials.
- Electroacupuncture. In a small three-arm randomised trial, electroacupuncture was superior to sham
  treatment and advice and exercise alone (64). In a recent prospective case series of 6 weeks of weekly
  electroacupuncture of 97 patients with PPS, 92% showed significant improvement in total NIH-CPSI
  score. Based on these studies, no definitive conclusion can be drawn.
- Posterior tibial nerve stimulation. One sham-controlled medium-sized study (n = 89) demonstrated
  significant improvement in total NIH-CPSI score and visual analogue scale for pain (65).
- Myofascial physical therapy. A randomised feasibility trial of myofascial physical therapy including PPS
  (n = 21) and patients with BPS showed a clinical benefit compared to global therapeutic massage (66).
  In the PPS group alone, there was no difference in the effect between the two treatment arms.

3.1.7.13 Surgical management
Surgical management, including transurethral incision of the bladder neck, radical transurethral resection of
the prostate, or in particular, radical prostatectomy, has a very limited role and requires an additional, specific
indication. In addition, the treatment effect of transurethral needle ablation of the prostate (TUNA) was only
comparable to sham treatment in two small randomised trials (67,68).

3.1.7.14 Psychological treatment
It is of note that QoL decreases as symptoms increase. Given prediction of QoL by psychological problems
(depression and catastrophising in particular), this means that psychological status should also be targeted in treatment, and the development of a psychologically focused treatment for patients refractory to drug treatment has been noted by the authors of the summary findings from the NIH Chronic Prostatitis Collaborative Research Network studies (69). There are no RCTs of psychological treatment for men with CPP, but Tripp et al. (70) have completed a feasibility trial, which represents the only known account of psychological treatment. Their 8-h intervention improved pain, catastrophising, and QoL, but not depression or some urinary symptoms. Details concerning appropriate treatment content and delivery are contained in Chapter 8.

3.1.8 Conclusions and recommendations: treatment of PPS

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapeutic treatment regimens in PPS may fail.</td>
<td>3</td>
</tr>
<tr>
<td>Phenotypically directed treatment may improve treatment success.</td>
<td>3</td>
</tr>
<tr>
<td>Alpha-blockers have moderate treatment effect regarding total pain-, voiding-, and QoL scores in PPS.</td>
<td>1a</td>
</tr>
<tr>
<td>Antimicrobial therapy has a moderate effect on total pain-, voiding-, and QoL scores in PPS.</td>
<td>1a</td>
</tr>
<tr>
<td>NSAIDs have moderate overall treatment effects on PPS.</td>
<td>1a</td>
</tr>
<tr>
<td>There are insufficient data on the effectiveness of steroids in PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>There are insufficient data on the effectiveness of opioids in PPS.</td>
<td>4</td>
</tr>
<tr>
<td>There are insufficient data on the effectiveness of 5-alpha-reductase inhibitors in PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>There are insufficient data on the effectiveness of allopurinol in PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPS.</td>
<td>1a</td>
</tr>
<tr>
<td>Pentosan polysulphate improves global assessment and QoL score in PPS.</td>
<td>1b</td>
</tr>
<tr>
<td>There are insufficient data on the effectiveness of muscle relaxants in PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>Pregabalin is not effective for the treatment of PPS.</td>
<td>1b</td>
</tr>
<tr>
<td>BTX-A injection into the pelvic floor may have a modest effect in PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>There are only limited data on the effectiveness of electromagnetic therapy in PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>There are only limited data on the effectiveness of microwave thermotherapy in PPS.</td>
<td>3</td>
</tr>
<tr>
<td>Perineal extracorporeal shock wave therapy probably is effective for the treatment of PPS.</td>
<td>1b</td>
</tr>
<tr>
<td>There are limited data on the effectiveness of electroacupuncture for the treatment of PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>Posterior tibial nerve stimulation is probably effective for the treatment of PPS.</td>
<td>1b</td>
</tr>
<tr>
<td>There are insufficient data on the effectiveness of myofascial physical therapy for the treatment of PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>There are limited data on lack of effectiveness of TUNA of the prostate for PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPS.</td>
<td>3</td>
</tr>
<tr>
<td>Cognitive behavioural therapy designed for PPS may improve pain, and QoL.</td>
<td>3</td>
</tr>
</tbody>
</table>
Recommendations

Consider multimodal and phenotypically directed treatment options for PPS. B

Alpha-blockers are recommended for patients with a duration of PPS < 1 year. A

Single use of antimicrobial therapy (quinolones or tetracyclines) is recommended in treatment-naïve patients over a minimum of 6 weeks with a duration of PPS < 1 year. A

NSAIDs are recommended for use in PPS, but long-term side effects have to be considered. B

Allopurinol is not recommended for use in PPS. B

Phytotherapy might be used in patients with PPS. B

Consider high-dose pentosan polysulphate to improve symptoms and quality of life in PPS. A

Pregabalin is not recommended for use in PPS. A

Perineal extracorporeal shock wave therapy might be considered for the treatment of PPS. B

Electroacupuncture might be considered for the treatment of PPS. B

Posterior tibial nerve stimulation might be considered for the treatment of PPS. B

TUNA of the prostate is not recommended for the treatment of PPS. B

For PPS with significant psychological distress, psychological treatment focussed on PPS should be attempted. B

PPS = prostate pain syndrome; TUNA = transurethral needle ablation.

Figure 5: Assessment and treatment algorithm for PPS

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td>Uroflowmetry</td>
<td>Alpha-blockers when duration is &lt; 1 year</td>
</tr>
<tr>
<td>Transrectal US prostate</td>
<td>Single use antibiotics (6 weeks) when duration is &lt; 1 year</td>
</tr>
<tr>
<td>NIH-CPSI scoring list</td>
<td>High dose Pentosan polysulfate to improve QoL and symptoms</td>
</tr>
<tr>
<td>Phenotyping</td>
<td>Grade B recommended</td>
</tr>
<tr>
<td>Pelvic floor muscle testing</td>
<td>NSAIDs. Be aware of long-term side effects</td>
</tr>
<tr>
<td></td>
<td>Phytotherapy</td>
</tr>
<tr>
<td></td>
<td>Perineal extracorporeal shock wave therapy</td>
</tr>
<tr>
<td></td>
<td>Electroacupuncture</td>
</tr>
<tr>
<td></td>
<td>Percutaneous tibial nerve stimulation (PTNS)</td>
</tr>
<tr>
<td></td>
<td>Psychological treatment focused on the pain</td>
</tr>
<tr>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Allopurinol [B]</td>
</tr>
<tr>
<td></td>
<td>Pregabalin [A]</td>
</tr>
<tr>
<td></td>
<td>TransUrethral Needle Ablation (TUNA) [B]</td>
</tr>
</tbody>
</table>

3.1.9 References


http://www.ncbi.nlm.nih.gov/pubmed/9510337
http://www.ncbi.nlm.nih.gov/pubmed/9170224


3.2  Bladder pain syndrome

3.2.1  Introduction

Interstitial cystitis (IC) describes a chronic, distressing bladder condition (1). The so-called ulcer, which is a typical cystoscopic finding in 10-50% of IC patients, was first described by Guy Hunner at the beginning of the last century (2,3). Subsequent research (4-6) has shown that IC encompassed a heterogeneous spectrum of disorders, with different endoscopic and histopathological presentations, with inflammation an important feature in only a subset of patients. To embrace all patients suffering from bladder pain, the terms painful bladder syndrome (PBS) or BPS have been suggested as more accurate when referring to pain in the bladder region, while assuming IC with Hunner’s lesion as a specific type of chronic inflammation of the bladder (7,8). The term BPS was put forward by the International Society for the Study of BPS (ESSIC) and will be used in
these guidelines. In accordance Classic IC (Hunner’s lesion and inflammation) will be referred to as BPS type 3 C (See Chapter 2, section 2.4 ‘Definitions of CPP terminology’).

3.2.2 **Definition**

Although generally accepted, the NIDDK criteria provide only a minimum framework to establish the diagnosis and have been felt to be too restrictive for clinical use (9-12). Recently, the ESSIC has suggested a standardised scheme of diagnostic criteria (13) to make it easier to compare different studies. BPS was preferred as the general term to match the current taxonomy of chronic pain syndromes.

3.2.3 **Diagnosis**

Bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 7) (8).

**Table 7: ESSIC classification of types of BPS according to the results of cystoscopy with hydrodistension and biopsies (8)**

<table>
<thead>
<tr>
<th>Cystoscopy with hydrodistension</th>
<th>Normal</th>
<th>Glomerulations(^a)</th>
<th>Hunner’s lesion(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>XX</td>
<td>1X</td>
<td>2X</td>
</tr>
<tr>
<td>Normal</td>
<td>XA</td>
<td>1A</td>
<td>2A</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>XB</td>
<td>1B</td>
<td>2B</td>
</tr>
<tr>
<td>Positive(^c)</td>
<td>XC</td>
<td>1C</td>
<td>2C</td>
</tr>
</tbody>
</table>

\(^a\) Cystoscopy: glomerulations grade 2-3  
\(^b\) Lesion per Fall’s definition with/without glomerulations  
\(^c\) Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Beyond subtyping, recent work has indicated the need to phenotype BPS patients. The - Urinary, Psychosocial, Organ Specific, Inflammation, Neurological/Systemic, Tenderness - UPOINT phenotyping system classifies patients according to clinically relevant domains, facilitating the use and appraisal of multimodal therapies (14).

3.2.4 **Pathogenesis**

Current thought implicates an initial unidentified insult to the bladder, triggering inflammatory, endocrine and neural phenomena (15-17). This may happen in patients with an underlying systemic defect. In fact, BPS is similar and frequently precedes, coexists or follows other so-called functional somatic syndromes (FSSs), occurring predominantly in women, with pain as the main symptom, no abnormal laboratory or anatomical findings, and exacerbated by stress, namely fibromyalgia (FM), IBS and chronic fatigue syndrome (CFS) (17-19). At the bladder level, multiple aetiological or pathophysiological mechanisms have been and are still sought after.

No infection has as yet been implicated (20-25). BPS patients and controls have equal UTI frequency (18,26). Nevertheless, UTI and urgency are significantly more frequent during childhood and adolescence, in patients who later develop BPS in adulthood (27). Pancystitis, with associated perineural inflammatory infiltrates, is an essential part of BPS type 3 C (23), but is scant in non-ulcer BPS (6). There is a 10-fold increase in the mast cell count in bladder tissue from patients with BPS type 3 C compared with controls. Mast-cell-secreted mediators (28,29) can indeed induce symptoms and findings of BPS type 3 C (30). In non-ulcer BPS, however, the mast cell count is normal or only slightly increased (6,29,31,32).

Cystoscopic and biopsy findings in both ulcer and non-ulcer BPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose the submucosal nerve filaments to noxious urine components (33-37). Furthermore, urinary uronate, and sulphated GAG levels are increased in patients with severe BPS (38). Uroplakin III-delta 4, caveolin-1, acid-sensing channels 2a and 3, muscarinic (M2-5) and purinergic receptors (P2X2 and P2X1), bradykinin B1 receptor, and cannabinoid receptor CB1 are also
upregulated and bladder urothelial sensitivity to carbachol enhanced in urothelial cells of BPS patients (39-41). In contrast, tight junction proteins zona occludens-1, junctional adherins molecule -1, and occludin genes are downregulated. Luminal nitric oxide (NO) urinary levels and inducible NO synthetase activity (iNOS) are increased in BPS patients (42). Urinary NO is significantly increased in ulcer patients and decreases with treatment, but not in non-ulcer BPS patients (43). iNOS-dependent NO production may have a role in urothelial dysfunction (44). Altogether, these data further point to increased urothelial permeability. Moreover, constituents of urine may exert a cytotoxic effect (45), especially in situations such as altered urothelial barrier or existence of unsialylated Tamm-Horsfall protein observed in BPS (46,47). Along with altered gene regulation, post translational epigenetic conditioning through micro RNA interference with messenger RNA transcription, may perpetuate the answer to aggression mode, induced on urothelial cells by an initial insult (39,48).

Microvascular alterations are present in BPS. Despite unaltered number of microvessels, the ratio of mature to total vessels is significantly lower (49) and decreased bladder perfusion upon filling is observed in BPS patients (50). Adding to that, proangiogenic vascular endothelial growth factor and hypoxia inducible factor (HIF)-1 expression is increased in the urothelium of BPS patients (49,51).

Involvement of neurogenic inflammation as the trigger to a cascade of events in BPS has been confirmed by multiple observations documenting its occurrence, followed by neuroplasticity and neuronal sensitisation, both in the peripheral and CNS of BPS patients. Thus, bladder sensory nerve fibres can induce bladder wall events through neurogenic inflammation sparked by an initial insult, as well as pain regionalisation and centralisation. In fact, several data have shown enhanced bladder peripheral nerve density and increased peripheral neuromediator release, along with neurotrophin and nerve fibre receptor increases, especially in sensory and sympathetic nerves. Furthermore, besides cytokines from umbrella cells, activation of mast cells in close proximity to nerve terminals can be influenced by oestriadiol as well as corticotrophin-releasing hormone (52-58). Regionalisation of pain is observed frequently in BPS patients (59). Moreover, autonomic responses and CNS processing of afferent stimuli are altered in patients with BPS (55,60,61).

Some of the clinical and histopathological characteristics are similar to autoimmune phenomena. However, only some BPS patients demonstrate autoantibodies, immune deposits or complement activation (62-69). Of note, differing T-cell infiltrates and B-cell nodules are seen in BPS type 3 C (70).

3.2.5 Epidemiology

Reports of the prevalence of BPS have varied greatly, along with the diagnostic criteria and populations studied. Recent reports generally show higher figures than earlier ones, ranging from 0.06% to 30% (71-80). There is a female predominance of about 10:1 (4,71,81,82) but contrary to prior belief, possibly no difference in race or ethnicity (83-85). The relative proportions of classic and non-ulcer disease are unclear. Incidence in various studies has ranged from 5 to 50% (5,12,86,87).

Evidence that BPS may have a genetic component has been presented in several studies, but may contribute to less than one third of total variation in susceptibility for BPS, with the remainder being environmental (19,88-91).

BPS has significant economic costs. Direct annual costs in the USA have been estimated to be $750 million (92).

3.2.6 References

   http://www.archive.org/stream/diseasesofbladd00sken


http://www.icsoffice.org/Abstracts/Publish/45/000009.pdf


3.2.7 Association with other diseases
An association has been reported between BPS and non-bladder syndromes (NBSs) - IBS, FM, CFS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma, systemic lupus erythematosus, inflammatory bowel disease (1-7). Risk of BPS correlates with a number of NBSs in each patient (8). Recent work showing non-ulcer BPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than ulcer patients emphasises the need for subtyping (9).

3.2.8 Diagnosis
The diagnosis of BPS is one of exclusion, using symptoms, examination, urine analysis, cystoscopy with hydrodistension, and biopsy (Figure 6).

The nature of the pain is the key symptom of the disease:
- Pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder content.
- It is located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum.
- Pain is relieved by voiding but soon returns (10-14).
- Pain is aggravated by food or drink (13).

The differences between the two BPS subtypes, BPS type 3 C and non-ulcer, include clinical presentation, age distribution (15), molecular features (16-22), which may be discriminated non-invasively (23), and response to treatment (24-27). BPS type 3 C is a highly damaging inflammation that often leads to a small-capacity fibrotic bladder or upper urinary tract outflow obstruction. This type of progression is not observed in non-ulcer disease (14,28). Endoscopically, BPS type 3 C displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit - the
Hunner lesion (14). The scar ruptures with increasing bladder distension, producing a characteristic waterfall-type of bleeding. There is a strong association between BPS type 3 C and reduced bladder capacity under anaesthesia (14,29,30).

Cystoscopy
Non-ulcer disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign. A recent report has shown that there is no difference in the cystoscopic appearance between patients with non-ulcer disease and women without bladder symptoms about to undergo tubal ligation (31). The observation of glomerulations may however not always be constant over time (32).

Some authors maintain that cystoscopy with hydrodistension provides little useful information in addition to the history and physical examination findings (33,34). In contrast, others have found a strong correlation between pain and cystoscopic findings in patients with untreated BPS, and this difference from the results of other studies may have been due to treatment effects (35). Glomerulations may be involved in the disease mechanism, because such findings are highly associated with overexpression of angiogenic growth factors in the bladder and neovascularisation (36). A recent pilot study has demonstrated feasibility of bladder distension and biopsy under local anaesthesia (37). ESSIC believes objective findings are important and that a standardised scheme of diagnostic criteria would help improve the uniformity and comparability of different studies (38).

Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-ulcer types of the disease (17,38-41). Important differential diagnoses to exclude by histological examination are carcinoma in situ and tuberculous cystitis.

Potassium chloride bladder permeability test has been used in the diagnosis of BPS (41), but recent reports have suggested that it lacks discriminating power (42,43). A modified test using less concentrated solution has been suggested. This test, although painless in contrast to the original procedure, decreases the maximum cystometric volume in 90% of patients with BPS, but not in controls (44). Furthermore, it has been suggested that the potassium sensitivity test can help to predict the response to GAG treatment (45).

Symptom scores may help to describe symptoms in an individual patient and as outcome measures. The O’Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) has recently been validated successfully in a large study (46).

Biological markers
It is an attractive idea to support or, even better, to confirm the clinical diagnosis using a biological marker. Finding a universally helpful one is hampered by heterogeneity within the diagnostic group of BPS. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, uroplakin III delta-4 mRNA, and YKL-40 have all presented as potential candidates (47-49). NO is interesting because of its ability to discriminate classic from non-ulcer disease with minimal invasiveness. However, all putative markers to date have yet to be validated (50).

3.2.9 BPS in children and males
According to NIDDK criteria, children aged < 18 years is an exclusion criterion. However, occasional cases of BPS of both subtypes have been identified in patients under this age (51). There is increasing evidence that children aged 2-11 may also be affected, although prevalence figures are low (52). Thus, BPS cannot be excluded on the basis of age.

It has been argued that PPS and BPS are inter-related (53,54). However, differences in urinary markers suggest that BPS and PPS are different disorders with distinct pathophysiology (55).
### Conclusions and recommendations: assessment and diagnosis BPS

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>BPS has no known single aetiology.</td>
<td>3</td>
</tr>
<tr>
<td>Pain in BPS does not correlate with bladder cystoscopic or histologic findings.</td>
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</tr>
<tr>
<td>BPS Type 3 C is not surely distinguishable by non-invasive means.</td>
<td>2a</td>
</tr>
<tr>
<td>Ulcer non-ulcer disease ratios of BPS are highly variable between studies.</td>
<td>2a</td>
</tr>
<tr>
<td>The prevalence of BPS-like symptoms is high in population-based studies.</td>
<td>2a</td>
</tr>
<tr>
<td>BPS associated non-bladder diseases are extremely prevalent, differ in BPS subtypes and correlate with BPS risk.</td>
<td>2a</td>
</tr>
<tr>
<td>BPS has a high impact on quality of life.</td>
<td>2a</td>
</tr>
<tr>
<td>There is significant overlap of symptoms with other conditions.</td>
<td>2a</td>
</tr>
<tr>
<td>Reliable instruments assessing symptom severity as well as phenotypical differences exist.</td>
<td>2a</td>
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<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Specific diseases with similar symptoms have to be excluded. It is therefore recommended to adapt diagnostic procedures to each patient and aim at identifying them.</td>
<td>A</td>
</tr>
<tr>
<td>After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with BPS by subtype and phenotype.</td>
<td>A</td>
</tr>
<tr>
<td>A validated symptom and quality of life scoring instrument should be considered for initial assessment as well as for follow-up.</td>
<td>B</td>
</tr>
<tr>
<td>BPS associated non-bladder diseases should be assessed systematically.</td>
<td>A</td>
</tr>
<tr>
<td>BPS associated negative cognitive, behavioural, sexual, or emotional consequences should be assessed.</td>
<td>A</td>
</tr>
</tbody>
</table>

BPS = Bladder pain syndrome.

### References


   [http://archpsyc.ama-assn.org/cgi/content/abstract/61/3/273](http://archpsyc.ama-assn.org/cgi/content/abstract/61/3/273)


http://www.icsoffice.org/Abstracts/Publish/45/000009.pdf


3.2.12 Medical treatment

Analgesics. Pain is often a dominant symptom, therefore, many patients try commonly used analgesics at some stage of the disease. However, pain relief is disappointing because the visceral pain experienced in BPS responds poorly to analgesic drugs. No systematic studies have been conducted on conventional analgesics. Short-term opioids may be indicated for breakthrough or exacerbated pain and periodic flare-ups. Long-term opioids may be considered after all other available therapeutic options have been exhausted. Urologists should obtain informed consent, arrange for regular follow-up, and be prepared to recognize opioid-induced side effects (1). BPS is a chronic disease, therefore, long-term opioids should be used only exceptionally and under close surveillance.

Corticosteroids. Reports on outcome with corticosteroid therapy have been both promising (2) and discouraging (3). Soucy et al. (4) have suggested a trial of prednisone (25 mg daily for 1-2 months, afterwards reduced to the minimum required for symptom relief) in patients with severe ulcerative BPS, which is otherwise unresponsive to conventional treatment. The side effects of steroids can be very serious, making it difficult to justify their use.

Antiallergics. Mast cells may play a role in BPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 (5) as well as the H2 (6) receptor subtypes, with variable results.

Hydroxyzine is a histamine H1-receptor antagonist, which blocks neuronal activation of mast cells by inhibiting serotonin secretion from thalamic mast cells and neurons (7). Hydroxyzine hydrochloride (Atarax) is usually given, starting with 25 mg at bedtime, increasing to 50 mg/day, or if tolerated, 75 mg. The most common side effects are sedation and generalised weakness, which usually resolve after a period of treatment. In the first series using hydroxyzine, > 90% of patients showed improvement across the whole range of symptoms. Interestingly, improvement was noted in associated symptoms including migraine, IBS and allergies (5).

Although these initial results were supported by a further uncontrolled study (5,8), a prospective RCT of hydroxyzine or sodium pentosan polysulphate compared to placebo failed to show a statistically significant effect (9). However, the study was underpowered, which may be why it failed to demonstrate a statistically significant outcome for either drug compared to placebo. Combination therapy showed the highest response...
rate of 40%, with a placebo response rate of 13%.

**Amitriptyline.** The tricyclic antidepressant amitriptyline has alleviated symptoms in BPS, probably via mechanisms such as blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and noradrenaline, and blockade of histamine H1 receptors. It is also an anxiolytic agent (10). Several reports have indicated amelioration after oral amitriptyline (11-13). In a prospective RCT, 48 patients were treated for 4 months with amitriptyline (14).

Drug dosages were escalated in 25 mg increments at 1-week intervals up to a maximum dosage of 100 mg. Amitriptyline significantly improved the mean symptom score, pain and urgency intensity, whereas frequency and functional bladder capacity improved, but not significantly. In a subsequent, prospective, open-label study (15), a response rate of 64% with an overall mean dose of 55 mg was seen with long-term amitriptyline for 20 months. Patient overall satisfaction was good to excellent in 46%, with significant improvement in symptoms.

A therapeutic response was observed in all 28 patients fulfilling NIDDK criteria and those with a clinical diagnosis of BPS. Anticholinergic side effects (mouth dryness and weight gain) were common and considered to be a drawback of amitriptyline. A multicentre, randomised, double-blind, placebo-controlled clinical trial comparing amitriptyline and placebo plus behavioural modification in 273 patients concluded that amitriptyline may be beneficial at ≥ 50 mg/daily (16). In clinical practice drowsiness is also a limiting factor with amitriptyline and a lower starting dose of 10 mg is often suggested. Nortriptyline is sometimes considered in place of amitriptyline when drowsiness is the limiting factor.

**Pentosan polysulphate sodium** (Elmiron) has been evaluated in double-blind, placebo-controlled studies. Pentosan polysulphate sodium is thought to substitute for a defect in the GAG layer. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported in patients taking the drug compared to placebo (17,18). In an open multicentre study, pentosan polysulphate sodium had a more favourable effect in BPS type 3 C than in non-ulcer disease (19). The normal dose is 150-200 mg twice daily between meals. However, absorption is incomplete. An RCT has compared 300 mg pentosan polysulphate sodium with evaluated dosages of 600 and 900 mg in 380 BPS patients. Mean ICSI scores improved significantly for all dosages (20). However, treatment response was not dose-dependent but related more to treatment duration. At 32 weeks, about half of all patients were responders. Most adverse events were mild and resolved without intervention. In contrast, a prospective RCT comparing pentosan polysulphate sodium and hydroxyzine against placebo failed to demonstrate a statistically significant outcome for either drug, although the former approached statistical significance (P = 0.064) (9). Combination therapy showed the highest response rate of 40% compared to 13% with placebo. For patients with an initial minor response to pentosan polysulphate sodium, additional subcutaneous administration of heparin appeared to be helpful (21).

**Antibiotics.** A prospective pilot RCT of sequential oral antibiotics in 50 patients found that overall improvement occurred in 12/25 patients in the antibiotic group and 6/25 in the placebo group, whereas 10 and 5 patients reported an improvement in pain and urgency, respectively. Antibiotics alone or in combination may be associated with decreased symptoms in some patients, but do not represent a major advance in therapy for BPS (22).

**Immunosuppressants.** Azathioprine, 50-100 mg daily, was given to 38 patients, resulting in disappearance of pain in 22 and urinary frequency in 20 (23). Cyclosporin A (CyA) (24) and methotrexate (25) were initially evaluated in open studies, with a good effect on pain, but a limited effect on urgency and frequency.

More recent studies of CyA have reported promising results (26,27). In 23 patients, daily voiding, maximal bladder capacity, and voided volume improved significantly after 1 year of treatment. The effect was maintained throughout 5 years follow-up, with 20/23 patients reporting no bladder pain. However, symptoms recurred within a few months of discontinuing CyA.

In a subsequent randomised study (27), 64 patients fulfilling the NIH criteria were randomised to 1.5 mg/kg CyA twice daily or low-dose (3x 100 mg) pentosan polysulphate sodium for 6 months. CyA was superior to pentosan polysulphate sodium in all clinical outcome parameters, with the frequency of micturition significantly reduced in CyA-treated patients, and clinical global response rates of 75% (CyA) and 19% (pentosan polysulphate sodium) (P < 0.001). However, there were more adverse events in the CyA arm (including induced hair growth, gingival pain and hyperplasia, paraesthesia in the extremities, abdominal pain, flushing, muscle pain and shaking), and only 29 patients completed the 6 months follow-up in both groups. During CyA therapy, careful follow-up is mandatory, including regular blood pressure measurement and serum creatinine.

**Gabapentin** is an antiepileptic drug, which is used as adjunctive treatment in painful disorders. Gabapentin
may reduce the use of concomitant therapeutics, such as opioids. Two patients with BPS showed improved functional capacity and received adequate pain control when gabapentin was added to their regimen (28). In an uncontrolled dose-escalation protocol with 21 chronic genitourinary pain patients (29), 10 improved with gabapentin at 6 months. The study included eight BPS patients, of whom, five responded to gabapentin.

*Pregabalin* is an alpha (2)-delta ligand that binds to and modulates voltage-gated calcium channels, exerting its intended effect to reduce neuropathic pain (30). Pregabalin is the second of only two medications that are US FDA-approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy; it is used for the treatment of postherpetic neuralgia. Studies on BPS are still lacking.

*Suplatast tosilate* (IPD-1151T) is an oral immunoregulator that suppresses helper-T-cell-mediated allergic processes. Fourteen women with BPS treated with suplatast tosilate reported significantly increased bladder capacity and decreased symptoms after 1 year of treatment. No major side effects occurred and therapeutic effects correlated with a reduction in blood eosinophils, IgE and urinary T cells (31). Comparative controlled data are unavailable.

*Quercetin* is a bioflavonoid that may be effective in male pelvic pain syndrome. It was first tested in a small open-label study of 29 patients, with hopeful results (32). Theoharides et al. (33) have studied the dietary supplement CystoProtek formulated from quercetin and the natural GAG components, chondroitin sulphate and sodium hyaluronate. In an uncontrolled study, symptoms were significantly improved in 37 BPS patients (NIH criteria), who had failed all forms of therapy and who took six capsules per day for 6 months. Larger controlled studies are warranted by this result.

3.2.12.1 References


3.2.13 **Intravesical treatment**

Intravesical application of medications establishes high concentrations at the target, with few systemic side effects. Disadvantages include the need for intermittent catheterisation, which can be painful in BPS patients, cost, and risk of infection.

*Local anaesthetics.* There are sporadic reports of successful treatment of BPS with intravesical lidocaine (1,2). Alkalisation of lidocaine before intravesical application improves pharmacokinetics (3). In an uncontrolled study, significant immediate symptom relief was reported in 94% of patients and sustained relief after 2 weeks in 80%, using instillations of combined heparin and alkalised lidocaine [40,000 U heparin, 2% lidocaine (160 mg), and 3 mL 8.4% sodium bicarbonate] (4). One hundred and two adult patients (99 women) with a clinical diagnosis of BPS were randomised from 19 centres in the USA and Canada to receive a daily intravesical instillation of alkalised lidocaine or placebo (double-blind), for 5 consecutive days. Treated patients had significant sustained symptom relief for up to 1 month (5).

**Pentosan polysulphate sodium** is a glycoprotein aimed at replenishing the GAG layer, which is applied intravesically due to poor bioavailability following oral administration. A double-blind placebo-controlled study (6) was performed in 20 patients, of whom 10 received intravesical pentosan polysulphate sodium (300 mg in 50 mL 0.9% saline) twice weekly for 3 months, and 10 received placebo.

At 3 months, four patients in the pentosan polysulphate sodium group and two in the placebo group achieved significant symptomatic relief. Bladder capacity showed a significant increase only in patients treated with pentosan polysulphate sodium. At 18 months, symptoms were relieved in eight patients, who were still receiving pentosan polysulphate sodium instillation, and in four patients not receiving the drug. In another study, a total of 41 women diagnosed with BPS were randomised to receive a combination of intravesical plus oral pentosan polysulphate sodium (21 in treatment group) or intravesical placebo plus oral pentosan polysulphate sodium (20 in placebo group) for 6 weeks. All subjects continued to receive oral pentosan polysulphate sodium for a further 12 weeks. At week 18, the treatment group showed significant improvement in all health-related QoL domains compared to baseline (P < or = 0.01), whereas the placebo group showed significant improvement in only three domains, (P < or = 0.05) compared to baseline (7).

**Intravesical heparin** has been proposed as a coating agent. In an open, prospective, uncontrolled trial (8), 48 BPS patients received instillations of 10,000 U in 10 mL sterile water three times weekly for 3 months. In over half of the patients, intravesical heparin controlled the symptoms, with continued improvement after 1 year of therapy. Kuo (9) reported another uncontrolled trial of intravesical heparin (25,000 U twice weekly for 3 months) in women with frequency-urgency syndrome and a positive potassium test. The study included 10 patients with BPS, of whom eight reported symptomatic improvement. Baykal et al. (10) have evaluated intravesical heparin plus dorsal tibial nerve stimulation in 10 refractory BPS patients. Voiding frequency, pain scores and maximum cystometric capacity were significantly better after 2 and 12 months compared to pretreatment values.

**Hyaluronic acid (hyaluronan)** is a natural proteoglycan aimed at repairing defects in the GAG layer. A response rate of 56% at week 4 and 71% at week 7 was reported in 25 patients treated with hyaluronic acid (11). After week 24, effectiveness decreased, but there was no significant toxicity. Nordling et al. (12) and Kallestrup et al. (13) have reported a 3-year follow-up of a 3-month, prospective, non-randomised study evaluating the effect of intravesical hyaluronic acid on BPS symptoms. Of the 20 patients, 11 chose to continue treatment beyond the initial trial, and modest beneficial long-term effects were noted in about two-thirds of patients. Reduction in urinary frequency was less effective and mostly due to an improvement in night-time voids.

Another study (14) has demonstrated a similar favourable effect of hyaluronic acid on pain reduction. Forty-eight patients with typical symptoms and a positive potassium (0.4 M) sensitivity test were treated with weekly instillations of 40 mg hyaluronic acid for 10 weeks. Visual analogue scale scores showed symptom relief due to hyaluronic acid therapy, irrespective of bladder capacity. The improvement was particularly evident in patients with a reduction in Cmax < 30% compared to patients with a reduction of < 30% with 0.2 M KCl solution (P = 0.003). Long-term effects were investigated in a study of 70 patients previously treated with hyaluronan. Of the 70 patients initially treated, 48 were available for evaluation. Of these, 50% reported complete remission with no further therapy. Another 41.7% of patients with symptom recurrence improved after retreatment (15).

**Chondroitin sulphate.** Intravesical chondroitin sulphate (16) demonstrated beneficial effects in patients with a
positive potassium stimulation test, in two non-randomised, uncontrolled, open-label pilot studies. Steinhoff (17) treated 18 patients with 40 mL instilled intravesically once weekly for 4 weeks and then once monthly for 12 months. Thirteen of 18 patients were followed for the entire 13-month study. Twelve of these patients responded to treatment within 3-12 weeks. A total of 6/13 (46.2%) showed a good response, 2/13 (15.4%) had a fair response, 4/13 (30.8%) had a partial response, and 1/13 (7.7%) showed no response. In a second trial (18), 24 refractory patients with BPS were treated with high-dose (2.0%) chondroitin sulphate instillations twice weekly for 2 weeks, then weekly with 0.2% solution for 4 weeks, and monthly thereafter for 1 year. The average symptom improvement reported in 20 patients completing the trial was 73.1% (range: 50-95%). The time to optimum response was 4-6 months. A more concentrated 2.0% solution was needed in eight patients to maintain results.

Sixty-five patients with BPS were treated in a prospective, randomised, double-blind, inactive vehicle-controlled, 12-week study (6 weeks treatment, followed by 6 weeks follow-up). At the primary endpoint analysis (week 7), 22.6% of the vehicle control group were responders compared with 39.4% of the active therapy group, however, the difference was not significant, probably due to underpowering of the study (19,20).

**Dimethyl sulfoxide (DMSO)** is a chemical solvent and water-soluble liquid that penetrates cell membranes. It is claimed to have analgesic, anti-inflammatory, collagenolytic, and muscle relaxant effects. It is also a scavenger of the intracellular OH radical, which is believed to be an important trigger of the inflammatory process. It has been tested empirically and found to alleviate symptoms in BPS. Dimethyl sulfoxide is now a standard treatment. In a controlled crossover trial (21), 33 patients received instillations of 50% DMSO solution and placebo (saline). All patients received both regimens, which were administered intravesically every 2 weeks for two sessions of four treatments each. Subjective improvement was noted in 53% of patients receiving DMSO versus 18% receiving placebo, and objective improvement in 93% and 35%, respectively.

Other uncontrolled trials with DMSO have reported response rates of 50-70% for a period of 1-2 months (22). Rössberger et al. (23) have evaluated the discomfort and long-term effects of DMSO instillations in a total of 28 patients. Side effects were no more common or pronounced in patients with classic compared to non-ulcer disease. After DMSO instillations, a residual treatment effect lasting 16-72 months could be seen. DMSO is contraindicated during UTIs or shortly after bladder biopsy. It temporarily causes a garlic-like odour. There is a case report in which DMSO treatment may have caused pigmented eye lens deposits (24), therefore, ophthalmic review should be considered during treatment.

**Bacillus Calmette Guérin (BCG).** The tuberculosis BCG vaccine is used for its immunomodulatory properties in the intravesical treatment of superficial bladder carcinoma. In 1997, a small prospective, double-blind pilot study showed that intravesical BCG demonstrated a 60% response rate versus 27% in the placebo group in 30 patients who received six weekly instillations of Tice strain BCG or placebo (25). In a subsequent 24-33-month follow-up study, eight of the nine responders reported BPS symptom amelioration. BCG did not worsen symptoms in non-responders (26). However, these results are at variance with two controlled trials. In a prospective, double-blind crossover trial of BCG and DMSO (27), BCG treatment failed to demonstrate any benefit. Another randomised, placebo-controlled, double-blind trial of 260 refractory BPS patients (28) reported global response rates of 12% for placebo and 21% for BCG (P = 0.062). Small improvements were observed for all secondary outcomes (voiding diary, pain, urgency, symptom indexes, and adverse events), some of which were greater with BCG, but with only borderline statistical significance.

In a subsequent study (29), 156 non-responders from both groups were offered treatment with open-label BCG. The low response rate (18%) for BCG in this series and the results of the same group’s (Interstitial Cystitis Clinical Trials Group; ICCTG) follow-up on the responders, which found no differences, have substantiated the argument against the routine use of BCG for BPS (30).

**Vanilloids** disrupt sensory neurons (31). Resiniferatoxin (RTX) is an ultrapotent analogue of the chilli pepper extract capsaicin, causing less pain on instillation and therefore no anaesthesia. Chen et al. (32) have investigated RTX tolerability (0.05 or 0.10 μM) in 22 BPS patients versus placebo. The most commonly reported adverse event was pain during instillation (RTX > 80.0%, placebo 25.0%) but no serious adverse events were reported. In a small RCT on 18 patients with hypersensitive bladder disorder and pain (33), RTX significantly reduced mean frequency, nocturia, and pain scores by about 50%. In another study of seven patients with detrusor hyper-reflexia, RTX improved urinary frequency, incontinence and bladder capacity (34). In a small open-label study with single-dose RTX in patients with frequency and urgency (35), RTX significantly improved LUTS, urodynamic parameters, and QoL for up to 6 months. These results are in contrast with an RCT in 163 BPS patients randomly assigned to receive a single intravesical dose of 50 mL of either placebo or RTX (0.01, 0.05 or 0.10 μM) (36). RTX resulted in a dose-dependent increase in instillation pain, but otherwise was well tolerated. It did not improve overall symptoms, pain, urgency, frequency, nocturia, or average void volume during 12 weeks follow-up.
More favourable results have been reported from a prospective study on multiple intravesical instillations of RTX (37) (0.01 μM once weekly for 4 weeks). Among 12 patients (one drop-out for severe pain), the overall satisfaction rate was 58.3%, with several scales of symptom and QoL significantly improved after RTX treatment. There was no significant increase in functional bladder capacity or change in urodynamic parameters. A prospective, randomised, double-blind, crossover study was performed in 26 women, who received instillations with various pH values. There was no evidence that changes in urinary pH affected the pain associated with BPS (38).

3.2.13.1 References
http://www.journals.elsevierhealth.com/periodicals/eurup/article/PII/S1569905603000368/abstract


3.2.14 Interventional treatments

Bladder distension. A frequently cited report by Bumpus (1) claims that hydrodistension achieved symptom improvement in 100 patients over several months. However, the study did not define either patient population or symptoms and the methods used were inadequately described. Reports by Ormond (2) and Longacre (3) were just as vague during the 1930s. In 1957, an uncontrolled retrospective study was presented by Franksson (4), who treated 33 patients with repeated, up to 10-fold, distensions. Twelve patients had improved symptoms for up to 4 weeks, in 14 patients for up to 6 months, and in seven patients for up to 1 year. British studies from the 1970s have reported contradictory results. Dunn et al. (5) have claimed to have achieved complete absence of symptoms in 16/25 patients during a mean follow-up of 14 months using the Helmstein method (6), in which an intravesical balloon is distended at the level of systolic blood pressure for 3 h. Bladder rupture occurred in two cases. These results disagree with those of Badenoch (7), who failed to note any improvement in 44/56 patients after hydrodistension. Twenty years later, McCahy (8) rejected balloon hydrodistension because of inefficacy and a complication rate of 20%. In the recent literature, bladder necrosis following hydrodistension has been extremely rare (9).

In 2002, Glémain et al. (10) reported an uncontrolled study on 65 BPS patients treated by 3 h balloon hydrodistension. Treatment efficacy in the 33 retrospectively and 32 prospectively studied patients was 38% and 60% at 6 months, and 22% and 43% at 1 year, respectively. Results were superior for bladder capacities > 150 mL.

Ottem and Teichmann reported a retrospective study of 84 BPS patients (11), and 56% reported short-lived improvement from hydrodistension. Rose et al. have investigated bladder distension using electromotive drug administration (EMDA) (12,13), as an alternative to general anaesthesia. Among 11 patients, the distension capacity achieved by EMDA was nearly identical to that in the operating room and cystoscopic findings were similar. Yamada et al. (14) have reported on repeated hydrodistension in 52 BPS patients (NIH criteria). Under epidural anaesthesia, the bladder was repeatedly distended to maximal capacity and distension was repeated on the following day for 30 min. Five patients were classified as good responders, 30 as moderate and 17 as poor. Overall, hydrodistension was effective for ~70% of patients for > 3 months, without serious complications.

According to a study by Erickson et al. (15), the median symptom score for newly diagnosed patients decreased after distension, but only a few patients had at least 30% symptom improvement. Bladder distension altered levels of urine antiproliferative factor and heparin-binding epidermal-growth-factor-like growth factor towards normal. However, the mechanism of symptom relief after distension remains unknown.

In a retrospective review of 185 patients who underwent hydrodistension (16), results failed to identify any statistically significant differences in objective findings (anaesthetic capacity, glomerulations) following distension, or any therapeutic benefits, when patients were categorised according to presenting symptoms.

Although bladder hydrodistension is a common treatment for BPS, scientific justification is scarce. It represents a diagnostic tool, but has a limited therapeutic role.

EMDA enhances tissue penetration of ionised drugs by iontophoresis. When adapted for the bladder, EMDA uses a transurethral anode and a suprapubic skin cathode. EMDA is expensive and has been the subject of uncontrolled studies only.
Six BPS patients were treated with EMDA using lidocaine (1.5%) and 1:100,000 adrenaline in aqueous solution, while the bladder was dilated to maximum tolerance (17). Significant bladder enlargement was achieved and voiding symptoms and pain decreased. In four patients, the results were reported as durable. Rosamilia et al. (18) treated 21 women using EMDA with lidocaine and dexamethasone, followed by bladder distension. A good response was seen in 85% of patients at 2 weeks, with 63% still responding at 2 months. Complete resolution of pain was achieved in 25% of patients reviewed at 6 months. Using a similar technique, Riedl et al. (19) noted complete resolution of bladder symptoms in 8/13 patients lasting 1-17 months. Partial or short-term improvement was observed in three patients. Two patients experienced aggravated pain for several days after therapy. A 66% increase in bladder capacity was observed. Upon symptom recurrence, treatments were repeated with equal efficacy in 11 patients.

**Transurethral resection (TUR) coagulation and laser.** Endourological ablation of bladder tissue aims to eliminate urothelial, mostly Hunner, lesions. In a case report, Kerr (20) has described TUR of a 1-cm ulcer in a woman who experienced symptom resolution for 1 year. Subsequently, Greenberg et al. (21) have reported 77 patients with Hunner ulcers treated over a 40-year period: 42 were managed conservatively, seven underwent fulguration, and 28 were treated by TUR in a non-randomised fashion. Fulguration improved symptoms in 5/7 patients. All patients experienced symptom recurrence in < 1 year and efficacy was not superior to non-surgical treatment.

In another series of 30 BPS type C patients (22), complete TUR of visible lesions resulted in an initial disappearance of pain in all patients and a decrease in frequency in 21. Relapse was noted in one-third of patients after 2-20 months, while the remaining two-thirds were still pain-free after 2-42 months. The same group recently has reported the largest series of patients with BPS type C treated by complete TUR of all visible ulcers (23). A total of 259 TURs were performed on 103 patients. Ninety-two patients experienced amelioration, with symptom relief lasting > 3 years in 40% of patients, and most of the remaining patients responded well to subsequent TUR.

Transurethral application of the (Nd-YAG) laser is suggested as an alternative to TUR for endoscopic treatment in BPS. Shanberg et al. (24) have treated 5 refractory BPS patients, 4 of whom demonstrated cessation of pain and frequency within several days. Follow-up at 3-15 months revealed no relapse, except for mild recurrent voiding symptoms. This series was extended to 76 patients treated at two institutions (25). Although 21 of 27 patients with Hunner ulcers noted symptom improvement, 12 experienced relapse within 18 months. In the group without ulcers, only 20 of 49 patients improved, of whom 10 required further therapy within 1 year.

In a later study, 24 patients with refractory BPS type C underwent ablative Nd-YAG laser ablation of Hunner’s ulcers (26). All patients showed symptom improvement within a few days, without complications. At 23 months, mean pain and urgency scores, nocturia and voiding intervals improved significantly. However, relapse in 11 patients required up to four additional treatments. Controlled studies are still lacking. Endourological resection is not applicable to non-ulcer BPS.

**Botulinum toxin A** (BTX-A) may have an antinociceptive effect on bladder afferent pathways, producing both symptomatic and urodynamic improvements (27). Thirteen BPS patients were injected with 100-200 IU of BTX-A (abobotulinumtoxin A or onabotulinumtoxin A) into 20-30 sites submucosally in the trigone and floor of the bladder. Overall, nine (69%) patients noted subjective improvement, and ICSI scores improved by 70% (P < 0.05). There were significant decreases in daytime frequency, nocturia and pain, and a significant increase in first desire to void and maximal cystometric capacity. However, these results are in contrast with those in another study of BTX-A (onabotulinumtoxin A) in 10 patients with BPS (28). One hundred units were injected suburothelially into 20 sites in five patients, while 100 U were injected into the trigone in the remaining five. None of the patients became symptom-free; two showed only limited improvement in bladder capacity and pain score.

To ascertain effect of repeat injections a total of 13 patients were followed up for 2 years, while 58 injections were administered with a mean of 4.8 ± 0.8 injections per patient. The mean interval between two consecutive injections was 5.25 ± 0.75 months. At 1 and 4 months follow-up, 10 patients reported a subjective improvement. Mean VAS scores, mean daytime and night-time urinary frequency decreased significantly. The three non-responders to the first intravesical treatment session underwent further treatment 3 months later with satisfactory results. At 1 and 2 years follow-up, the beneficial effects persisted in all patients (29).

In an RCT, the difference between hydrodistension and hydrodistension plus intravesical BTX-A (onabotulinumtoxin A) was analysed. Of the 67 patients, 44 were divided in two groups: one received 200 U and the other 100 U, and cystoscopic hydrodistension was performed after 2 weeks. The remaining 23 patients received hydrodistension only. There was symptomatic improvement in all groups. However, in the hydrodistension group, 70% had returned to their previous symptoms after the first month, while in the BTX-A-
treated groups, there was improvement of VAS, functional bladder capacity and cystometric bladder capacity at 3 months. At 12 and 24 months, the results in the active group were 55 and 30% versus 26 and 17% in the hydrodistension group (30).

Trigonal-only injection seems effective and long-lasting because 87% of patients (n = 23) reported improvement after a 3-month follow-up period in a study by Pinto et al. Over 50% referred continuity of the beneficial effect 9 months after the first treatment. When retreatment was needed, similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated (31).

Hyperbaric oxygen (HBO). In a prospective pilot study, six patients underwent 30 sessions of 100% HBO inhalation and were followed up for > 15 months. Four patients rated the therapeutic result as excellent or good, while two showed only short-term amelioration (32). In a subsequent double-blind, sham-controlled study (33), 3/14 patients on HBO and no control patients were identified as responders (P < 0.05). At 12 months, three patients (21.4%) still reported a treatment response. Hyperbaric oxygenation resulted in a decrease of baseline urgency and pain (P < 0.05). ICSI scores decreased from 26 to 20 points in patients on HBO, while sham treatment did not result in any improvement. These results suggest that HBO is a safe and feasible therapeutic approach, with moderate effects on a small subgroup of BPS patients. Disadvantages include high costs, limited availability of treatment sites and time-consuming treatment.

Neuromodulation. In the first prospective, single-blind, crossover trial of sacral nerve stimulation (SNS) versus pudendal nerve stimulation (PNS) for patients with BPS (n = 22), PNS gave an overall 59% improvement in symptoms, whereas SNS gave an overall 44% improvement (P = 0.05). Most patients who tested both a sacral and pudendal electrode chose PNS as the better site. Follow-up showed marked improvements in voiding variables and validated BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again (34). Long-term results were verified in a retrospective study of 78 patients treated from 1994 to 2008. Permanent sacral neuromodulation implantation was performed in patients who showed at least 50% improvement in their symptoms with a temporary peripheral nerve evaluation test. Median follow-up was 61.5 (SD± 27.7 months). Good long-term success of sacral neuromodulation was seen in 72% of the patients. The explantation rate was 28%. The most frequent reason for explantation was poor outcome (54% of the failed patients). The revision rate was 50% (35). In another observational, retrospective, case-controlled review (January 2002-March 2004), 34 female patients underwent permanent device implants. Mean pre-/postoperative pelvic pain and urgency/frequency scores were 21.61 ± 8.6/9.22 ± 6.6 (P < 0.01), and mean pre-/postoperative visual analogue pain scale (VAPS) scores were 6.5 ± 2.9/2.4 ± 1.1 (P < 0.01). Mean follow-up was 86 ± 9.8 months. Sacral neuromodulation showed adequate improvement for the symptoms of refractory BPS. Reoperation rate was 25% (36).

3.2.14.1 References


3.2.15 Treatments of limited efficacy and absence of recent publications
Cimetidine. The H2-blocker cimetidine has been reported to improve symptoms in BPS (1). Thirty-six patients were enrolled in a double-blind clinical study with oral cimetidine versus placebo for 3 months. Patients receiving cimetidine showed a significant improvement in symptom scores, pain and nocturia, although histologically, the bladder mucosa showed no qualitative changes in either group (2).

Prostaglandins. Misoprostol is a prostaglandin that regulates various immunological cascades. Twenty-five BPS patients received 600 μg/day misoprostol for 3 months, with responders treated for a further 6 months. At 3 months, 14 had significantly improved, with 12 showing a sustained response after a further 6 months. However, the incidence of adverse drug effects was 64% (3).

L-Arginine. Oral treatment with l-arginine, the substrate for NO synthase, has been reported to decrease BPS-related symptoms (4-6). Nitric oxide level has been shown to be elevated in patients with BPS (7). However, others could not demonstrate either symptomatic relief or change in NO production after treatment (8,9).

Anticholinergics. Oxybutynin is an anticholinergic drug used in overactive detrusor dysfunction. Intravesically administered oxybutynin was combined with bladder training in one study, with improvement of functional bladder capacity, volume at first sensation and cystometric bladder capacity (10). However, the effect on pain was not reported.

Duloxetine inhibits both serotonin and noradrenaline reuptake. In an observational study, 48 women were prospectively treated with duloxetine for 2 months following an up-titration protocol to the target dose of 2-40 mg/day duloxetine over 8 weeks (11). Duloxetine did not result in significant improvement of symptoms. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended as a therapeutic approach for BPS.

Clorpactin is a detergent of hypochloric acid previously used to treat BPS (12-16). Due to high complication rates (14-17), clorpactin instillations can no longer be recommended.
3.2.15.1 References


3.2.16 Non-pharmacological treatments

Behavioural bladder training techniques are attractive for BPS patients with predominant symptoms of frequency/urgency but hardly any pain. Parsons et al. (1) included 21 selected BPS patients in a protocol that focused on progressively increasing micturition intervals. Fifteen patients reported a 50% decrease in urgency, frequency and nocturia, and there was a moderate increase in bladder capacity. Chaiken et al. (2) retrospectively analysed 42 patients, who had been instructed in diary keeping, timed voiding, controlled fluid intake, and pelvic floor muscle training. After 12 weeks, voiding intervals increased by a mean 93 min and daily...
micturition was reduced by an average of nine voids. Overall, 88% of the patients reported markedly improved or improved symptoms.

**Diet.** Dietary restrictions are among the many physical self-care strategies found among BPS patients (3). In an analysis of the Interstitial Cystitis Data Base (ICDB) cohort study, special diets were among the five most commonly used therapies (4). Bade et al. (5) have found that BPS patients consume significantly fewer calories, less fat and coffee, but more fibre. Scientific data on a rationale for such diets are unavailable. The concentration of some metabolites and amino acids appears to be changed in BPS (6).

A study of the metabolism of the arylalkylamines (tryptophan, tyrosine, tyramine and phenylalanine) in 250 patients revealed an inability to synthesise normal amounts of serotonin and MHPG noradrenaline metabolite. In this study, dietary restriction of acid foods and arylalkylamines lessened the symptoms, but did not alter specific abnormalities in dopamine metabolism. In another, non-randomised, prospective study of BPS patients with nutrition-related exacerbations, calcium glycerophosphate was reported to ease food-related flares (7). The observed efficacy seems little better than would be expected with placebo.

Overall, dietary management is a common self-care strategy in BPS and offers a cost-effective therapeutic approach. Comprehensive instructions on how to identify individual trigger foods are given in the IC-Network Patient Handbook (8). However, scientific data are limited and dietary restriction alone does not produce complete symptomatic relief.

**Acupuncture.** In non-curable and agonising diseases like BPS, desperate patients often try complementary medicines, such as acupuncture. However, scientific evidence for such treatments is often poor, with contradictory results from a few low-evidence reports on acupuncture, with any effects appearing to be limited and temporary. A significant increase in capacity occurred after acupuncture in 52 women with 85% reporting an improvement in frequency, urgency and dysuria and symptoms (9). However, at follow-up at 1 and 3 years, these effects were no longer detectable and the authors concluded that repeated acupuncture was necessary to maintain beneficial effects (10).

In a non-randomised comparison in women with urethral syndrome, 128 treated by acupuncture and traditional Chinese medicine were compared with 52 treated by western medicine as controls. Efficacy rates and urodynamic parameters were significantly better in the acupuncture group (11). In contrast, in a prospective study on the effect of acupuncture in BPS (12), no differences in frequency, voided volumes or symptom scores were noted, and only one patient improved for a short period of time.

**Hypnosis** is a therapeutic adjunct in the management of cancer, surgical disease and chronic pain. Although used in urological patients (13,14), there are no scientific data on its effect on BPS symptoms.

**Physiotherapy.** General body exercise may be beneficial in some BPS patients (15). An uncontrolled trial of transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in 21 BPS patients with high-tone dysfunction of the pelvic floor resulted in significant improvement on several assessment scales (16). Langford et al. (17) have prospectively examined the role of specific levator ani trigger point injections in 18 women with CPP. Each trigger point was identified by intravaginal palpation and injected with 5 mL of a mixture of 10 mL 0.25% bupivacaine, 10 mL 2% lidocaine and 1 mL (40 mg) triamcinolone. Thirteen (72%) women improved with the first trigger point injection, with six (33%) women being completely pain-free.

**Intravaginal electrical stimulation** was applied to 24 women with CPP in the form of ten 30-min applications, two or three times weekly. Stimulation was effective in alleviating pain, as evaluated at the end of treatment and 2 weeks, 4 weeks and 7 months after completion of treatment (P < 0.05). There were significantly fewer complaints of dyspareunia following treatment (P = 0.0005) (18).

### 3.2.16.1 References


### 3.2.17 Surgical treatment

When all efforts fail to relieve disabling symptoms, surgical removal of the diseased bladder is the ultimate option (1–4). Three major techniques of bladder resection are common:

- **Supratrigonal (i.e. trigone-sparing) cystectomy**
- **Subtrigonal cystectomy**
- **Radical cystectomy** including excision of the urethra.

All techniques require substitution of the excised bladder tissue, mostly performed with bowel segments.

**Techniques without bladder removal.** As early as 1967, Turner-Warwick reported that mere bladder augmentation without removal of the diseased tissue was not appropriate (5). Sporadic reports that unrected BPS bladders cease to cause symptoms when excluded from the flow or urine are scarce (6,7).

**Supratrigonal cystectomy** with subsequent bladder augmentation represents the most favoured continence-preserving surgical technique. Various intestinal segments have been used for trigonal augmentation, including...
ileum (8-16), ileocaecum (15-22), right colon (8,16,23), and sigmoid (10,12,13,18,22). Substituting gastric segments (24,25) seems to be less helpful because the production of gastric acids may maintain dysuria and persistent pain.

The therapeutic success of supratrigonal cystectomy has been reported in many studies. In 1966, von Garrelts reported excellent results in 8/13 patients with a follow-up of 12-72 months (12). In 1977, Bruce et al. achieved satisfactory relief of BPS symptoms by ileocystoplasty and colocystoplasty in eight patients (10). Dounis and Gow have reported seven BPS patients whose pain and frequency were considerably improved after supratrigonal cystectomy with ileocaecal augmentation (26).

In 1991, Kontturi et al. used segments of colon and sigmoid colon in 12 cases (22). All five patients augmented with sigmoid colon remained symptom-free over 4.7 years of follow-up. Two of seven cases augmented with colon required secondary cystectomy with formation of an ileal conduit. Nielsen et al. have reported a series of eight patients undergoing supratrigonal cystectomy with ileoceacocystoplasty.

Although symptoms resolved in two patients, treatment failure in another six necessitated secondary cystectomy and ileal conduit formation (17).

Linn et al. (27) have followed six BPS patients after supratrigonal cystectomy with ileocaecal augmentation for a period of 30 months, and have reported that all patients were symptom-free and voided spontaneously.

In 2002, Van Ophoven et al. (1) reported the long-term results of trigone-preserving cystectomy and consecutive orthotopic substitution enteroplasty in 18 women with BPS, using ileocaecal (n = 10) or ileal (n = 8) segments. At a mean follow-up of nearly 5 years, 14 patients were completely pain-free, 12 voided spontaneously, and 15 had complete resolution of dysuria. Ileocaecal bowel segments showed superior functional results, because in the group augmented with ileum, three patients required self-catheterisation and one a suprapubic catheter. Overall, surgery achieved a significant improvement in diurnal and nocturnal frequencies, functional bladder capacity and symptom scores, with only two treatment failures.

In more recent reports with longer follow-up, the debate on the outcome of BPS patients undergoing cystectomy continues and results vary greatly between different surgeons and patient populations.

Chakravarti et al. (28) presented a retrospective review of 11 patients, who had undergone a trigone-preserving orthotopic substitution caecocystoplasty for intractable BPS Type 3 C and were followed up for a mean period of 9 years. All had symptomatic relief and an increase in bladder capacity to normal. There was no mortality and minimal postoperative morbidity, with two patients requiring intermittent self-catheterisation due to high residual volumes. No significant urinary reflux or metabolic complications were noted. However, two patients required cystectomy after 4 and 6 years, respectively, due to recurrent trigonal disease in one patient and urethrotrophic hypersensitivity following intermittent self-catheterisation in the other. One patient developed an advanced adenocarcinoma in the caecal segment 7 years after the primary operation.

Blaivas et al. (29) have reported less favourable results. Long-term outcomes of augmentation enterocystoplasty or continent urinary diversion were analysed in 76 patients with benign urological disorders, including seven with a clinical diagnosis of BPS. The BPS patients all failed surgical treatment because of persistent pelvic pain and failure to achieve adequate bladder capacity, rather than because of incontinence. The authors currently consider BPS to be a contraindication for enterocystoplasty.

In contrast, Navalón et al. (30) have reported a 32-month follow-up of four women with refractory BPS who underwent supratrigonal cystectomy with orthotopic substitution ileocystoplasty. Suprapubic pain disappeared in all cases, as well as lower urinary tract symptoms, with good control of urinary frequency day and night in the immediate postoperative period. All patients reported high satisfaction with the outcome.

**Subtrigonal cystectomy.** Although less popular, subtrigonal cystectomy has also been reported (27,31-34). Subtrigonal resection has the potential of removing the trigone as a possible disease site, but at the cost of requiring ureteral reimplantation with associated risks of leakage, stricture, and reflux. Nurse et al. reported trigonal disease in 50% within their cohort (13/25) and blamed surgical failures on the trigone left in place (35).

In contrast, Linn et al. have indicated that the level of resection was not solely responsible for treatment success. While completely curing six patients by supratrigonal resection, there were three failures among 17 subtrigonal resections, and half of the successful subtrigonal resections required self-catheterisation to support voiding of the ileocaecal augmentate (27). A recent report on female sexuality after cystectomy and orthotopic ileal neobladder (36) describes eight patients. Pain was relieved in all eight, but only one regained a normal sexual life postoperatively.

**Selecting patients and technique.** BPS is benign and does not shorten life, so that operative procedures rank last in the therapeutic algorithm. However, severely refractory patients should not have to tolerate unsuccessful conservative treatments for several years when surgical options are available.

Detailed counselling and informed consent must precede any irreversible type of major surgery.
which should only be undertaken by experienced surgeons. The choice of technique is influenced by the experience of the surgeon. The appropriate extent of tissue resection should be based on the endoscopic and histopathological findings. Some surgeons recommend preoperative cystoscopy and bladder capacity as a prognostic parameter for operative success (7). Responders and failures following orthotopic substitution differed in mean preoperative bladder capacity (200 vs. 525 mL, respectively) (17). These findings have been supported by Peek et al. (37), who found that patients with end-stage BPS Type 3 C had excellent results following ileocystoplasty, whereas patients with non-ulcer disease were not helped. These results have recently been confirmed by another study from the same institution.

A retrospective analysis of 47 patients fulfilling the NIH criteria, who underwent reconstructive surgery using various techniques during 1978-2003 (38), resulted in complete symptom resolution in 32/34 patients with classic Hunner-type disease, but only 3/13 patients with non-ulcer disease.

Cystectomy with formation of an ileal conduit still ranks first in current US practice trends in surgical BPS therapy (39). For cosmetic reasons, however, techniques of continent diversion are preferred, particularly in younger patients. After orthotopic bladder augmentation, particularly when removing the trigone, voiding may be incomplete and require intermittent self-catheterisation. Patients considering these procedures should be advised and must be considered capable of performing, accepting and tolerating self-catheterisation. For patients with BPS who develop recurrent pain in the augmented bladder or continent pouch after enterocystoplasty or continent urinary diversion, Elzawahri (40) has recommended retubularisation of a previously used bowel segment to form a urinary conduit.

For younger patients, it may be important to know that pregnancies with subsequent lower-segment Caesarean section after ileocystoplasty have been reported (41). Reconstructive surgery for refractory BPS is an appropriate last resort only for well-selected patients with refractory end-stage disease. The decision to embark on major reconstructive surgery should be preceded by a thorough preoperative evaluation, with an emphasis on assessment to determine the relevant disease location and subtype.

A summary of the treatment options for BPS, including LE and GR is given in the next section. Figure 6 and 7 are algorithms for the diagnosis and therapy of BPS based on the information discussed above.

### 3.2.18 Conclusions and recommendations: treatment of BPS

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>None of the present existing treatments have effect on all BPS subtypes or phenotypes.</td>
<td>4</td>
</tr>
<tr>
<td>Conventional analgesics have little efficacy. Opioids are effective in controlling BPS pain.</td>
<td>2b</td>
</tr>
<tr>
<td>Corticosteroids are not recommended as long-term treatment.</td>
<td>3</td>
</tr>
<tr>
<td>Hydroxyzine has limited efficacy shown in RCT and is effective in associated non bladder diseases.</td>
<td>1b</td>
</tr>
<tr>
<td>Limited data exist on effectiveness of cimetidine in BPS.</td>
<td>2b</td>
</tr>
<tr>
<td>Amitriptyline is effective in pain and related symptoms of BPS.</td>
<td>1b</td>
</tr>
<tr>
<td>Oral pentosanpolysulphate sodium is effective in pain and related symptoms of BPS.</td>
<td>1a</td>
</tr>
<tr>
<td>Oral pentosanpolysulphate sodium plus subcutaneous heparin is effective in pain and related symptoms of BPS especially in patients initially low responders to pentosanpolysulphate sodium alone.</td>
<td>1b</td>
</tr>
<tr>
<td>Only limited data exist on the effectiveness of antibiotics in the treatment of BPS.</td>
<td>2b</td>
</tr>
<tr>
<td>Insufficient data for the effectiveness of prostaglandins in BPS exist. Adverse effects are frequent.</td>
<td>3</td>
</tr>
<tr>
<td>Global response on cyclosporin A was superior to pentosanpolysulphate sodium, but associated with more adverse effects.</td>
<td>1b</td>
</tr>
<tr>
<td>Duloxetin has shown no effect and tolerability is poor.</td>
<td>2b</td>
</tr>
<tr>
<td>Oxybutynin has limited effect in BPS pain, but data are scant.</td>
<td>3</td>
</tr>
<tr>
<td>Only insufficient data exist for the effectiveness of gabapentin in BPS.</td>
<td>3</td>
</tr>
<tr>
<td>Only insufficient data exist for the effectiveness of suplatast tosilate in BPS.</td>
<td>3</td>
</tr>
<tr>
<td>Preliminary data showed effectiveness of quercetin alone and in multimodal uncontrolled studies.</td>
<td>3</td>
</tr>
<tr>
<td>Intravesical lidocaine plus sodium bicarbonate is effective in the short term.</td>
<td>1b</td>
</tr>
<tr>
<td>Intravesical pentosanpolysulphate sodium is effective based on limited data and may enhance effect of oral treatment.</td>
<td>1b</td>
</tr>
<tr>
<td>There are limited data on the effectiveness of intravesical heparin.</td>
<td>3</td>
</tr>
<tr>
<td>Intravesical hyaluronic acid may have long term effects in BPS patients with positive intravesical modified KCI test.</td>
<td>2b</td>
</tr>
</tbody>
</table>
Intravesical chondroitin sulphate may be effective according to non-randomised studies. Published RCTs are underpowered. 2b
Intravesical DMSO is effective in the treatment of BPS, but side effects have to be considered. 1b
Intravesical submucosal BTX-A injection plus hydrodistension has sustained and significantly improved effect over hydrodistension alone. 1b
Only limited data exist on the effectiveness of BTX-A injection into detrusor or trigone. 3
Data on effectiveness of intravesical vanilloids are contradictory. Largest of RCTs without efficacy. 1b
Intravesical Bacillus Calmette Guérin (BCG) is not effective in BPS. 1b
Intravesical clorpactin has insufficient data to support effectiveness and high complication rates. 3
There is only insufficient data to support effectiveness of bladder distension. 3
Scarce data indicate electromotive drug administration may have a beneficial effect in patient subsets. 3
Transurethral resection (Coagulation and laser) may be effective in BPS type 3 C. 3
Sacral neuromodulation may be effective in BPS. 3
Pudendal nerve stimulation is superior to sacral nerve stimulation for the treatment of BPS. 1b
Bladder training may be effective in patients with predominant urinary symptoms and little pain. 3
Manual and physical therapy may have limited effects. 3
Avoidance of some food and drink avoids pain triggering. 3
Acupuncture: data contradictory. 3
Psychological therapy may be effective in ameliorating coping with disease. 3
No definitive conclusion on the effectiveness of surgical organ removal for BPS can be drawn based on large variability results in reported series. 3

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer subtype and phenotype-oriented therapy for the treatment of BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments for BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Opioids might be used in BPS in disease flare-ups. Long-term application solely if all treatments failed.</td>
<td>C</td>
</tr>
<tr>
<td>Corticosteroids are not recommended as long-term treatment.</td>
<td>C</td>
</tr>
<tr>
<td>Offer hydroxyzine for the treatment of BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Consider cimetidine as valid oral option before invasive treatments.</td>
<td>B</td>
</tr>
<tr>
<td>Administer amitriptyline for use in BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Offer oral pentosanpolysulphate sodium for the treatment of BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Treatment with oral pentosanpolysulphate sodium plus subcutaneous heparin is recommended especially in low responders to pentosanpolysulphate sodium alone.</td>
<td>A</td>
</tr>
<tr>
<td>Antibiotics can be offered when infection is present or highly suspected.</td>
<td>C</td>
</tr>
<tr>
<td>Prostaglandins are not recommended. Insufficient data on BPS, adverse effects considerable.</td>
<td>C</td>
</tr>
<tr>
<td>Cyclosporin A might be used in BPS but adverse effects are significant and should be carefully considered.</td>
<td>B</td>
</tr>
<tr>
<td>Duloxetin is not recommended for BPS treatment.</td>
<td>C</td>
</tr>
<tr>
<td>Oxybutynin might be considered for the treatment of BPS.</td>
<td>C</td>
</tr>
<tr>
<td>Gabapentin might be considered in oral treatment of BPS.</td>
<td>C</td>
</tr>
<tr>
<td>Administer intravesical lidocain plus sodium bicarbonate prior to more invasive methods.</td>
<td>A</td>
</tr>
<tr>
<td>Administer intravesical pentosanpolysulphate sodium before more invasive treatment alone or combined with oral pentosanpolysulphate sodium.</td>
<td>A</td>
</tr>
<tr>
<td>Consider intravesical heparin before more invasive measures alone or in combination treatment.</td>
<td>C</td>
</tr>
<tr>
<td>Consider intravesical hyaluronic acid before more invasive measures.</td>
<td>B</td>
</tr>
<tr>
<td>Consider intravesical chondroitin sulphate before more invasive measures.</td>
<td>B</td>
</tr>
<tr>
<td>Administer intravesical DMSO before more invasive measures.</td>
<td>A</td>
</tr>
<tr>
<td>Consider intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies failed.</td>
<td>C</td>
</tr>
<tr>
<td>Administer submucosal injection of BTX-A plus hydrodistension if intravesical instillation therapies failed.</td>
<td>A</td>
</tr>
</tbody>
</table>
Intravesical therapy with Bacillus Calmette Guérin is not recommended in BPS. A
Intravesical therapy with chlorapactin is not recommended in BPS. A
Intravesical therapy with vanilloids is not recommended in BPS. C
Bladder distension is not recommended as a treatment of BPS. C
Electromotive drug administration might be considered before more invasive measures. C
Consider transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only. B
Neuromodulation might be considered before more invasive interventions. B
Consider bladder training in patients with little pain. B
Consider manual and physical therapy in first approach. B
Consider diet avoidance of triggering substances. C
Acupuncture is not recommended. C
Consider psychological therapy in multimodal approach. B
All ablative organ surgery should be last resort for experienced and BPS knowledgeable surgeons only. A

DMSO = dimethyl sulphoxide; BPS = bladder pain syndrome.

Figure 6: Diagnosis and therapy of BPS

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture</td>
<td>Standard: Hydroxyzine, Amitriptyline, Pentosanpolysulphate</td>
</tr>
<tr>
<td>Uroflowmetry</td>
<td>Intravesical: PPS, DMSO, onabotulinum toxin A plus hydrodistension</td>
</tr>
<tr>
<td>Cystoscopy with hydrodistension</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td>Bladder biopsy</td>
<td>Oral: Cimetidine, cyclosporin A</td>
</tr>
<tr>
<td>Micturition diary</td>
<td>Intravesical: hyaluronic acid, chondroitin sulphate</td>
</tr>
<tr>
<td>Pelvic floor muscle testing</td>
<td>Electromotive drug administration for intravesical drugs</td>
</tr>
<tr>
<td>Phenotyping</td>
<td>Neuromodulation, bladder training, physical therapy</td>
</tr>
<tr>
<td>ICSI score list</td>
<td>Psychological therapy</td>
</tr>
<tr>
<td>Other comments</td>
<td>Data on surgical treatment are largely variable</td>
</tr>
<tr>
<td></td>
<td>Coagulation and laser only for Hunner’s lesions</td>
</tr>
</tbody>
</table>
Figure 7: Algorithm for BPS Type 3 C

Bladder Pain Syndrome

Hunner lesion at cystoscopy

yes

TUR / laser

Adequate:
* Retreat when necessary

Inadequate:
* Start other treatment

* Oral agents
* TENS
* Complementary medicine

Inadequate relief:
* Start Intravesical therapy

Still inadequate response:
* Refer to specialist pain management unit

no

3.2.19 References


3.3 Genital pain syndrome

3.3.1 Scrotal pain syndrome

Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised within the organs of the scrotum, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.

3.3.2 Pathogenesis

The pathogenesis of chronic scrotal pain is diverse and in most cases unknown. Pain in the scrotum can be divided into direct pain localised in the scrotum, or referred pain coming from another place or system in the body. The problem is that we cannot always make that division in clinical practice. Direct pain is located in the testes, epididymis, inguinal nerves or the vas deferens.

3.3.2.1 Testicular pain syndrome

Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Previous terms have included orchitis, orchialgia and orchodynia. These terms are no longer recommended.
3.3.2.2 Epididymal pain syndrome
Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.

Structural abnormalities of the epididymis can be visualised using ultrasound. Patients with multiple cysts may have pain caused by the compression that these cysts exert on the epididymis. Another local entity is chronic epididymitis (1). Chronic epididymitis may be associated with signs of inflammation: inflammatory or obstructive chronic epididymitis (2).

3.3.2.3 Nerves
The ilioinguinal and genitofemoral nerves are the most prominent afferent nerves for the scrotum (3). The inguinal nerves are especially important. It is generally accepted that pain after inguinal surgery (hernia) is a consequence of damage to the nerves inside the spermatic cord (4). This is based on the anatomical knowledge that all nerves involved in testicular pain merge in the spermatic cord (5). This fact has consequences for the choice of treatment. The pudendal nerve supplies the skin of the perineum and the posterior side of the scrotum. Pain in this area is pathognomonic for pudendal neuropathy.

3.3.2.4 Postvasectomy pain syndrome
Postvasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Postvasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Postvasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and it is for that reason considered a special form of scrotal pain syndrome. Pathogenetically, it is thought that postvasectomy pain is caused by the fact that the vas deferens is no longer patent. This may lead to congestion in the epididymis which in turn gives rise to pain because of dilatation of hollow structures (6). Incidence of postvasectomy pain is 2-20% among all men who have undergone a vasectomy (7). In men with postvasectomy pain, only 2-6% have a VAS score > 5 (8). In a large cohort study of 625 men, the likelihood of scrotal pain after 6 months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of scrotal pain was significantly lower in the no-scalpel vasectomy group, at 11.7% compared with 18.8% in the scalpel group (9).

3.3.2.5 Post-inguinal hernia repair
Chronic pain after inguinal hernia surgery is a well recognised phenomenon. An international working group has set up guidelines for prevention and management of postoperative chronic pain following inguinal hernia surgery. They have stated that the most important way of preventing pain is to identify and preserve all three inguinal nerves (10). Chronic scrotal pain is a complication of hernia repair, but in trials, it is seldom reported or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group (4,11-13). In one particular study, there was no difference at 1 year but after 5 years, the open group had far fewer patients with scrotal pain (14).

3.3.2.6 Referred pain
Growing knowledge of pain mechanisms has taught us that pain felt in organ A can be caused by dysfunction of structure B. The best known referred pain is of myofascial origin, especially the trigger points (see Chapter 9). Problems inside the bladder or abdominal cavity can also give rise to pain in the scrotal area. When making a treatment plan for patients with scrotal pain, it is important to remember this phenomenon.

3.3.3 Diagnosis
A physical examination is mandatory in patients with scrotal pain. Gentle palpation of each component of the scrotum is performed to search for masses and painful spots. A rectal examination is done to look for prostate abnormalities and to examine the pelvic floor muscles. Scrotal ultrasound has limited value in finding the cause of the pain. In > 80% of patients, ultrasound does not show abnormalities that have clinical implications (15,16). If physical examination is normal, ultrasound can be performed to reassure the patient that there is no pathology that needs therapy (mainly surgery). Ultrasound can be used to diagnose hydroceles, spermatoceles, cysts and varicoceles. When abnormalities such as cysts are seen, this may play a role in therapeutic decision making. In general practice, it seems that many urologists are performing ultrasound examination in almost all...
patients. Swiss urologists, for instance, perform it in 93% of cases (17).

3.3.4 Treatment
Treatment of chronic scrotal pain is based on the principles of treating chronic pain syndromes, described throughout these guidelines. It is becoming increasingly clear that advances in the nonsurgical management of testicular pain are mainly based on the emergence of pain relief as a specialty. Knowing this, it seems obvious that referring to a multidisciplinary pain team or pain centre should be considered in an early phase of the consultation (18). By doing this, surgery can be postponed or even avoided.

3.3.4.1 Conservative treatment
For conservative treatment, apart from pharmacotherapy, myofascial therapy by specialised physiotherapists should be considered. The pelvic floor muscles should be tested and will often be found overactive, which means that they contract when relaxation is needed. An overactive pelvic floor should be treated with physiotherapy (19-21). More specific myofascial trigger points are found in the pelvic floor, but also in the lower abdominal musculature. Treatment consists of applying pressure to the trigger point and stretching the muscle (22,23) (see Chapter 9).

3.3.4.2 Surgery
In a survey among Swiss urologists, it was found that 74% would do an epididymectomy, 7% an inguinal orchiectomy, and 6% a denervation (17). In the literature, there is consensus on postponing surgery until there is no other option. The only treatment that seems to be effective is microsurgical denervation. Epididymectomy is a choice in selected cases and orchiectomy is the last resort.

3.3.4.1.1 Microsurgical denervation
Considering the fact that all the nerves for the scrotal organs merge into the spermatic cord, it seems reasonable to cut all these nerves in patients with pain. All the studies that have been done were cohort studies but their success rates were high. The size of effect was so remarkable that it is recommended that randomised studies are performed to obtain better proof. The three cohort studies that are found were consistent in the indication criteria, the diagnostic methods applied, and the surgical approach used. All had a follow-up of at least 20 months. They included patients with chronic scrotal pain who did not respond to conservative treatment. Ultrasound showed no abnormalities and a spermatic cord block showed pain relief of > 50%. The surgical approach is inguinal. The cord is transected in such a way that all identifiable arterial structures, including testicular, cremasteric, deferential arteries and lymphatic vessels are left intact. The surgery is performed under magnification by loupe or microscope. Complete relief of pain is achieved in 71-96% and partial relief in 9-17%. This means that 12-15% had no relief of pain after denervation. The complication of testicular atrophy was seen in 3-7% of the operated patients (24-26). There is no difference in success based on the cause of pain. The laparoscopic route for denervation seems feasible but the results are unclear (27).

3.3.4.1.2 Epididymectomy
There is to date no hard evidence available, but expert opinion is clear that epididymectomy should be reserved for patients who have undergone denervation but still have pain. Epididymectomy shows different results in various groups of patients. Epididymectomy shows the best results in patients with pain after vasectomy, or pain on palpation of the epididymis and when ultrasound shows multiple cysts. Patients with chronic epididymitis show bad results with epididymectomy.

The percentage of patients that are cured ranges from 50 to 92% (1,6,28-30). These results are also from cohort studies but the fact that assessment can help in predicting the chance of success makes further studies worthwhile. One study in our search has yielded different results, namely, that postvasectomy patients fared worse and that ultrasound did not help in predicting the result of the operation. No reason was found for this result (9).

3.3.4.1.3 Orchiectomy
Orchiectomy is seen as the last resort in patients with intrascrotal pain, who do not respond to any other treatment. There have been no studies than can help in making a rational decision on whether to perform orchiectomy.

3.3.4.1.4 Vasovasostomy
In postvasectomy pain syndrome, a vasovasostomy might help to overcome the obstruction and thereby improve the pain. Some studies have shown good results but the quality of these studies was limited. Results are as high as 69-84% (31,32).
3.3.5  **Conclusions and recommendations: scrotal pain syndrome**

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The nerves in the spermatic cord play an important role in scrotal pain.</td>
<td>2b</td>
</tr>
<tr>
<td>Ultrasound of the scrotal content is not of help in diagnostics nor treatment of scrotal pain.</td>
<td>2b</td>
</tr>
<tr>
<td>Postvasectomy pain is seen in a substantial number of men undergoing vasectomy.</td>
<td>2b</td>
</tr>
<tr>
<td>Scrotal pain is more often noticed after laparoscopic then after open inguinal hernia repair.</td>
<td>1b</td>
</tr>
<tr>
<td>Microsurgical denervation of the spermatic cord is an effective therapy for scrotal pain syndrome.</td>
<td>2b</td>
</tr>
<tr>
<td>Vasovasostomy is effective in postvasectomy pain.</td>
<td>2b</td>
</tr>
<tr>
<td>Orchietomy is the last resort in treating scrotal pain syndrome.</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with general treatment options for chronic pelvic pain (see chapter 10).</td>
<td>A</td>
</tr>
<tr>
<td>Inform about the risk of postvasectomy pain when counselling patients planned for vasectomy.</td>
<td>A</td>
</tr>
<tr>
<td>To reduce the risk of scrotal pain, open instead of laparoscopic inguinal hernia repair is recommended.</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended that during inguinal hernia repair all the nerves in the spermatic cord are identified.</td>
<td>A</td>
</tr>
<tr>
<td>For patients who are treated surgically, microsurgical denervation of the spermatic cord is recommended.</td>
<td>A</td>
</tr>
<tr>
<td>For patients who do not benefit from denervation it is recommended to perform epididymectomy.</td>
<td>B</td>
</tr>
<tr>
<td>We recommend that orchietomy should not be done, unless all other therapies, including pain management assessment have failed.</td>
<td>C</td>
</tr>
</tbody>
</table>

**Figure 8: Assessment and treatment algorithm for scrotal pain syndrome**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen culture</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td></td>
<td>General treatment options for chronic pelvic pain - chapter 10</td>
</tr>
<tr>
<td></td>
<td>Microsurgical denervation of the spermatic cord</td>
</tr>
<tr>
<td></td>
<td>Inform patients undergoing vasectomy about the risk of pain</td>
</tr>
<tr>
<td>Uroflowmetry</td>
<td>For surgeons: open hernia repair yields less scrotal pain</td>
</tr>
<tr>
<td>Ultrasound scrotum (see text)</td>
<td>For surgeons: identify all nerves during hernia repair</td>
</tr>
<tr>
<td>Pelvic floor muscle testing</td>
<td>Grade B recommended</td>
</tr>
<tr>
<td></td>
<td>Epididymectomy, in case patient did not benefit from denervation</td>
</tr>
<tr>
<td>Phenotyping</td>
<td>Grade C recommended</td>
</tr>
<tr>
<td></td>
<td>In case all other therapies, including pain management assessment have failed, orchietomy is an option.</td>
</tr>
<tr>
<td></td>
<td>Other comments</td>
</tr>
<tr>
<td></td>
<td>Ultrasound is only used to reassure the patient</td>
</tr>
</tbody>
</table>

3.3.6  **References**


3.4 Urethral pain syndrome
3.4.1 Definition
Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women.

3.4.2 Pathogenesis
Based on the definition, there is no well-known pathogenetic mechanism responsible for urethral pain syndrome. There are no data available to answer the question: “how common is dysuria in the presence of negative rigorous investigation of the bladder and urethra?” Some suggestions have been proposed. The intimate relation of the urethra with the bladder (both covered with urothelium) makes it plausible that pathology seen in the bladder is also found in the urethra and causes the same symptoms. This is the case in classifying urethral pain syndrome as a form of BPS. It is obvious that what might cause pain in the bladder could be responsible for urethral pain. Mechanisms thought to be basic for BPS also apply to the urethra. This means that the specific testing with potassium is used to support the theory of epithelial leakage (1,2). Urethral syndrome is supposed to be the same as BPS in that the epithelium is leaking, thereby causing pain.

Another possible mechanism is the neuropathic hypersensitivity following urinary tract infection (3). Symptoms recorded in patients with urethral pain syndrome can also be classified as referred pain from other organs or from the myofascial system. Attention to the phenomenon of referred pain is important. See Chapter 9 for more on the myofascial origin of the pain.

The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multiparity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis (4).

3.4.3 Treatment
There is no specific treatment that can be advised. Management should be multidisciplinary and multimodal (5). Laser therapy of the trigonal region may be a specific treatment. One trial comparing two forms of laser reported good results, but did not compare with sham treatment (6). The majority of publications on treatment of urethral pain syndrome have come from psychologists. In a 2007 review of treatment, Kaur and Arunkalavann have concluded that “treatment at its best” is by “behavioural therapy including biofeedback, meditation, bladder retraining, and hypnosis has been used with some success”, but no reference is given,
and no trials of these arose from the search (3). Baldoni et al. (7) have reported high rates of anxiety and depression, and worsening of symptoms related to stress in patients with urethral pain syndrome. The only treatment trial found was by Baldoni et al. The psychological model that he used is not entirely clear: they have described how “in some cases” psychotherapy enables patients to recognise “the emotional implications” of their urinary problem, leading to both physical and psychological improvement. “Emotional implications” could mean either emotional consequences, consistent with a cognitive behavioural model of chronic pain in which those consequences, rather than the pain itself, are targeted to improve QoL, or it could mean implications for exposure of - emotional conflict or similar psychological disorder, which is presumed to be the aetiology of the urethral pain.

Baldoni et al. recruited 36 female patients diagnosed with urethral syndrome in an Italian urology clinic after negative urography, cystoscopy and urine culture, and urodynamic examination. Thirteen women were randomly selected for psychotherapy, but the method was not blind or free of possible bias. Psychotherapy was 12-16 weekly 1-h sessions, with additional fortnightly group discussion, and focused on associations between urinary symptoms and emotion. Four patients were also prescribed low-dose antidepressants. The control group received usual care but no psychological treatment.

Assessment of symptoms at 6 months and four years after the end of treatment (with loss of two patients from each arm) showed substantial improvement in total urinary symptoms and additionally in pelvic pain, with 9/11 psychotherapy patients with normal levels of urinary function at 6 months, and 8/11 with normal levels at 4 years. Control patients were unchanged at both follow-up points. The trial had significant weaknesses; in particular, the non-blind assignment to treatment condition, the non-standardised measures, and, for the purposes of this review, the combination of all urinary symptoms so that treatment effects on pain were obscured. The authors have noted that the lack of any credible intervention with controls makes it difficult to conclude that it was the particular treatment, rather than the general provision of treatment, which brought about recorded improvement. However, the results can be taken as encouraging the trial of psychological methods, using orthodox outcome measures and more rigorous methodology.

3.4.4 Conclusions and recommendations: urethral pain syndrome

**Conclusions**

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethral pain syndrome may be a part of BPS.</td>
<td>2a</td>
</tr>
<tr>
<td>Urethral pain may be neuropathic hypersensitivity following urinary tract infection.</td>
<td>2b</td>
</tr>
<tr>
<td>There is no specific treatment for urethral pain syndrome.</td>
<td>4</td>
</tr>
<tr>
<td>In patients with significant distress associated with bladder or urethral symptoms, psychological treatment may be worth using to reduce distress and thereby improve function and quality of life.</td>
<td>4</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with general treatment options for chronic pelvic pain (see chapter 10).</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended that patients with urethral pain syndrome are treated in a multidisciplinary and multimodal programme.</td>
<td>B</td>
</tr>
<tr>
<td>When patients are distressed, it is recommended to refer them for pain-relevant psychological treatment to improve function and quality of life.</td>
<td>B</td>
</tr>
</tbody>
</table>

**Figure 9: Assessment and treatment algorithm for urethral pain syndrome**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uroflowmetry</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td>Micturition diary</td>
<td>General treatment options for chronic pelvic pain - chapter 10</td>
</tr>
<tr>
<td>Pelvic floor muscle testing</td>
<td>Grade B recommended</td>
</tr>
<tr>
<td>Phenotyping</td>
<td>Treat in a multidisciplinary and multimodal programme</td>
</tr>
<tr>
<td></td>
<td>Pain-relevant psychological treatment to improve QoL and function</td>
</tr>
<tr>
<td></td>
<td>Data on urethral pain are very sparse and of limited quality</td>
</tr>
</tbody>
</table>

other comments
4. GYNAECOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

4.1 Introduction
Chronic pelvic pain in urological and gynaecological practice is often complex and difficult to treat. The aim is to try and determine a remediable cause and treat it using the most effective available therapy. However, in 30% of cases, no cause is ever determined and this presents a therapeutic challenge to the attendant physician (1).

4.2 Clinical history
Taking a detailed medical history is essential to making a diagnosis. The nature, frequency and site of the pain, and its relationship to precipitating factors and the menstrual cycle, may provide vital clues to the aetiology. A detailed menstrual and sexual history, including any history of sexually transmitted diseases and vaginal discharge is mandatory. Discrete inquiry about previous sexual trauma may be appropriate.

4.3 Clinical examination
Abdominal and pelvic examination will exclude any gross pelvic pathology (tumours, scarring, and reduced uterine mobility), as well as demonstrating the site of tenderness if present. Abnormalities in muscle function should also be sought. Clinical pelvic examination should be a single digit examination if possible, but in most cases a gentle double digit examination is tolerable and sometimes necessary. The usual bimanual examination can generate severe pain so the examiner must proceed with caution. The examination of a woman with CPP can be very difficult, and many authors recommend that it should be directed to the determination of cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3). The degree of tenderness of the muscles and on the perineum (perineal body, levators and obturator internus) should be determined.

4.3.1 Investigations
Vaginal and endocervical swabs to exclude infection are mandatory and cervical cytology screening is advisable. Pelvic imaging, using ultrasound scanning or magnetic resonance, can provide useful information about pelvic anatomy and pathology. Any areas of tenderness detected can provide information related to the possible presence of current or pre-existing visceral disease (2,3). Laparoscopy is perhaps the most useful...
invasive investigation to exclude gynaecological pathology (4,5) and to assist in the differential diagnosis of CPP in women (6). Often, it is combined with cystoscopy (7,8) and/or proctoscopy to help identify the site of multi-compartment pain.

Psychological considerations around laparoscopy
There have been three diverse studies of laparoscopy. Elcombe et al. have shown, by comparing waiting time for laparoscopy, that there was a distinct and lasting improvement in pain consequent on laparoscopy, which was greater than the gradual improvement without further treatment before or after laparoscopy. Improvement was related to beliefs about pain and its meaning in terms of serious disease, and not to medical variables (9).

In another study, showing women a photograph of their pelvic contents taken during laparoscopy, during postlaparoscopy feedback, did not improve pain ratings or beliefs about pain more than feedback without a photograph (10).

Peters et al. compared standard clinical care of patients with CPP (where organic causes of pelvic pain were excluded first and diagnostic laparoscopy was routinely performed, before attention being given to other causes such as psychological disturbances) with a second group, where an integrated approach was chosen from the beginning (equal attention was given to somatic, psychological, dietary, environmental, and physiotherapeutic factors and laparoscopy was not routinely performed) (11). Both groups were similar with respect to clinical characteristics of the patients and the severity of their pain as assessed by various pain parameters. Evaluation of the pain 1 year after the institution of treatment revealed that the integrated approach improved pelvic pain significantly more often than the standard approach for three out of four pain parameters. Though laparoscopy played no important role in the treatment of pelvic pain it was found to be an essential tool to rule out any organic cause for the pain. Equal attention to both organic and other causative factors from the beginning of therapy is more likely to result in a reduction of pelvic pain than just using a standard approach (11). Pain and function improved somewhat more in the integrated group, but scoring was not standardised and hard to interpret.

4.4 Pain associated with well-defined conditions

4.4.1 Dysmenorrhoea
Pain in association with menstruation may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth (6). Secondary dysmenorrhoea suggests the development of a pathological process and it is essential to exclude endometriosis (5), adenomyosis (12) and pelvic infection.

Treatment
Reassurance and an explanation of the cause of dysmenorrhoea are usually helpful, together with the use of simple analgesics, followed by non-steroidal anti-inflammatory drugs (NSAIDs) (13), which are particularly helpful if they are started before the onset of each menstrual cycle. NSAIDs are effective in dysmenorrhoea, probably because of their effects on prostaglandin synthetase.

Suppression of ovulation using oral contraceptive tablets (either combined or progesterone only) or the use of a levonorgestrel intra-uterine device reduces dysmenorrhoea dramatically in most cases and may be used as a therapeutic test. As a result of the chronic nature of the condition, potentially addictive analgesics should be avoided and multidisciplinary pain management strategies, including psychology should be engaged.

4.4.2 Infection
In premenopausal women, a history of pelvic inflammatory disease (PID) must be excluded. Swabs to exclude infections with organisms such as chlamydia and gonorrhoea, as well as vaginal and genital tract pathogens (14), should be taken. Patients’ sexual contacts need to be traced in all cases with a positive culture. If there is any doubt about the diagnosis, laparoscopy may be helpful.

Pelvic inflammatory disease can cause the same clinical findings as endometriosis and can lead to a chronic pain state. Although PID often has a bacterial origin, viral infections such as primary herpes simplex infection need to be excluded because they also present with severe pelvic/vaginal/vulvar pain (15). They are usually associated with ulcerating lesions and inflammation, which may lead to urinary retention (16). Hospitalisation and opiates may be needed to achieve adequate analgesia.

Treatment
Treatment of infection depends on the causative organisms. Subclinical chlamydial infection may lead to tubal pathology, which can result in subfertility in the future. Thus, screening for this organism in sexually active young women is essential to prevent this complication. Standard broad-spectrum antibiotics targeting Gram-
positive and negative organisms are normally recommended. Chronic PID is no longer common in developed countries, but still poses a significant problem for women in developing countries.

4.4.3 Endometriosis and adenomyosis
The incidence of endometriosis is rising in the developed world. The precise aetiology is still a source of debate, but an association with nulliparity is well known.

A diagnosis is usually made when a history of secondary dysmenorrhoea and often dyspareunia exists. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool (17-19).

Endometriotic lesions affecting the urinary bladder or causing ureteric obstructions can occur, as well as lesions affecting the bowel, which may lead to rectal bleeding in association with menstruation. Adenomyosis is associated with augmented pain during menses. It is diagnosed by an ultrasound scan of the uterus, which often shows cystic dilatation of the myometrium (20).

Treatment
As in primary dysmenorrhoea, analgesics and NSAIDs are helpful in easing pain at the time of menstruation. Hormone treatment with progestogens or the oral contraceptive pill may halt progress of endometriosis, but is not curative. A temporary respite may be obtained by using luteinising hormone releasing hormone analogues to create an artificial menopause, although the resulting oestrogen deficiency does have marked long-term side effects, such as reduced bone density and osteoporosis. Thus, these drugs are normally only used before surgery to improve surgical outcome and reduce surgical complications in patients with endometriosis. Surgery for endometriosis is challenging and the extensive removal of all endometriotic lesions is often thought to be essential. This is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief in the removal of early endometriosis compared to sham surgery (21,22). Nevertheless, the best results are achieved laparoscopically, by highly trained and skilled laparoscopic surgeons, in specialist centres (19,23).

A multidisciplinary team is required for the treatment of extensive disease, including a pain management team.

The pain associated with endometriosis is often not proportionate to the extent of the condition and, even after extensive removal of the lesions and suppression of the condition, the pain may continue. In this situation, multidisciplinary pain management strategies, including psychology, should be engaged.

In patients with adenomyosis, there is no curative surgery other than hysterectomy but patients can benefit from hormonal therapy (oral or levo-norgestrol containing intra-uterine devices) and analgesics as outlined above.

4.4.4 Gynaecological malignancy
The spread of gynaecological malignancy of the cervix, uterine body or ovary will cause pelvic pain depending on the site of spread. Treatment is of the primary condition, but all physicians dealing with pelvic pain must be fully aware of the possibility of gynaecological malignancy.

4.4.5 Injuries related to childbirth
Tissue trauma and soft tissue injuries occurring at the time of childbirth may lead to CPP related to the site of injury. Dyspareunia is a common problem leading to long-term difficulties with intercourse and female sexual dysfunction (24). This is often due to transient oestrogen deficiency, commonly seen in the postpartum period and during breastfeeding. Denervation of the pelvic floor with re-innervation may also lead to dysfunction and pain.

Treatment
Treatment with a short course of hormone replacement cream can be therapeutically beneficial. However, often reassurance that the situation will improve on the cessation of breastfeeding is also helpful.

4.4.6 Pain associated with pelvic organ prolapse and prolapse surgery
Pelvic organ prolapse is often an asymptomatic condition, unless it is so marked that it causes back strain, vaginal pain and skin excoriation (25). Prolapse is often a disease of older women, and it is often associated with postmenopausal oestrogen deficiency, which may lead to pain associated with intercourse. Hormone replacement therapy is usually helpful in this circumstance. However, in severe cases associated with a “dragging pain”, the only options are specially designed supportive plastic vaginal devices or surgery. In the past few years, pelvic organ prolapse surgery has gained a new dimension. Most tissue surgery is now augmented by the use of non-absorbable mesh (usually in the form of “mesh kits”) (26-28). Although they may have a role in supporting the vagina, they are also associated with several complications including bladder,
bowel and vaginal trauma (27). In a subset of these patients, chronic pain may ensue, because mesh insertion may cause nerve and muscle irritation (23,24).

**Clinical evaluation**
It is essential that patients are fully evaluated clinically. They may also benefit from specialised imaging, using contrast mediums if necessary, to identify problematic areas. Most patients can be treated by mesh-excisional surgery (29,30), if appropriate, or multidisciplinary pain management strategies, including psychology, should surgery not be relevant.

4.5 **Vaginal and vulvar pain syndromes**

Pain in the vagina or the female external genital organs (the vulva, which includes the labia, clitoris, and entrance to the vagina) is most commonly due to infection or trauma. The latter is usually as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for > 6 months, it can be diagnosed as “vulvodynia” or “chronic vaginal/vulvar pain syndrome” with no known cause. It is still a poorly understood condition and often many doctors do not recognise it as a real pain syndrome. Many women feel isolated because it remains a difficult condition to treat.

There are two main subtypes of vulvodynia: generalised vulvodynia, where the pain occurs in different areas of the vulva at different times; and vulvar vestibulitis, where the pain is at the entrance of the vagina. In generalised vulvodynia, the pain may be constant or occur occasionally, but touch or pressure does not initiate it, although it may make the pain worse. In vulvar vestibulitis, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.

The causes of vulvodynia are many and include:
- History of sexual abuse
- History of chronic antibiotic use
- Hypersensitivity to yeast infections, allergies to chemicals or other substances
- Abnormal inflammatory response (genetic and non-genetic) to infection and trauma,
- Nerve or muscle injury or irritation
- Hormonal changes

Although therapeutic options remain limited and require a multidisciplinary pain management approach, with psychological and physiotherapy input, they can be treated effectively with physiotherapy, stretching exercises and even botulinum toxin, though in the case of the latter the evidence is variable.

**Psychological treatment of chronic vulvar pain**

There are few published accounts of psychological treatment for chronic vulvar pain, distinct from provoked vulvar pain (also known as vulvar vestibulitis, provoked vestibulodynia, or dyspareunia). Three reviews in the past decade, all of provoked as well as chronic vulvar pain, have acknowledged the lack of understanding of aetiology and maintenance of this problem, and emphasise different components of what is known.

Damsted-Peterson et al. have described peripheral and central nervous system changes most consistent with models of chronic pain, as well as local inflammation and pelvic floor tension, and recommend multimodal treatment (31). Lotery et al. have focused on local factors, and recommend education, support, and counselling, but provide no evidence to support these (32). Nanke & Rief have described interaction of physiological, psychological and interpersonal factors, and recommend biofeedback on the basis of uncontrolled studies (33).

The only RCT found has compared cognitive behavioural therapy (CBT), adapted for vulvar pain from a previously published model, with supportive psychotherapy, for a mixed population of women with provoked and chronic vulvar pain (34). CBT consists of behavioural therapy (for sexual problems, increasing general activity, and pain control), relaxation, and cognitive coping skills. Supportive psychotherapy, also for 10 one hour sessions, involves non-directive talking therapy by an accepting and reflective therapist. Follow-up to 1 year has shown that ~40% of patients with both conditions achieve at least 33% (clinically significant) pain relief, with improvement in sexual and emotional function; CBT shows superiority in some outcomes.

4.6 **Summary**

Pain in association with urinary and gastrointestinal symptoms must be considered carefully. For example, patients with bladder pain quite often present with dyspareunia due to bladder base tenderness, so though the dyspareunia may be the focus it is the bladder component that is the main problem. Similarly, in those with anal pain it may be the evacuatory dysfunction that is the main culprit. Conditions, such as pelvic congestion has been cited as a cause of pelvic pain of unknown aetiology, but this diagnosis is not universally recognised (15,16).

It is only when all the above conditions have been excluded that the physician may declare that the
patient has ‘unexplained’ pelvic pain. Treating these patients remains a challenge for all physicians, but quite clearly the best results are obtained from a multidisciplinary approach that considers all possible causes.

4.6.1 Conclusions and recommendations: gynaecological aspects of chronic pelvic pain

<table>
<thead>
<tr>
<th>Clinical state</th>
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<tbody>
<tr>
<td>Clinical history and examination</td>
<td>Mandatory to making a diagnosis</td>
</tr>
<tr>
<td>Investigations</td>
<td>Mandatory to making a diagnosis</td>
</tr>
<tr>
<td>Pain associated with well-defined conditions</td>
<td>Laparoscopy is well tolerated and does not appear to have negative psychological effects</td>
</tr>
<tr>
<td>Dysmenorrhoea: effective therapeutic options</td>
<td>3</td>
</tr>
<tr>
<td>Infection: effective therapeutic option</td>
<td>3</td>
</tr>
<tr>
<td>Endometriosis: effective therapeutic options</td>
<td>1b</td>
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<tr>
<td>Gynaecological malignancy: effective therapeutic options</td>
<td>3</td>
</tr>
<tr>
<td>Injuries related to childbirth: effective therapeutic options</td>
<td>3</td>
</tr>
<tr>
<td>Pain associated with pelvic organ prolapse: effective therapeutic options</td>
<td>3</td>
</tr>
<tr>
<td>Vaginal and vulvar pain syndrome</td>
<td>Diagnosis and therapeutic interventions</td>
</tr>
<tr>
<td>Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function</td>
<td>1b</td>
</tr>
</tbody>
</table>

Recommendations:

All women with pelvic pain should have a full gynaecological history and evaluation, and including laparoscopy is recommended to rule out a treatable cause (e.g. endometriosis).

Provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.

Provide a multidisciplinary approach to pain management in persistent disease states.

Recommend psychological treatment for refractory chronic vulvar pain.

Use alternative therapies in the treatment of chronic gynaecological pelvic pain.

Figure 10: Assessment and treatment gynaecological aspects in chronic pelvic pain

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynaecological examination</td>
<td>Laparoscopy to rule out treatable causes</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Hormonal therapy in well defined states</td>
</tr>
<tr>
<td>Laparoscopy (see text)</td>
<td>Multidisciplinary approach in persistent disease states</td>
</tr>
<tr>
<td></td>
<td>Psychological treatment for refractory chronic vulvar pain</td>
</tr>
</tbody>
</table>

4.7 References


5. **GASTROINTESTINAL ASPECTS OF CHRONIC PELVIC PAIN**

5.1 **Introduction**

This chapter describes CPP perceived to be associated with the gastrointestinal tract, which is mainly due to functional disorders and cannot be explained by structural or specific well-defined diseases of the pelvis.

Some points to note:

- There may be a considerable overlap of the gastrointestinal with other pelvic pain syndromes.
- Defined gastrointestinal conditions with specific structural defects and diseases may coexist. Behavioural changes such as straining can lead to organic diseases such as rectal prolapse, solitary rectal ulcer syndrome, or pudendal nerve injury with consecutive faecal incontinence.
- Some structural gastrointestinal abnormalities (e.g., postpartum anal sphincter defects, or small rectoceles) are often observed in asymptomatic individuals and may be coincidental with the gastrointestinal pelvic pain syndrome.
- Different diseases can aggravate previously asymptomatic functional disorders which may become symptomatic such as faecal incontinence in patients with diarrhoea of different origins or anal fissure in patients with dyssynergic defecation.
- Finally, we need to consider that all functional disorders such as anorectal pain are defined on the basis of retrospectively evaluated longstanding symptoms, which ideally would have been registered prospectively with symptom diaries (1,2).
5.2 Clinical history

Functional anorectal disorders are diagnosed by symptoms, supplemented by objective findings. The predominant symptoms patients are interviewed about are discomfort or pain in relation to their bowel habits, daily activities, and eating. A precise history of dysfunctional voiding or defecation should be asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III questionnaire for anorectal pain). Excessive straining at most defecations, anal digitations in dyssynergic defecation, and a sensation of anal blockage may be found in patients with chronic anal pain. History of anxiety and depression with impaired QoL is often encountered in anorectal functional disorders and should be evaluated.

5.2.1 Clinical examination and investigations

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be searched thoroughly in patients with anal pain. Rectal digital examination findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the levator ani syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and Unspecified Functional Anorectal Pain and is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during bimanual examination by the gynaecologist to diagnose an enterocele or cystocele.

5.2.2 Diagnostic assessment

The Rome III criteria for diagnosis of functional anorectal diseases include symptoms for each specific functional disorder as listed below. The gastrointestinal diagnostic assessment should be performed in an interdisciplinary manner, preferably at a pelvic floor centre by a dedicated team and appropriate testing. The most frequently performed investigations are flexible rectosigmoidoscopy or colonoscopy, pelvic ultrasound, anorectal endosonography and anorectal manometry combined with anal EMG and balloon expulsion test. Three-dimensional anorectal ultrasound has become an indispensable readily available tool for the specialised proctologist. Perineal ultrasound offers the advantage of sphincter imaging without insertion of the transducer into the rectum. MRI in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. MRI studies outline simultaneously the anatomy of the pelvic floor and allow us to visualise different structural and functional pathologies, by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g., ultrasound gel). The following pathologies can be visualised: pelvic floor descent, an abnormal anorectal angle while squeezing and straining, rectal intussusception, rectocele, enterocele and cystocele. However, limitations of MR defecography are the left lateral position and the limited space for the patient, which may reduce the ability to strain and hereby reduce the sensitivity of the method, underestimating the size of entero-and rectoceles as well as the amount of intussusception. Surgical consultations should be available for all patients, plus referral to an urogynaecologist or urologist when indicated. Biofeedback treatment, botulinum toxin injection, and percutaneous tibial nerve and sacral nerve stimulation should be available as a complementary therapeutic option to medical and surgical treatment.

5.3 Pain associated with well-defined conditions

5.3.1 Haemorrhoids

Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapsed or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anticoagulation therapy, or those with clotting disorders. Different treatments of haemorrhoids have been evaluated by two systematic Cochrane reviews. Excisional haemorrhoidectomy (EH) has been compared to the less-invasive technique of rubber band ligation (RBL), and has been shown to increase pain, with more complications and time off work. However, despite these disadvantages of EH, complete long-term cure of symptoms is increased by surgery, and minor complications are accepted by patients. RBL is the choice of treatment for grade II haemorrhoids, whereas EH should be reserved for grade III haemorrhoids or recurrence after RBL (3). New stapler techniques of haemorrhoidopexy are associated with a higher long-term risk of recurrence and prolapse compared to conventional EH. Further studies are needed (4).

5.3.2 Anal fissure

Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond 6 weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn’s
disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures. Medical therapy with nitrates and calcium channel blockers resulting in sphincter relaxation is effective (5). Botulinum A toxin injection is indicated for fissures that are refractory to topical nitrates. Surgery with lateral internal sphincterotomy is the most studied procedure but carries the risk of postoperative faecal incontinence, and may be replaced by fissure excision combined with botulinum toxin or anal advancement flap.

5.3.3 Proctitis
Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids. Tricyclic antidepressants at low dose can be effective in this situation when acute exacerbation has been ruled out (6,7).

5.3.4 Constipation
Constipation is usually not associated with CPP but is often associated with and may induce increased pelvic discomfort and psychological distress. Dyssynergic defecation is the most common aetiology and responsible for 50% of causes of constipation. Dyssynergia describes an overactivity of pelvic floor muscles during defecation and the partial or complete inability to relax voluntarily pelvic floor muscles. Stool diaries and physiological testing followed by biofeedback treatment when indicated have been established as standard care in randomised controlled trials (8).

5.4 Chronic anal pain syndrome
5.4.1 Diagnostic criteria for chronic anal pain syndrome (chronic proctalgia) according to the Rome III criteria are as follows and must include all of the following:
1. Chronic or recurrent rectal pain or aching.
2. Episodes last at least 20 min.
3. Exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and coccygodynia.

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis (2).

The chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle. This common and debilitating condition is frustrating to treat. Pathophysiology of pain is thought to be due to overactivity of the pelvic floor muscles. Chiarioni et al. have recently published an RCT demonstrating that biofeedback treatment was superior to electrogalvanic stimulation and massage for treatment of the levator ani syndrome. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. Eighty-seven percent of patients with tenderness of the puborectalis muscle (Rome II: Highly likely Levator Ani Syndrome) reported adequate relief after one month of biofeedback versus 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at 12 months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: Highly likely and Possible Levator Ani Syndrome), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50-ml water-filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome (9). The pathophysiology of the chronic anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

5.4.2 Botulinum toxin in pelvic pain
Chronic pelvic pain associated with spasm of the levator ani muscles and treatment of the puborectalis and pubococcygeus muscle by botulinum toxin appears to be promising in some women, as shown in a pilot study (n = 12). The inclusion criteria were dependent only on vaginal manometry with overactivity of the pelvic floor muscles, defined as a vaginal resting pressure > 40 cm H$_2$O. Although dyspareunia and dysmenorrhoea improved, non-menstrual pelvic pain scores were not significantly ameliorated (10). In the following double-blinded, randomised, placebo-controlled trial, the same group defined pelvic floor myalgia according to the two criteria of tenderness on contraction and hypertension (> 40 cm H$_2$O) and included 60 women. In this larger study, non-menstrual pelvic pain was significantly improved compared to that treated with placebo (VAS score 51 vs. 22; P = 0.009). It was concluded therefore that botulinum toxin is effective for reducing pelvic-floor-muscle associated pain with acceptable adverse effects such as occasional urinary and faecal stress incontinence (11).
However, recently, a small RCT failed to show any benefit of botulinum toxin, and sacral nerve stimulation has been reported to be somewhat beneficial in an uncontrolled study, showing improvement in less than half the patients (12,13).

5.4.3 **Intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for 3 months and before 3 months:**

1. Recurrent episodes of pain localised to the anus or lower rectum.
2. Episodes last from several seconds to minutes.
3. There is no anorectal pain between episodes.

Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 min. The pain may be cramping, aching or stabbing and may become unbearable. However, most patients do not report it to their physicians and pain attacks occur less than five times a year in 51% of patients. Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled beta-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration (14). Other treatment options are topical diltiazem and botulinum toxin (15). However, there is still some controversy as regards the duration of pain of intermittent chronic and chronic anal pain syndrome and RCTs do often use different definitions extending the pain duration in order to better evaluate the study-drug action.

5.5 **Summary**

Chronic pelvic pain is an interdisciplinary entity needing multispecialty and multidisciplinary diagnostic assessment by a gastroenterologist, urologist, gynaecologist and pain teams as appropriate, with the input of physicians, psychologists and physiotherapists amongst others. Anorectal pain is investigated best by endoscopic and functional testing to rule out structural disease that can be treated specifically. Chronic pelvic pain due to functional disorders remains a therapeutic challenge that may respond to biofeedback therapy, electrogalvanic syndrome and botulinum toxin in the case of levator ani syndrome and defecatory defects associated with pelvic pain.

5.5.1 **Conclusions and recommendations: anorectal pain syndrome**

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5.6 References


6. PERIPHERAL NERVE PAIN SYNDROMES

6.1 Neuropathic pain
Much has been written on the subject of peripheral neuropathic pain (1-4) including its diagnosis and treatment. There are some fundamental principles that are worth considering:

1. Nerve injury is associated with changes both within the peripheral nervous system (PNS) and the central neural axis including the higher centres. These changes serve to produce an increasing disparity between stimulus and response (Chapter 2).

2. In the PNS, nerve damage may produce a neuroma that can source a ongoing afferent central activity. The neuroma may be discreet and palpable to touch or en-passage and not palpable. Neuromas are sensitive and respond to: compression (e.g., by the surrounding tissue or digital pressure), temperature change and adrenergic stimulation. Sympathetic nerve fibres can grow into neuromas as well as the associated dorsal root ganglia, which may result in sensitivity to body adrenaline changes such as through mood and environment with subsequent changes in pain.

3. Windup is a progressive increase in centrally elicited action potentials per unit peripheral stimulus. A severe acute insult or a chronic repeated stimulus may result in a transient windup phenomenon becoming permanent through immediate gene activation and neurochemical and structural neuronal changes within the CNS. These long-term changes in central sensitisation are associated with dysfunction of the afferent sensory nervous system and perception, as well as efferent motor, vasomotor and pseudomotor activity within the pathways of the injured nerve (5).

4. These central changes may result in abnormal afferent processing for nerves other than those originally damaged, so that increased perception (pain, allodynia and hyperaesthesia) from an area greater than the expected pattern may occur. In the case of tissues with innervation that overlaps with an injured nerve, somatic and visceral hypersensitivity (e.g., sensory urge with increased frequency of
voiding/evacuation) may be perceived from those tissues.

Essentially, what may be considered a simple nerve injury may be magnified by the CNS so that a whole region may be involved and a non-specific regional pain syndrome may arise. There is also a suggestion that involvement of both the peripheral and CNS in the control of the endocrine and immunological system may also become abnormal. Certainly, there is a complex interaction between nerve injury, emotional well being, disability and widespread pain. A proportion of patients go on to develop chronic fatigue syndrome, fibromyalgia and immunological disorders (6-8).

6.2 Anatomy
When considering pelvic pain mechanisms, nerves associated with the pelvis/genitalia are generally divided into thoraco-lumbar and sacral root afferents. The hypogastric plexus is mixed autonomic (sympathetic and parasympathetic) and may contain afferents associated with pain.

6.2.1 The anterior groin nerves
The iliohypogastric nerve arises from L1 and its anterior branch supplies the skin above the pubis; its lateral cutaneous branch is distributed to the anterolateral part of the buttock.

The ilioinguinal nerve is smaller than the iliohypogastric nerve; it also arises from L1 and is distributed to the skin of the groin and mons pubis.

The genitofemoral nerve arises from L1 and L2. It passes through the psoas muscle, then down it to emerge through the deep inguinal ring. Its genital branch supplies the cremaster muscle and a part of the anterior and lateral scrotum. The femoral branch passes close to the external iliac artery, the deep circumflex iliac artery and the femoral artery to be distributed to the upper part of the femoral triangle. The two branches of the femoral branch may separate at any level, therefore, sensory phenomena associated with nerve damage depend upon the level of the lesion and individual variability.

The lateral cutaneous nerve of the thigh arises from L2 and L3 and eventually leaves the abdomen behind or through the inguinal ligament at a variable distance medial to the anterior superior iliac spine. In the thigh, it divides into an anterior branch that supplies the anterolateral skin of the thigh, approximately 10 cm down from the inguinal ligament to the knee. The posterior branch supplies the skin more laterally from the greater trochanter, down to the mid-thigh.

The obturator nerve arises from L2-L4, descends through the psoas muscle, runs around the pelvis in close proximity to the obturator internus muscle and obturator vessels, and leaves the pelvis via the obturator foramen. This nerve has significant motor innervation, and its cutaneous branch is distributed primarily to the skin on the medial aspect of the knee.

6.2.2 The posterior subgluteal triangle nerves
The posterior triangle area is the area defined superiorly by the upper border of the piriformis, inferiorly by the lower border of quadratus femoris, laterally by the greater trochanter and medially by and lateral border of the sacrum, the lateral borders of the sacrotuberous ligament and ischial tuberosity. This region contains the sciatic nerve, posterior femoral cutaneous nerve (which branches into the posterior cutaneous perineal branch and the cluneal nerves), the nerve to the obturator internus muscle, and the pudendal nerve. These nerves pass deep to the piriformis muscle and superficial to the superior gemellus and obturator internus muscles. Injury in this area may damage one or more of these nerves (Figure 13) (9-15).

6.2.3 Branches of the pudendal nerve
The pudendal nerve has its origins at the S2-S4 levels. S2 and S3 also contribute to the sciatic nerve and S4 to the coccygeal plexus and the anococcygeal nerves.

The pudendal nerve has three main branches: the inferior anorectal nerve, the superficial perineal nerve (which terminates as cutaneous branches in the perineum and posterior aspect of the scrotum), and the deep perineal nerve, which is distributed to the pelvic structures (innervating parts of the bladder, prostate and urethra). This branch terminates as the dorsal nerve of the penis/clitoris, which innervates the glans. In addition to sensory branches, the pudendal nerve provides motor innervation to anal and urethral sphincters, as well as to the bulbospongiosus and ischiocavernous muscles (involved in the bulbocavernosal response, orgasm and ejaculation). Autonomic fibres also pass with the pudendal nerve and are derived from the presacral parasympathetic as well as sympathetic fibres via the hypogastric plexi.

6.2.4 Anatomical relations of the pudendal nerve (Figure 13)
The anatomy may be variable, however, the three roots that form the pudendal nerve usually merge anterior to the sacrum and inferior to the piriformis muscle.

The pudendal nerve leaves the pelvis via the greater sciatic notch to enter the subgluteal region. In the
posterior subgluteal triangle (the area bordered by the inferior edge of the piriformis muscle, the sarotuberous ligament medially and the upper border of the rectus femoris muscle inferiorly), the nerve emerges from under the inferior border of the piriformis muscle with its associated pudendal artery and veins; it is medial to the nerve innervating the obturator internus muscle, which is medial to the posterior femoral cutaneous nerve (which divides into its cutaneous branch but also the inferior cluneal nerves and perineal nerves), which is medial to the sciatic nerve. These anatomical relations are important for neurotracing techniques used for nerve blocks and because symptoms in those nerve territories also help with diagnosis (16-20).

The pudendal nerve leaves the subgluteal region as it wraps around the superficial surface of the ischeal spine/sacrospinal ligament to re-enter the pelvis (9,10) via the lesser sciatic notch (between the more ventral sacrospinal ligament and the more dorsal sacrotuberal ligaments). This occurs 15% of the time at the enthesis of the spine and the ligament; 75% of the time, it is more medial, and 10% of the time, it wraps around the spine. The sacrotuberal ligament may have a sharp superior border, be wide, and as a result, close to the spinosacral ligament, or be divided with the pudendal nerve passing through it. All of these features may predispose to nerve injury.

As the pudendal nerve re-enters the pelvis below the levator muscles, it runs within a fascial canal medial to the internal obturator muscle (Alcock’s canal).

The inferior anorectal branch may never be a true branch of the pudendal nerve, and may have its origins directly from the sacral roots. As a consequence, pain associated with pudendal nerve injury may not involve the anorectal area. Similarly, pain may only be perceived in the anorectal area if the main pudendal nerve is not involved. In 11% of cases, the inferior anorectal nerve pierces the sacrospinal ligament, possibly increasing the risk of entrapment. Other variations of the anorectal branch exist with the nerve branching off from the main pudendal nerve at any point in the gluteal region or within the pelvis. In 56% of cases, the pudendal nerve is a single trunk as it re-enters the pelvis. Some people have two or three pudendal nerve trunks.

**Figure 13: Anatomical relations of the pudendal nerve**

Source: Drake, Vogel, & Mitchell: GRAY’s ANATOMY FOR STUDENTS, 2004 Elsevier Inc.
6.2.5 **Afferent nerves and the genitalia**

- The afferents from the skin of the genitals pass via a complex of multiple sensory nerves and this makes the anatomical diagnosis of nerve injury as a cause of pain difficult.
- The anterolateral part of the scrotum/labia majora has afferents associated with the genitofemoral nerve primarily; there may also be some involvement of the ilioinguinal and iliohypogastric nerves.
- The posterior scrotal/labia branches of the pudendal nerve transmit sensation from the posterior scrotum/labia majora.
- The penis shaft is innervated on its dorsal surface by the genitofemoral, ilioinguinal and iliohypogastric nerves, and the ventral surface by the perineal branches of the posterior femoral cutaneous nerve and cutaneous branches of the pudendal nerve.
- The glans penis/clitoris is associated with the dorsal nerve of the penis/clitoris, the terminal branch of the pudendal nerve.
- All the nerves that are associated with the scrotum may also receive afferents from the testes, although classically, the nerves from the testes are usually associated with the genitofemoral nerve (thoracolumbar as opposed to sacral roots).
- The superficial branches of the pudendal’s superficial perineal nerve and the perineal branch of the posterior femoral cutaneous nerve receive afferents from the perineal skin.
- Deeper afferents from the perineum and from some of the pelvic organs pass to the pudendal nerve via its deep perineal branch.

6.2.6 **Afferents in the autonomic plexus**

The pelvic plexus is associated with both the parasympathetic and sympathetic nerves, and as well as afferents associated with these pathways, afferents may travel back to the sacral and thoracolumbar roots with these autonomic nerves. Sites for injury and possible intervention may thus include: the ganglion impar, superior hypogastric plexus, inferior hypogastric plexus, and lumbar sympathetic trunk, as well as more central spinal root areas.

6.3 **Aetiology of nerve damage**

6.3.1 **Anterior groin nerves - aetiology of nerve damage**

The primary afferents of the anterior groin nerves enter the spinal cord at the thoracolumbar level (T10 to L3). Thoracolumbar spinal pathology and any pathology along the course of the nerve may result in neuropathic pain in the distribution of these nerves. As well as neoplastic disease, infection and trauma, surgical incisions and postoperative scarring may result in nerve injury (21-23).

6.3.2 **Pudendal neuralgia - aetiology of nerve damage**

**Anatomical variations**

Anatomical variations may predispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) (8,10).

The pudendal nerve may be damaged due to local anatomical variation at the level of:

1. The piriformis muscle. For example, as part of a piriformis syndrome: in some cases, the nerve may pass through the muscle and hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.
2. The sacrospinal/sacrotuberous ligaments, possibly accounting for 42% of cases.
3. Within Alcock’s canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.

The site of injury determines the site of perceived pain and the nature of associated symptoms (e.g., the more distal the damage, the less likely the anal region will be involved).

6.3.3 **Surgery**

In orthopaedic hip surgery, pressure from the positioning of the patient, where the perineum is placed hard against the brace, can result in pudendal nerve damage (24,25). The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous colpopexy is clearly associated with pudendal nerve damage in some cases (26,27). In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.
6.3.4 **Trauma**
Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.

6.3.5 **Cancer**
Tumours in the presacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer (13).

6.3.6 **Birth trauma**
This is more difficult to be certain about (12). The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life.

6.3.7 **Elderly women**
Child birth (28) and repeated abdominal straining associated with chronic constipation (29) are thought to predispose elderly women to postmenopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor.

In the Urogenital Pain Management Centre, the commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting (especially young men working with computer technology); and postmenopausal older women. Trauma- and cancer-related pain is less frequent, cycling whereas classical appears to be rarely seen.

6.4 **Diagnosis for pudendal neuralgia**

6.4.1 **Differential diagnosis of other disorders**
Other forms of neuropathic pain (30,31).

As well as the pudendal nerve, there are several other nerves that may mimic the symptoms of pudendal neuralgia if they are damaged.

**Inferior cluneal nerve.** This is a branch of the posterior femoral cutaneous nerve. This nerve is prone to injury in the ischial region. Cluneal nerve injury produces a sensation of pain perceived more laterally than that for pudendal neuralgia.

**Sacral nerve roots.** The S2-S4 nerve roots may be involved. This is an important differential diagnosis as tumours must be excluded.

**Cauda equina syndrome.** Lumbar spinal pathology involving the cauda equina may result in an intractable neuropathic pain.

**Ilioinguinal, iliohypogastric and genitofemoral nerves.** Injury to these nerves or their roots may occur from thoracolumbar pathology, abdominal posterior wall conditions, surgery, and entrapment in the groin. The pain may extend into the groin, anterior perineum and scrotum/labia majorum. If the femoral branch of the genitofemoral nerve is involved, pain may extend into the inner thigh.

**Referred spinal pain**
Pain from thoracolumbar pathology may refer to the groin. Spinal pain may become associated with muscle hyperalgesia and trigger points. The muscle associated pain may spread to involve a range of muscles, including the pelvic floor muscles with resultant pelvic pain.

**Musculoskeletal disorders**

**Trigger points** associated with localised tenderness and pain may be detected in the piriformis, obturator internus, levator ani, bulbocavernosal and ischeocavernosal muscles, as well as the gluteal, adductor, rectus abdominus and spinal muscles. All of these may refer the pain to or close to the pelvis.

**Pathology of the joints** (sacroiliac, pubic symphysis, hip and spinal) may also refer into the pelvis.

**Coccyx pain syndrome,** a painful coccyx may occur for a number of reasons (Chapter 2).

6.4.2 **Clinical presentation of pudendal neuralgia**

6.4.2.1 **Age**
There is a wide age range, as one would expect with a condition that has so many potential causes. There is a suggestion that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem (32-34).
6.4.2.2 Sex
Six out of ten cases are observed in women.

6.4.2.3 History
A proportion of patients will be able to relate the onset of pain to an acute event such as surgery, sepsis or trauma, and occasionally, cycling for a prolonged period. Chronic injury is more frequent, such as associated with sitting for prolonged periods over time. Many will be idiopathic.

The pain is classically perceived in the perineum from anus to clitoris/penis. However, less-specific pain distribution may occur, and this may be due to anatomical variation, involvement of branches of the nerve rather than the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pains develop in the muscles due to immobility and disability, possibly magnified by the CNS changes.

Burning is the most predominant adjective used to describe the pain. Crushing and electric may also be used, indicating the two components - a constant pain often associated with acute sharp episodes. Many patients may have the feeling of a swelling or foreign body in the rectum or perineum, often described as a golf or tennis ball. The term pain has different meanings to patients and some would rather use the term discomfort or numbness.

Aggravating factors include any cause of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

6.4.2.4 Associated features
Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); alldynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for the visceral and muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dispareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with CPP are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers.

Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also to the lack of afferent perception.

6.4.2.5 Clinical examination
A full clinical examination of the spinal, muscular, nervous and urogenital systems is necessary to aid in diagnosis of pudendal neuralgia, especially to detect signs indicating another pathology. Often, there is little to find in pudendal neuralgia and frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, alldynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischeal spine and/or Alcock’s
canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominis or paraspinal muscles).

6.4.2.6 Investigations
Magnetic resonance imaging scans of the pelvis are usually normal although some practitioners claim them to be useful (35,36). However, MRI scans of the pelvis and spine (mid thoracic to coccyx) are considered essential to help with the differential diagnosis of pudendal neuralgia. Electrophysiological studies may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernous reflex (25,34,37-39). However, for an abnormality to be detected, significant nerve damage is probably necessary. Pain may be associated with limited nerve damage, therefore, these investigations are often normal in patients thought to have pudendal neuralgia.

6.5 Management of pain associated with nerve damage
The approach to managing a patient with pain following nerve damage is similar irrespective of the nerve involved. There is a suggestion that early treatment has a better prognosis. The general principles are covered in chapter 10 of this document.

6.5.1 Pudendal neuralgia and injections
The role of injections may be divided into two. First, an injection of local anaesthetic and steroid at the sight of nerve injury may produce a therapeutic action. The possible reasons for this are related to the fact that steroids may reduce any inflammation and swelling at the site of nerve irritation, but also because steroids may block sodium channels and reduce irritable firing from the nerve. The second possible benefit of local infiltration is diagnostic. It has already been indicated that when the pudendal nerve is injured there are several sites where this may occur. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped (16-20,35,40-44).

Infiltration at the ischeal spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of ultrasound. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block.

Currently, infiltration of the pudendal nerve within Alcock’s canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Similarly, trigger point injections into tender areas within muscles may also be considered. Pulsed radiofrequency stimulation has also been suggested as a treatment (45).

6.5.2 Pudendal neuralgia and surgery
Decompression of an entrapped or injured nerve is a routine approach and probably should apply to the pudendal nerve as it applies to all other nerves. There are several approaches and the approach of choice probably depends upon the nature of the pathology. The most traditional approach is the transgluteal approach; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery (11,14,33,35,46-48).

Currently, there has been only one prospective randomised study (11). This suggests that, if the patient has had the pain for < 6 years, 66% of patients will see some improvement with surgery (compared to 40% if the pain has been present for > 6 years). Surgery is by no means the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut, most patients are grateful to have undergone surgery but many still have symptoms that need management.

6.5.3 Pudendal neuralgia and neuromodulation
Pudendal neuralgia represents a peripheral nerve injury and as such should respond to neuromodulation by implanted pulse generators. However, it is important that the stimulation is perceived in the same site as the perceived pain. Spinal cord stimulation (SCS) may be effective for thoraco-lumbar afferents. However, it is difficult to obtain appropriate stimulation from SCS for the sacral nerves including pudendal. There is limited experience with sacral root stimulation and as a result stimulation for pudendal neuralgia should only be undertaken in specialised centres and in centres that can provide multidisciplinary care (49-51).
6.6 Conclusions and recommendations: pudendal neuralgia

Conclusions

<table>
<thead>
<tr>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur as a result of injury to one or more of many nerves. The anatomy is complex.</td>
<td>2</td>
</tr>
<tr>
<td>There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.</td>
<td>1</td>
</tr>
<tr>
<td>Investigations are often normal.</td>
<td>2</td>
</tr>
<tr>
<td>The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.</td>
<td>1</td>
</tr>
<tr>
<td>There are multiple treatment options with varying levels of evidence.</td>
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Recommendations

<table>
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<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>It is important to rule out confusables diseases.</td>
<td>A</td>
</tr>
<tr>
<td>If a peripheral nerve pain syndrome is suspected, early referral should occur to an expert in the field, working within a multidisciplinary team environment.</td>
<td>B</td>
</tr>
<tr>
<td>Imaging and neurophysiology may help with the diagnosis, but the gold standard investigation is an image and nerve locator guided local anaesthetic injection.</td>
<td>B</td>
</tr>
<tr>
<td>Neuropathic pain guidelines are well established. Standard approaches to management of neuropathic pain should be utilised.</td>
<td>A</td>
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Figure 14: Assessment and treatment algorithm for peripheral nerve pain syndrome

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Extended neurological tests</td>
<td>Refer to an expert when a peripheral nerve problem is suspected</td>
</tr>
<tr>
<td>Extended history on nature of pain</td>
<td>Imaging may be of help (53)</td>
</tr>
<tr>
<td>Standardised questionnaires (52)</td>
<td>Neurophysiology may be of help (54)</td>
</tr>
<tr>
<td></td>
<td>Treatment is as for any other nerve injury.</td>
</tr>
<tr>
<td></td>
<td><a href="http://publications.nice.org.uk/neuropathic-pan-cg96">http://publications.nice.org.uk/neuropathic-pan-cg96</a></td>
</tr>
</tbody>
</table>

6.7 References


7. SEXOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

7.1 Introduction
In general, human sexuality has three aspects - sexual function, sexual self-concept, and sexual relationships. Pain can affect self-esteem, one’s ability to enjoy sex and relationships. Healthy sexuality is a positive and life-affirming part of being human. The capacity to experience optimal comfort and satisfaction in sexual expression also requires basic physical abilities. Essentially, these include intact sensory and motor processes, and the ability to move with ease.

Chronic pain may hinder the ability to move freely, and thus, may limit the positions one can get into to have sex. Second, chronic pain may affect the ability to respond sexually and conversely; in CPP the sex act can be associated with pain that can be inhibiting. Research on male sexual dysfunction highlights the importance of considering partners and the impact that male sexual problems have on their partners. Sexual dysfunction occurs in an interpersonal context and has implications for both partners in a relationship. Chronic pain also impacts the sexual and interpersonal functioning of couples; declines in sexual activity and reduced relationship satisfaction have been noted among patients with chronic pain and their partners (1,2).

It is recommended that a biopsychosocial model of CPPS should be incorporated into future research, and that research considers the role that sexual and relationship variables may play in couples’ adjustment.

The sexual-response cycle is divided into five phases: desire, arousal (excitement), plateau, orgasm and resolution. They are actually all part of a continuous process of sexual response. There is much variation among individuals, as well as between different sexual events and there are different models to describe the sexual responses (3).
During the sexual response cycle, the different phases are controlled by a different part of the brain and spinal cord. In each of these phases chronic pain and CPP in particular can cause disturbances (4).

- The Desire Phase begins in the “pleasure centres” of the brain and controls a person’s sexual appetite or drive. Pain or even the fear of pain can decrease desire, making the person uninterested in sex. In some cases, however, having sex may actually help to relieve pain.
- The Arousal Phase is associated with the swelling of the blood vessels in a man’s penis and in a woman’s labia, vagina, and clitoris. This swelling causes an erection in the penis and in the clitoris and release of lubricating fluids. If a person experiences pain at the time of becoming excited, the excitement may be reversed, in a man the penis will become limp and in a woman the lubrication will stop, leading to dryness.
- The Orgasm Phase describes a genital reflex controlled by the spinal cord, which causes the genital muscles to contract, involuntarily releasing sexual tension and swelling that build up during the excitement phase. In some cases, pain prevents people from reaching this phase.

7.2 General considerations
Pelvic pain in women (5) and in men (6) is associated with significant sexual dysfunction. While chronic pain impacts all aspects of functioning, including work, family relationships, and social activities, the most frequent complaint cited by patients with CPP is sexual dysfunction (7). Factors contributing to sexual dysfunction in patients with chronic pain are multifactorial and contextual (8), and may be related to comorbidity with depression (9,10), use of antidepressant medications (11), and relationship satisfaction (12), among many other factors. There are reports of increased rates of past sexual abuse which may have negative impact on sexual function (13,14). Chronic pelvic pain may have a higher association with sexual dysfunction than other types of chronic pain. CPP specifically involves areas intimately connected to sexuality, which may negatively impact one’s body image and sexual self-esteem (15), and also affects both partners in the relationship (16).

7.3 Pelvic floor involvement in sexual function and dysfunction
The pelvic floor of the male appears to have some impact on sexual function, although its exact role is unclear. Erection is a neurovascular event in which the smooth and striated musculature of the corpora cavernosa and pelvic floor play a role in facilitating and maintaining the erection (17). In ejaculation and orgasm the rhythmic contraction of the bulbocavernous and ischiocavernous muscles is perceived as pleasurable. Ejaculation is controlled by the sympathetic nervous system and performed with help of the pelvic floor muscles. Controlling the pelvic floor muscles may delay the onset of ejaculation through an active relaxation of the pelvic floor muscles. This is a learned technique, which may be mastered using pelvic floor biofeedback. Pelvic floor exercise and biofeedback for the treatment of both erectile dysfunction (ED) and premature ejaculation (PE) have been reported on in the literature.

Early studies maintained that strong pelvic floor muscles in women, particularly the ischiocavernous muscle that attaches to the clitoral hood, were crucial for adequate genital arousal and attainment of orgasm (18), and that weak muscles may provide insufficient activity necessary for vaginal friction or blood flow, and inhibit orgasmic potential (19). It has also been proposed that sexual pleasure is enhanced for both partners by genital responses provided by contraction of the levator ani (20). It stands to reason, therefore, that better control over pelvic floor muscle contraction and relaxation could improve sexual function.

However, few studies are available to support this notion. In a Scandinavian randomised controlled study pelvic floor muscle training has been demonstrated to improve QoL and sexual function in women with urinary stress incontinence (20). In a Turkish study, improvement in sexual desire, performance during coitus, and achievement of orgasm were reported in women (n = 42) who received pelvic floor muscle re-education (21).

The effectiveness of physical therapy in treating sexual pain disorders has been reported upon in the literature as well. Retrospective studies have reported on a success rate of 77% (22,23). Goetsch recently reported her findings that physical therapy may serve as important adjunct to surgery for “vulvar vestibulitis” (vulvar pain syndrome) (24).

7.4 Chronic pelvic pain and sexual dysfunction of the male
In the BACH study, Hu et al. found that men who reported having experienced sexual, physical, or emotional abuse had increased odds (1.7 compared to 3.3) for symptoms suggestive of PPS. The authors suggested that clinicians may wish to screen for abuse in men presenting with symptoms suggestive of PPS. Conversely, clinicians may wish to inquire about pelvic pain in patients who have experienced abuse (25).

A key feature of PPS is chronic pain. Chronic pain and its treatment can impair our ability to express sexuality. In a study in England 73% of patients with chronic pain had some degree of sexual problems as result of the pain (8). These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea
and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin reuptake inhibitors, SSRI) can also decrease libido (26) and delay ejaculation.

The evaluation of the effects of PPS on sexual function should take into consideration the adverse effects of drug therapy of PPS on sexuality, as well as the more interesting direct interactions between the PPS symptoms and disorders of libido, erectile function and ejaculation.

The number of studies on the effects of CPP on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At the present, the most commonly used tool is the international index of erectile function (IIEF) questionnaire (27). Post-ejaculation pain is not mentioned in this questionnaire.

In the 1980s an association between PPS and sexual dysfunction was postulated (28). This study reported a high incidence of decreased libido in patients with PPS, and they also concluded that this syndrome should be viewed as a psychosomatic disorder. Whereas psychology may play a role in the genesis of the pain, nowadays, we would say there is little evidence to support PPS as being a psychiatric disorder, but rather a biopsychological disorder in certain cases. For more information on this issue see Chapter 3.1.

In 2 reviews the relation between PPS and health status, with influence on sexual activity, were addressed (29,30).

In a Chinese study of men with PPS 1768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction is the most investigated sexual dysfunction in PPS patients. The reported prevalence of ED ranges from 15.1% to 48%, varying with the evaluation tools and populations (31,32). Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 (33), 15.2% among Turkish men (significantly higher than control group) (34) and 43% among Finnish men with PPS (35). The prevalence of ED was found to be higher in young men with PPS than in the general population.

According to other studies men with pelvic pain had higher chance of suffering from ED (36,37). Recently, a significant correlation between “chronic prostatitis”, PPS symptoms (measured by NIH-CPSI) and ED (measured by IIEF) was confirmed (38), while other studies using the same questionnaires were not able to confirm such a correlation (27,39). Some studies also report ejaculatory dysfunction, mainly premature ejaculation (6,22,31,32). According to the definition set up by the International Society for Sexual Medicine, PE is “a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and inability to delay ejaculation on all or nearly all vaginal penetrations” (40). The reported prevalence of PE varies widely in PPS patients, but unlike ED the prevalence does not increase with age (32).

A study from Turkey concerning the interaction between PPS and premature ejaculation (PE) according to intravaginal ejaculation latency time showed that 77% of men with PPS suffered from PE (34). Screponi et al. reported the high incidence of prostatic inflammation symptoms in men with PE (41). Premature ejaculation associated with PPS is hypothesised to be caused by infection or inflammation, thus treatment with antibiotics should reduce PE symptoms. In 2 studies antibiotic treatment has shown a significant increase in patients IELT (intravaginal ejaculation latency time). Despite these improvements, the mean IELT was still very low and questionable. Before these results can be recommended, further placebo controlled studies are mandatory (42,43).

Furthermore, there are reports which highlight the appearance of ejaculatory pain in patients with PPS (44), while some studies suggested PPS symptoms improvement by increased ejaculatory frequency and sexual activity (45,46).

The presence of pelvic pain may increase the risk for erectile dysfunction independently of age (47). On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation (30). In a study bridging the gap between LUTS and ED, Muller and Mulhall have speculated on the negative impact of PPS on QoL, leading to consecutive impairment of erectile function (48). Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms and imaging suggestive of a more severe inflammatory condition (6). These arguments are important for the understanding of the close relationship between CPP symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression (29-32,49).

Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the relationship and the partner. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with PPS have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking (29,48). Prostate pain syndrome patients reported greater sexual and relationship problems: 45% reported an increase in pain during or following intercourse, and many reported avoiding sexual relationships for fear of spreading an infection to their partner (50). On the other hand, Smith et al. found that men with PPS did not report significant decrease of sexual satisfaction compared to control. The results of the
study suggested that while men with PPS and their partners may experience some sexual difficulties, PPS may not have a large negative impact on patients’ intimate relationships (51). Aubin et al. found that men appeared open to the initiation of sex and assumed their partners were sexually satisfied (52).

There is a consensus that therapeutic strategies reducing symptoms, especially against pelvic pain, are of relevance in relation to changes of sexuality. On the other hand, having sex and intimacy can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

7.5 Chronic pelvic pain and sexual dysfunction of the female

Chronic pelvic pain is a clinical condition that results from the complex interactions of physiological and psychological factors and has a direct impact on the social, marital, and professional lives of women. Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions (53-56).

It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with pain may report a variety of sexual problems ranging from decreased pleasure and frequency of intercourse, superficial or deep dyspareunia, and problems in reaching orgasm to a total aversion toward sexual intimacy of any kind. Ter Kuile et al. found in their study that women with CPP reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of “vaginismus” (57).

Chronic pelvic pain is more directly associated with sexual dysfunction than chronic pain at other sites. In one study of CPP patients’ feelings and beliefs about their pain or illness, 40 out of 64 participants cited sexual dysfunction as one of the chief problems the illness had caused, making it the most frequent complaint (58). Collett and colleagues (59) also found that patients with CPP reported more sexual problems than women with any other type of chronic pain problem.

The quality of intimate relationships is closely connected with sexual function (60). Satisfaction with the sexual relationship appears to be associated with higher marital functioning (61). In addition to its relationship with marital dissatisfaction, sexual dissatisfaction is related to sexual dysfunction. In cases in which one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning (61).

In community-based studies in the UK (7), New Zealand (54) and Australia (62), a substantially larger proportion of the women with CPP reported dyspareunia (varying between 29% and 42%) than women without CPP (varying between 11% and 14%). Only a few studies have investigated sexual problems within clinical populations (59,63,64). The study of Veritt et al. shows that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with CPP than in women without CPP (64). In line with the results of the community based studies, patients with CPP reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without CPP (63-65).

One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems (8). Approximately two-thirds of patients in another study have reported reduced frequency in their sexual relations as a result of CPP (66).

One study demonstrated that CPP patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without sexual dysfunction (67).

Maruta et al. interviewed 50 chronic pain sufferers and their spouses, of whom 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life (1). In another study, in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain (8).

The female sexual function index (FSFI) has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The study of Veritt FF et al. showed that when FSFI was used women with CPP reported worse sexual function in all subscales and total score than did women without CPP; the largest differences between women with CPP and without CPP were seen for the domains of pain and arousal; the correlations of FSFI corresponded well to each other; the total score and the subscales of the FSFI had high levels of internal consistency and test-retest reliability when assessed in a sample of women with CPP; and finally, that the FSFI showed good ability to discriminate between women with and without CPP (67).

Some studies report a significant association between sexual abuse before the age of 15 years and later CPP (13). It is suggested that there is increased frequency of sexual abuse or trauma history, anxiety and depression in women with CPP (68-72). While the study of Fry et al. with 164 women with CPP show that child sexual abuse did not apparently differ in prevalence from that in the general population, which must throw into question previous assertions about its widespread and general role in CPP.
7.6 Treatment of sexual dysfunctions and CPP

Couples often benefit from early referral for relationship and sexual counselling during their treatment course (73). Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting thrusting to less than that that causes. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of postcoital flares. Other behavioural changes involve pre- and postcoital voiding, application of ice packs to the genital or suprapubic area (73,74), and use of vaginal dilators before penile penetration. An alternative is to use natural dilators such as different fingers or sex toys. Hypoallergenic non-irritating lubricants can be used to reduce vulvar, urethra, and vaginal friction, and women with signs of vulvovaginal atrophy may benefit from introital application of minimally absorbed locally applied oestrogen cream (75). In patients with an overactive pelvic floor, referral for physical therapy, myofascial release, and internal pelvic floor muscle massage may offer relief (4).

7.7 In summary

Problems with sexual functioning resulting from CPP have to be addressed and assessed by the health care professional. The attention directed toward these patients must be focused not only on the disease but also on the woman as a whole. As treatment solely of the underlying disease is not acceptable, the care of these suffering women should also address the emotional, sexual, and social problems that the disease causes.

7.8 Conclusions and recommendations: sexological aspects in CPP

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.</td>
<td>2a</td>
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<tr>
<td>Patients who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of PPS.</td>
<td>2b</td>
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<tr>
<td>Sexual dysfunctions are prevalent in patient with PPS.</td>
<td>2b</td>
</tr>
<tr>
<td>In men with PPS the most prevalent sexual complaints are erectile dysfunction and ejaculatory dysfunction.</td>
<td>3</td>
</tr>
<tr>
<td>In females with CPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and “vaginismus”.</td>
<td>2a</td>
</tr>
<tr>
<td>Vulvar pain syndrome is associated with BPS.</td>
<td>3</td>
</tr>
<tr>
<td>Women with BPS suffer significantly more from fear of pain, dyspareunia and less desire.</td>
<td>2a</td>
</tr>
<tr>
<td>Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.</td>
<td>3</td>
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<tr>
<td>Chronic pain can cause disturbances in each of the sexual response cycle phases.</td>
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<tr>
<td>Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.</td>
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<th>Recommendations</th>
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<tr>
<td>Patients presenting with symptoms suggestive for chronic pelvic pain syndrome, should be screened for abuse, without suggesting a causal relation with the pain.</td>
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<tr>
<td>The biopsychosocial model should be applied in the evaluation of the effect of chronic pelvic pain syndrome on the sexual function of the patient.</td>
<td>B</td>
</tr>
<tr>
<td>The biopsychosocial model should be incorporated in research in the role of chronic pelvic pain in sexual dysfunction.</td>
<td>B</td>
</tr>
<tr>
<td>Offer behavioural strategies to the patient and his/her partner to cope with sexual dysfunctions.</td>
<td>B</td>
</tr>
<tr>
<td>Training of the pelvic floor muscles is recommended to improve quality of life and sexual function.</td>
<td>B</td>
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Figure 15: Assessment and treatment algorithm for sexological aspects in chronic pelvic pain

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>History of sexual functioning</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td>History of negative experiences</td>
<td>Refer to sexologist when sexual dysfunction or trauma is present</td>
</tr>
<tr>
<td>Ask about abuse</td>
<td>Grade B recommended</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>Screen for sexual abuse</td>
</tr>
<tr>
<td>History of relationship</td>
<td>Use a bio-psycho-social model in treating the pain</td>
</tr>
<tr>
<td></td>
<td>Offer behavioral strategies to cope with sexual dysfunctions</td>
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7.9 References


8. PSYCHOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

This chapter first addresses general issues concerning the psychological contribution to pelvic pain and its presenting problems, and assessment and treatment, and then it describes the same areas in relation to CPP in women. This is by far the area with the greatest psychological contribution to pelvic and urogenital pain, and exemplifies many of the problems raised in the first part of the chapter.

8.1 Understanding the psychological components of pain

8.1.1 Neurophysiology of pain

Models that integrate the psychological factors consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain with current neurobiological understanding of pain are few but of high quality. Symptom-related anxiety and central pain amplification may be measurably linked, as in IBS (1). Bajaj et al. (2) have demonstrated central sensitisation in symptomatic endometriosis, and this model is more extensively dealt with in Chapter 4. The various mechanisms of facilitation, amplification, and failure of inhibition, mean that there should be no expectation of a simple relationship between physical findings, pain experienced, and resulting distress and restriction of activities. Difficulty disengaging even from expected painful stimuli, undergone voluntarily and within tolerable levels, is characteristic in people struggling with chronic pain (3). However, difficult as it is to relieve chronic pain, the pain system is plastic and treatment attempts are not entirely unsuccessful.

8.1.2 Sexual abuse and trauma

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, usually in hospital care samples, and particularly by women with pelvic pain (4). However, all these studies are retrospective, and there appears to be a relationship between poor study quality and likelihood of reporting this association (5). The only prospective investigation into the relationship between childhood sexual abuse, physical abuse, or neglect, and “medically unexplained pain”, including pelvic pain, used court records concerning sexual abuse before the age of 11 years to establish a definite history, comparing those with such a history with demographically matched classmates (6). The conclusions of this study were that physically and sexually abused individuals were not at risk for increased pain symptoms, although those individuals with pain problems as adults were more likely to report earlier sexual or physical abuse or neglect; however, this did not correspond with the established early history of abuse.

The correlation between childhood victimisation and pain symptoms is less straightforward than previously thought, and may be more about retrospective explanatory frameworks used by women for pain for which no major pathology is found than about occurrence or extent of abuse. In particular, findings of depression and/or post-traumatic stress disorder in adult women reporting childhood sexual abuse are common, with or without pain. Disentangling the influences and inferences requires prospective studies or careful comparisons rather than, as in many published studies, comparing women with a history of sexual abuse and CPP with women without either (7). No studies have been found about sexual or physical abuse in childhood and pelvic pain in men, although it is evident that they suffer other adverse effects on psychological and physical health (8,9).

8.1.3 Interpreting psychological differences

An important review (7) of CPP in women identifies as problematic the notion that women without physical findings to which pain can be causally attributed differ in psychological characteristics from women with physical findings. They have critically examined the methodologies of studies purporting to show such differences, and the bias introduced by sampling and by unsuitable measures. They argue for better methodology in replication of these studies, particularly those sampling life events, and for greater use of idiographic methods.
In summary, women with pelvic pain often have other ‘medically unexplained’ symptoms, and current or lifetime anxiety and depression disorder; they may have a history of physical or sexual abuse in childhood but the significance of this for pelvic pain is unclear. Studies that invoke ‘medically unexplained’ or ‘psychosomatic’ or ‘somatoform’ disorders do not engage with current understanding of pain, such as viscerovisceral cross sensitisation in relation to multiple pain sites (10), referring instead to a dualistic model in which absence of physical findings is taken to indicate psychological origins of the complaint of pain (11,12). At the extreme, pain is overshadowed by diagnosis as a sexual problem (‘dyspareunia’) when pain is in fact the central problem and not contingent only on sexual activity (13).

8.2 Psychological assessment of pain
The report of anxiety, depression and sexual problems is sufficiently common for these to be important in assessment and in planning treatment. Distress, described in the patient’s terms or within a psychodiagnostic framework, is best understood in the context of pain and the meaning of pain to the individual.

Anxiety probably refers to fears of missed pathology as the cause of pain (cancer being foremost among these) and to uncertainties about the possibilities of treatment and the likely prognosis if treated or untreated. A question such as that suggested by Howard (14), “What do you believe or fear is the cause of your pain?” is more suitable than a general anxiety questionnaire.

Depression is also commonly found in men and women with persistent pelvic pain (15). In a study comparing men and women with low back pain, and women with pelvic pain and men with urogenital pain (16), it was found that, when differences in age and pain duration and severity were taken into account, there were no differences in depression according to pain site, and pain site predicted disability.

However, there is a risk when using diagnostic or standard assessment instruments of attributing pain-related problems to neurovegetative signs of depression (17,18). As Stones et al. (19) has cautioned: “Psychological distress may be a consequence and not a cause of persistent pain: while identification of depression is important as part of treatment, caution is required before attribution of causality” (p416).

Pain ratings themselves may be predicted by cognitive and emotional variables (20). Furthermore, target outcomes of pain severity, distress and disability vary only partly, and improvement in one does not necessarily imply improvement in the others. Therefore, it is particularly important when the primary outcome is pain to anchor its meaning in a study such as that by Gerlinger et al. (21), who determined clinically important differences in pain in relation to overall satisfaction with treatment.

There are many measures of restricted function, or disability, most suited to musculoskeletal pain and mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. Some include one or more items related to sexual activity, but there has perhaps been an over-emphasis on the effects of pain on sexual performance, although the overall relationship may be more important (22).

In the Cochrane review of pelvic pain in women (23), the outcomes of pharmacotherapy, surgery and physical therapy trials consist of pain scores (patient-rated and physician-estimated); functional measures such as urinary peak flow rate (for persistent pelvic pain in men); examination findings such as pelvic tenderness (women); and uptake of further treatment following the trial treatment. A few trials have included QoL, but none have measured mood change. This indicates a general but mistaken assumption that improvement in pain leads to resolution of other problems. Furthermore, if all treatments sampled the same domains of pain in their evaluation, comparison across treatments, by medical personnel and patients, would be more easily achieved (24). Suggested instruments for assessment in each of these domains can be found in the consensus paper by Turk et al. (25).

8.3 Psychological issues in the treatment of pain
Provision of information that is personalised and responsive to the presenting problem and the concerns of the patient, conveying belief and concern, is a powerful way to allay anxiety (26). It can be helpful to provide additional written information or direct the patient to reliable sources. Many practitioners rely on locally produced material or pharmaceutical products of variable quality, although they endorse the need for independent materials for patients (27).

Ideally, treatment arises from general principles and practice in the field of chronic pain, with specific study of the population of concern and design of appropriate treatment trials (28). The field of pelvic pain shows a curious phenomenon whereby few of the mainstream psychologically based treatments are subjected to trials and published, but instead there are often rather idiosyncratic versions of treatment components, or combinations of interventions, published in single, often underpowered trials. It is hard to conclude anything from these, as is seen in the psychological treatment section of several other chapters.

Psychological interventions may be directed at the pain itself, with the intended outcome of reducing pain and its consequent impact on life, or adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction. The major psychologically based treatment that improves adjustment, which is aimed more at reducing distress and disability than pain, is cognitive behavioural therapy,
for which there have been > 10 systematic reviews (29), although its effects may be small and maintenance in the longer term is uncertain. For less disabled and distressed patients, this can be delivered in part over the internet (30). A systematic review of short-term psychodynamic psychotherapy (31) has reported similar improvements in “somatic disorders”, which often includes pelvic pain, although it was not among the trials reviewed. Pain-focused interventions, again with no trials in pelvic pain, have been subjected to systematic review, including hypnotherapy (32) and autogenic training (33).

However, all these systematic reviews suffer from heterogeneity among the trials, shortcomings in trial methodology, and little longer term follow-up to establish maintenance of treatment gains. The crucial question, of what works best for whom, is unanswered and possibly unanswerable given the complexity of variables, outcomes, and the difficulties in standardising treatments.

### 8.4 Female pelvic pain

#### 8.4.1 Psychological risk factors in development and maintenance of pelvic pain

A thorough review from nearly 15 years ago (34) argues against division of aetiology into organic versus psychogenic, and concludes that, given the methodological problems of many studies, the evidence for sexual abuse as a risk factor is uncertain. A large review and meta-analysis of risk factors, including physical pathology, psychological distress, and sexual abuse (35) drew mainly on retrospective studies, which introduced various biases. Pelvic pain and distress may be variously related, each as the consequence of the other, or arising independently.

The only systematic review (5) of risk factors for chronic non-cyclical pelvic pain in women included the following as well as medical variables: sexual or physical abuse (ORs from 1.51 to 3.49); psychological problems such as anxiety (OR: 2.28, 95% CI: 1.41-3.70) and depression (OR: 2.69, 95% CI: 1.86-3.88); hysteria, i.e., multiple somatic problems (OR: 4.83, 95% CI: 2.50-9.33); and psychosomatic symptoms (OR: 8.01, 95% CI: 5.16-12.44). The terms hysteria and psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with or indicative of any serious disease process, and personality variables are not reliably associated with pelvic pain in women. Although some of these risk factors are doubtless interrelated - history of sexual abuse and depression, for instance - such effects cannot be disentangled from the studies available.

Issues of early trauma such as childhood sexual or physical abuse as a risk factor are addressed in more detail earlier in this chapter, but it is important to say that better quality studies, including one prospective study using court records of childhood abuse (6), have reported a weaker or no relationship, or not one which is specific to pelvic pain (5,36-38). However, another systematic review (9) has concluded that there is some evidence for a specific relationship between rape and CPP (and also with fibromyalgia and functional gastrointestinal disorders). It is also important to recognise the possible role of recent sexual assault on the presentation of pelvic pain (4,39).

There have been fewer studies of maintenance of or recovery from pelvic pain in relation to psychological factors. Weijenborg et al. (40) have found that, in 25% of women treated surgically, recovery from pelvic pain over a mean 3 years follow-up was not predicted by pain variables at baseline, nor by a general measure of psychological distress or sociodemographic variables, or reports of childhood sexual abuse.

Studies that have described pelvic pain as medically unexplained or psychosomatic, due to the lack of physical findings, have been discarded. This is because such a distinction is unhelpful and is not informed by our understanding of pain mechanisms (11). When diagnostic investigations are used to assign symptoms to physical and mental origins, with no suggested connection between them, and with interest only in the former type of symptoms, explanations are often experienced by women as scepticism about the reality or severity of the pain (41). This can undermine the therapeutic relationship between the patient and the doctor (42). Ehler et al. (43) have found that women with pelvic pain with and without laparoscopic findings do not differ from one another; only from pain-free controls, as anticipated by Savidge & Slade (7). Distress, described in the patient’s terms or within a psychodiagnostic framework, is best understood in the context of pain and the meaning of pain to the individual (7). In a large primary care study, Zondervan et al. (44) have noted the tendency to attribute pelvic pain without obvious pathology to a psychological cause, and that it is increasingly recognised as unhelpful; depression and anxiety are common in any chronic pain, not pelvic pain alone. They have found that restriction by pain does not distinguish between women who do and do not seek health care, and that there may be an anxiety-related cause of the pain in both groups.

#### 8.4.2 Psychological assessment of pelvic pain

Anxiety and post-traumatic stress symptoms are common in some women with CPP (44,45), and may account for substantial variance in health status and treatment use. Negative investigative findings do not necessarily resolve women’s anxieties about what might be causing pain (26). Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with...
pain, anxiety and distress may be best assessed by questions about concerns about the cause of pain, its implications, and its consequences for everyday life (46).

Reference to the studies of the IMMPACT group (24) is recommended for guidance on outcome measures suitable for pain trials.

8.4.3 Psychological factors in treatment of persistent pelvic pain

Untreated, there is a significant rate of symptom improvement. In one study, 25% of patients reported recovery (nearly half with total recovery) over a 3-4-year period, and neither pain nor distress at baseline, nor intervention received, was found to be associated with recovery (40). This recovery rate should be borne in mind when interpreting results of treatment trials.

There is one Cochrane systematic review and meta-analysis of treatments for pelvic pain, excluding that due to endometriosis, IBS, and chronic PID (47). All treatments were included although the update protocols split surgical from non-surgical (48), and outcomes were mainly pain scores, QoL, and resource use, including health care resources. The 14 treatment trials included counselling, psychoeducation, reassurance, and emotional disclosure, as well as a multicomponent pain management programme. The authors concluded in favour of educational counselling combined with ultrasound scanning, which improved pain and mood; and a multidisciplinary rehabilitative approach including surgery, pharmacotherapy, physiotherapy, and psychosocial intervention, which improved function but not pain. Emotional disclosure (a stress reduction method) through writing brought about a small improvement in some pain scores.

Several other reviews make positive comments on psychological involvement (49), and recommend addressing psychological concerns from the outset rather than after other treatment has failed. Psychological interventions may be directed at the pain itself, with the intended outcome of reducing pain and its consequent impact on life (1), or at adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction (2).

In the first category are relaxation and biofeedback methods of controlling and decreasing pain by reducing muscle tension, and this is applied in mainly uncontrolled trials to pelvic floor retraining both in men and women. The only RCT applied a specific type of cognitively enhanced physical therapy to overall muscle tension, but not to the pelvic floor, combined with normal gynaecological treatment compared with gynaecological treatment alone (50). Pain was reduced by 50% and motor function improved in various aspects by 10 h of physical therapy, with particular attention to tension and relaxation and to the thoughts and emotions that interfere with balanced posture and movement.

In the second category, multicomponent pain management, involving education, physical retraining, behavioural change, and increasing activity, relaxation and cognitive therapy, is often applied to mixed groups of chronic pain patients, including those with pelvic pain. A systematic review and meta-analysis which shows a good outcome for mixed chronic pain or back pain groups across pain experience, mood, coping, and activity, cannot with confidence be extrapolated to women with pelvic pain alone (51). The only RCTs in CPP used elements of this approach in combination with medroxyprogesterone acetate (MPA) or placebo (52). Combining MPA and psychological therapy outperformed other treatment methods in the long-term, with nearly three quarters of women reporting > 50% pain relief.

Several single treatments with benefits in other chronic pain or chronic health problems have been tried in pelvic pain. Norman et al. have compared emotional disclosure by writing about pain with writing about positive events as a control (53). The differences were small but in favour of emotional disclosure on one measure of pain appraisal, particularly in women with more distress at baseline. Given the extent of problems associated with pelvic pain, this intervention on its own is unlikely to produce much change, but could be combined with other components described above.

In a different intervention, Fenton et al. have conducted a small RCT of transcranial direct current stimulation compared to sham stimulation (54). Pain reduction was greater in the treatment group, in the first week only, as was reduction in disability.

8.5 Conclusions and recommendations: psychological aspects of CPP

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.</td>
<td>2b</td>
</tr>
<tr>
<td>Current or recent sexual abuse should be assessed as possible contributory factors in pelvic pain.</td>
<td>2a</td>
</tr>
<tr>
<td>Psychological intervention in general can produce benefits in pain, mood, and quality of life, depending on its content and focus.</td>
<td>1a</td>
</tr>
<tr>
<td>Psychologically informed physical therapy can improve pain and function.</td>
<td>1b</td>
</tr>
</tbody>
</table>
Combined exercise and cognitive behavioural therapy with medroxyprogesterone acetate can reduce pain in a majority of women with pelvic pain.

Transcranial direct current stimulation may reduce pain in the short term.

Recommendations

Psychological distress is common in pelvic pain in women, but should be interpreted in the context of pain.

Ask the patient what she thinks may be wrong to cause pain, to allow the opportunity to inform and reassure as appropriate.

Try psychological interventions in combination with medical and surgical treatment, or alone.

Figure 16: Assessment and treatment algorithm for psychological aspects of chronic pelvic pain

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological history</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td>Investigate pain-related beliefs and behavior</td>
<td>Grade B recommended</td>
</tr>
</tbody>
</table>

8.6 References


9. PELVIC FLOOR FUNCTION AND CHRONIC PELVIC PAIN

9.1 Introduction
The pelvic floor is made up of muscles and fascia. The muscles usually function as a composite, although the anterior and posterior components may act in isolation. The pelvic floor has three functions: support, contraction and relaxation.

9.2 Function
In its resting state, the pelvic floor supports the bladder and the urethra in the anterior compartment, the uterus and the vagina in the middle compartment, and the rectum and the anus in the posterior compartment. The integrity of the support function depends on the anatomical position of the muscles, on the resting tone and on the integrity of the fascia. When intra-abdominal pressure rises, the pelvic floor muscles must respond with a contraction occurring simultaneously or before the pressure rise. The latter is termed an anticipatory response or feed-forward loop. Contraction of the pelvic floor muscles results in inward movement of the perineum and upward movement of the pelvic organs. In many situations, other muscles such as the abdominal, adductor and gluteal muscles also contract.

There are two types of contraction that can be distinguished: a voluntary contraction, resulting from impulses arising in the cerebral cortex, and a reflex contraction. These contractions not only maintain support of the pelvic organs, they close the urethra, anus and vagina, thus avoiding loss of urine or stools. Contractions also form a defence against introduction of foreign objects into the anus or vagina, and in women, they can protect against sexual penetration. Additionally, detrusor muscle inhibition occurs in parallel with pelvic floor muscle contraction. Pelvic floor muscle contractions play an important role in sexual function. During the arousal phase, pelvic floor muscle contractions are used to increase vasocongestion.

During the final phase of the sexual response cycle, a series of involuntary contractions is associated with the physical sensations of orgasm. Pelvic floor muscle relaxation results in a decrease or termination of the squeezing of the urethra, vagina and anus. The perineum and the pelvic organs return to their anatomical resting position. Relaxation of the pelvic floor muscles is needed for voiding, defecation and for sexual intercourse. The muscles of the pelvic floor are integrated in the total muscular girdle of the pelvis, yielding the stability needed for bearing the trunk. Instability in its turn leads to compensatory pelvic floor muscle (over) activity.

9.3 Dysfunction
Pelvic floor dysfunction should be classified according to “The standardisation of terminology of pelvic floor muscle function and dysfunction” (1). This is an international multidisciplinary report from the International Continence Society. By palpation of the pelvic floor muscles, the contraction and relaxation are qualified. Voluntary contraction can be absent, weak, normal or strong, and voluntary relaxation can be absent, partial or complete. Involuntary contraction and relaxation is absent or present.
Based on these signs, pelvic floor muscles can be classified as follows:

- non-contracting pelvic floor
- non-relaxing pelvic floor
- non-contracting, non-relaxing pelvic floor.

Based on symptoms and signs, the following conditions are possible:

- normal pelvic floor muscles
- overactive pelvic floor muscles
- underactive pelvic floor muscles
- non-functioning pelvic floor muscles.

Normal pelvic floor muscles relax during urination and contract during coughing. Overactive pelvic floor muscles do not relax during micturition, defecation or during sex and cause dysfunctional voiding, overactive bladder, constipation and dyspareunia (2). Underactive pelvic floor muscles do not contract sufficiently to keep the patient dry. Non-functioning pelvic floor muscles do not show any activity whatsoever and can cause every type of pelvic organ dysfunction.

Overactivity tends to develop over a protracted period, with many causes. A psychological mechanism that is thought to play a role is that contraction of the pelvic floor muscles closes some of the exits of the body (anus and vagina), and helps to keep urine and stool inside. It gives women a defence mechanism against unwanted vaginal penetration of any type. The pelvic floor muscles also help to postpone micturition, which can be of benefit in a social or working environment. In summary, the pelvic floor muscles assist in adaptation to different situations in life.

9.4 Pelvic floor muscles and myofascial pain

Chronic pelvic pain can simply be a form of myalgia, due to misuse of muscles, in this case, the pelvic floor muscles. Studies in the field of chronic prostatitis support the idea that patients with CPP have more muscle spasm and increased muscle tone and pain when palpating the pelvic floor muscles (3). Muscle relaxation can diminish spasm and pain (4). Repeated or chronic muscular overload can activate trigger points in the muscle.

A report from the Chronic Prostatitis Cohort Study showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPP group (5).

9.4.1 Muscular aspects

The relationship between muscular dysfunction (especially overactivity) and pelvic pain has been found in several studies. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles (6). The vast majority (92.2%) of men visiting a tertiary centre for pelvic pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) (7). This relationship has been found in chronic prostatitis (8), BPS (9) and vulvar pain (10). Dysfunction of the pelvic floor directly affects function of the pelvic viscera and vice versa. Both systems can act as the primary signal to the spinal cord, with a cascade of reactions ascending to the CNS as a result. The muscle itself ends up with a diminished length, leading to restrictions even when it is in a relaxed state.

9.4.2 Neurological aspects

In 1999, the first ideas about the neurological aspects of the pelvic floor muscles in relation to CPP were published. The probability of CNS breakdown in the regulation of pelvic floor function was suggested as a mechanism for development of CPP. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor function (11). Basic studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them (12).

9.4.3 Myofascial trigger points

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyperirritable spots within a taut band. Other criteria for trigger points are: recognition of the pain as ‘familiar’, and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and ileopsoas muscles.
Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions (e.g., pain related to voiding or defecation).

### 9.5 Diagnostics of pelvic floor muscle function

Diagnosing pelvic floor muscle function in patients with CPP starts by taking a complete functional history of the pelvic organ function. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psycho-social aspects.

#### 9.5.1 Physical examination

After taking a history, physical examination should be done. Special attention must be paid to the abdominal, inguinal and genital areas, but also to the pelvic alignment. The patient should be asked to point at the location of maximal pain and at the secondary pain points. Palpation of the abdomen with special attention to the muscles may yield pain points that are important for making a treatment plan. A vaginal or rectal examination should be performed to assess the function of the pelvic floor muscles, according to the ICS report. This assessment has been tested and shows satisfactory face validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice (13). Rectal examination is a good way to test the pelvic floor muscle function in men (14).

#### 9.5.2 Electromyography and pressure measurement (EMG)

Additional examination can be done using electromyography. This is preferably done using an intravaginal or intra-anal probe. This measures the electrical activity of the pelvic floor muscles as a group. It does not reveal anything about the efficacy of the contraction or relaxation. There is good correlation between digital palpation and intravaginal surface EMG (15). To measure the effect of pelvic floor muscle contraction, a pressure probe can be used. The measurement of anal pressure is reliable (16). Performance of EMG in different positions gives more insight into the properties of the pelvic floor. Electromyography is one of the most used input methods for biofeedback. Intraluminal pressure can also be used for this purpose.

#### 9.5.3 Imaging

Anatomical imaging of the pelvic floor muscles can be done using MRI. It is still debatable whether MRI can be of help in diagnosing pudendal entrapment. Functional imaging can be done using techniques such as video-urodynamics (pelvic floor muscles in relation to bladder function) or defecography (pelvic floor muscles in relation to defecation). The reason for this is to exclude disease-specific pain. Repeated imaging studies may be detrimental for the patient because they emphasise somatic causes of the pain.

#### 9.5.4 Myofascial trigger points

There is no accepted reference standard for the diagnosis of trigger points. Data on the reliability of physical examination are conflicting. Reliability is relatively good for tenderness and for recognisable referred pain. It is lower for taut band recognition and local twitch response. The reliability improves when examination is done by experts, who are specially trained in diagnosing trigger points. Other techniques are used for diagnosing trigger points but none have become standard. Among these are imaging techniques and EMG (17).

In a cohort study of 72 men with CPP, the relationship between the locations of the trigger point and the referred pain was examined. Ninety percent of the patients showed tenderness in the puborectalis muscle and 55% in the abdominal wall muscles. Of the patients in whom trigger points were found in the puborectalis, 93% reported pain in the penis and 57% in the suprapubic region. Patients with trigger points in the abdominal muscles reported pain in the penis (74%), perineum (65%) and rectum (46%) (18).

### 9.6 Treatment of pelvic floor muscle pain

Treating pelvic floor overactivity and myofascial trigger points should be considered in the management of CPP. Treatment should be done by specialised physiotherapists who are trained not only in the musculoskeletal aspects of pain, but also in the psychological mechanisms and the role of the CNS in chronic pain.

#### 9.6.1 Pelvic floor muscle exercise

For patients with CPP and dysfunction of the pelvic floor muscles, it is very helpful to learn how to relax the muscles when the pain starts. By doing this, the circle of pain-spasm-pain can be interrupted. In the case of shortened muscles, relaxation alone is not enough. Stretching of the muscle is mandatory to regain length and function. Studies on physical therapy for pelvic floor pain syndrome have been sparse. A single blinded RCT with myofascial physical therapy and general massage was carried out in patients with prostate or bladder pain. The global response rate to treatment with massage was significantly better in the prostate than in the bladder pain group (57% vs. 21%). In the prostate pain group, there was no difference between the two...
treatment arms. In the bladder pain group, myofascial treatment did significantly better than the massage. Massage only improved complaints in the prostate pain group. The fact that the prostate pain group consisted of only men is mentioned as a possible confounding factor (19).

9.6.2  **Biofeedback and electrostimulation**
Biofeedback can be helpful in the treatment of pelvic floor pain in the process of recognising the action of the muscles. Visualising the action of the pelvic floor muscles by using biofeedback is an eye opener to many patients. Biofeedback should always be used in consultation with the patient. Special care should be taken when there is a history of negative physical or sexual experiences. The numbers of patients in most studies concerning biofeedback have been small but the results are promising. In a cohort study, 31 patients with CPPS participating in a pelvic floor biofeedback re-education programme were followed. The mean chronic prostatitis symptom index decreased from 23.6 to 11.4. They also measured the pelvic floor muscle activity by EMG using an anal probe. The resting amplitude was taken as a parameter for the ability to relax the pelvic floor muscles. This parameter was 4.9 μV at the start and 1.7 μV at the end of the treatment, so the relaxation improved markedly. There was also a correlation between the decline in EMG values and improvement in prostatitis symptom score (20).

In a study among patients with levator ani syndrome, biofeedback was found to be the most effective therapy. Other modalities used were electrostimulation and massage. Adequate relief was reported by 87% in the biofeedback group, 45% for electrostimulation, and 22% for massage (6). A review on biofeedback in pelvic floor dysfunction has shown that biofeedback is better than placebo or sham treatment. An odds ratio of 5.8 favouring biofeedback has been calculated based on three studies (21).

9.6.3  **Myofascial trigger point release**
The treatment of myofascial trigger points has different options. There are three groups of treatment: (1) manual therapy: pressure and release, compression, spray and stretch; (2) dry needling: putting a solid filiform needle directly in the trigger point, repeatedly and in an up and down pecking motion; and (3) wet needling: injection of lidocaine or botulinum toxin into the trigger point. The evidence for all the different treatments is weak. In most studies, no significant difference between these techniques has been found. One problem is that most of the studies were small and heterogeneous with regard to the patients and methods. This is especially true for comparing any technique with sham or placebo treatment. For manual therapy, central trigger points are treated by stretching the muscle because this inactivates it. Trigger points lying in the attachment of the muscle to the bone are treated using direct manual therapy.

Other well-known techniques such as biofeedback and neuromuscular stimulation have been used in the treatment of trigger points. There is no evidence that manual techniques are more effective than no treatment (22). In most studies of dry needling, it has been compared with wet needling. Different systematic reviews have come to the conclusion that, although there is an effect of needling on pain, it is neither supported nor refuted that this effect is better than placebo (23). Other reviews have concluded that the same is true for the difference between dry and wet needling (24,25).

9.6.4  **Botulinum A toxin**
Botulinum A toxin (BTX-A) is an inhibitor of acetylcholine release at the neuromuscular junction and has a paralysing effect on striated muscles. BTX-A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective (26). Reviews do not support the injection of BTX-A into trigger points (27).

Pelvic floor muscle overactivity plays a role in CPP. BTX-A, as a muscle relaxant, can be used to reduce the resting pressure in the pelvic floor muscles. In women with high resting pressure in the pelvic floor muscles, it has been found that BTX-A lowers this pressure significantly. The magnitude of reduction was significantly higher than that in the placebo group. On the pain score (VAS), no intergroup differences were found in this relatively small randomised study (28). BTX-A can also be injected at the sphincter level to improve urination or defection. Relaxation of the urethral sphincter alleviates the bladder problems and secondarily the spasm. In a cohort study of 13 patients with CPP, BTX-A was injected into the external urethral sphincter. Subjectively, 11 patients reported a substantial change in pain symptoms, from 7.2 to 1.6 on a visual analogue scale (29).
9.6.5 **Pain management**

The physiotherapist is part of the pain management team, together with the pain doctor and the psychologist. The therapeutic options for physiotherapists may not be the same in every country. Physiotherapists can either specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome.

9.7 **Conclusions and recommendations: pelvic floor function**

<table>
<thead>
<tr>
<th>Conclusions</th>
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<tbody>
<tr>
<td>The ICS classification is suitable for clinical practice.</td>
<td>2a</td>
</tr>
<tr>
<td>Overactivity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.</td>
<td>2a</td>
</tr>
<tr>
<td>The overactivity of the pelvic floor muscles is an input to the central nervous system causing central sensitisation.</td>
<td>2b</td>
</tr>
<tr>
<td>There is no accepted standard for diagnosing myofascial trigger points.</td>
<td>2a</td>
</tr>
<tr>
<td>There is a relation between the location of trigger point and the region where the pain is perceived.</td>
<td>3</td>
</tr>
<tr>
<td>Myofascial treatment is effective in prostate- and bladder pain syndrome.</td>
<td>1b</td>
</tr>
<tr>
<td>Biofeedback improves the outcome of myofascial therapy for pelvic floor dysfunction.</td>
<td>1a</td>
</tr>
<tr>
<td>Trigger point release is effective in treating muscle and referred pain, but there is no preference from one method over another.</td>
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<table>
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<tr>
<th>Recommendations</th>
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<tr>
<td>The use of the ICS classification on pelvic floor muscle function and dysfunction is recommended.</td>
<td>A</td>
</tr>
<tr>
<td>In patients with chronic pelvic pain syndrome it is recommended to actively look for the presence of myofascial trigger points.</td>
<td>B</td>
</tr>
<tr>
<td>In patients with chronic pelvic pain syndrome it is recommended to apply pelvic floor muscle treatment as first line treatment.</td>
<td>B</td>
</tr>
<tr>
<td>Apply pelvic floor muscle treatment as first line treatment in patients with chronic pelvic pain syndrome.</td>
<td>A</td>
</tr>
<tr>
<td>When myofascial trigger points are found treatment by pressure or needling is recommended.</td>
<td>A</td>
</tr>
</tbody>
</table>

**Figure 17: Assessment and treatment pelvic floor function**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Palpation of the muscles</td>
<td>Grade A recommended Use the International Continence Society classification of dysfunction</td>
</tr>
<tr>
<td>Testing of pelvic floor function</td>
<td>Use biofeedback in combination with muscle exercises</td>
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<tr>
<td>Pelvic floor muscle EMG</td>
<td>Treat myofascial trigger points using pressure or needling</td>
</tr>
<tr>
<td>Test for myofascial trigger points</td>
<td>Grade B recommended Look actively for the presence of myofascial trigger points</td>
</tr>
<tr>
<td>History of all the involved organs</td>
<td>Apply pelvic floor muscle therapy as first line treatment</td>
</tr>
<tr>
<td>Standardised questionnaires</td>
<td>Other comments The role and options of a physiotherapist may differ between countries</td>
</tr>
</tbody>
</table>

9.8 **References**


http://www.prostatitis.org/myofascial.html


10. GENERAL TREATMENT OF CHRONIC PELVIC PAIN

10.1 Introduction

Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous chapters. The management requires a holistic approach with biological, psychological and social components. This chapter looks solely at general treatments and should be used as part of a management plan including the interventions suggested in the specific chapters.

Despite the developments in basic science, there has not been the same in pharmacological intervention. It is recognised that there are often central mechanisms involved in CPP. This chapter looks at general treatments for pain (both peripheral and central) and not the specific treatments mentioned in the Chapters 2 and 6.

Despite the frequency of CPP, relatively few studies have specifically looked at the medications used in CPP patients (1). As a result, a wider look at the literature has been undertaken, including the agents used for central and neuropathic pain. Further specific research is required in this group of patients.

The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents. They may also allow lower dosages of each agent and thus minimise the side effects.

The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the addition of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent to provide benefit does not mean that there is an alternative. If the benefit is limited by side effects, then the lowest effective dose should be found (by dose titration). In some circumstances, patients can tolerate a higher level of pain and have fewer side effects.

If the use of simple analgesics fails to provide adequate benefit, then one should consider using the neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain.

10.2 Simple analgesics

Paracetamol (acetaminophen)

Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central
mechanism of action (2). It is often available over the counter without prescription. There is evidence that paracetamol is beneficial in managing somatic and arthritic pain. (3-5). There is little evidence for its use in CPP, but it should be considered if it has not already been tried.

**Non-steroidal anti-inflammatory agents (NSAIDs)**

This is a group of agents that include salicylic acid. They have had significant publicity over recent years. They are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclo-oxygenase (COX). They have a peripheral effect, hence their use in painful conditions involving peripheral or inflammatory mechanisms.

They are commonly used for pelvic pain because many are available over the counter and are usually well tolerated. The evidence for their benefit is often weak or non-existent. It should be remembered that they do have side effects, which may be significant. There is no good evidence to suggest one NSAID over another for pelvic pain.

For pelvic pain in which inflammatory processes are considered to be involved, such as dysmenorrhoea (6), NSAIDs are more effective than placebo and paracetamol, but with a higher incidence of side effects. For pelvic pain in which central mechanisms may be incriminated, such as endometriosis (7), then the evidence is lacking for NSAIDs despite their common use.

Guidelines for use of NSAIDs and COX-2 selective agents have been developed. They have more side effects than paracetamol, including indigestion, headaches and drowsiness.

At a practical level, NSAIDs could be considered as analgesics for patients with pelvic pain. They should be tried (having regard for the cautions and contraindications for use) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or there are side effects, then the NSAID should be stopped.

**Neuropathic analgesics**

This is a group of agents that are not simple analgesics but are used to modulate neuropathic or centrally mediated pain. There are several classes used with a recognised benefit in pain medicine. They are taken on a regular basis rather than as required. They all have side effects that limit their use in some patients.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has reviewed the pharmacological management of neuropathic pain (8). There is further guidance in progress for the management of neuropathic pain in the non-specialist setting.

Not all the agents have a licence for use in pain management but there is a history and evidence to demonstrate their benefit. The evidence for treatment of CPP is lacking but is present for other painful conditions. For this chapter, most of the evidence is from non-pelvic pain sources. The general method for using these agents is by titrating the dose against benefit and side effects. The aim is for patients to have an improvement in their QoL, which is often best assessed by alterations in their function. Side effects frequently limit the use of these agents. It is common to use these agents in combinations but studies comparing different agents against each other or in combination are lacking.

10.2.1 **Antidepressants**

10.2.1.1 **Tricyclic antidepressants**

This is a group of drugs with multiple mechanisms of action. They have a long history of use in pain medicine and have been subjected to a Cochrane review (9). This suggests that they are effective for neuropathic pain with numbers needed to treat (NNT) of approximately three.

Amitriptyline is the most commonly used member of this group at doses from 10 to 75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side effects and taken at night (8). Nortriptyline and imipramine are often used as alternatives.

10.2.1.2 **Other antidepressants**

Venlafaxine is a serotonin and noradrenalin reuptake inhibitier (SNRI). It does not have a license for managing neuropathic pain but there is evidence of its benefit in chronic pain (8). There are cautions particularly in patients with heart disease. This is a drug best used by those familiar with its use.

Duloxetine is a newer SNRI antidepressant. It is used for depression, urinary stress incontinence and neuropathic pain. There is moderately strong evidence for a benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day (10). Side effects are common and may result in its discontinuation.
Selective serotonin reuptake inhibitors (SSRIs) are antidepressants with fewer side effects. They are effective for depression, but there have been insufficient studies to demonstrate their benefit in pelvic or neuropathic pain (9,11,12).

10.2.2 Anticonvulsants

This group of drugs are commonly used in the management of neuropathic pain. There have been general studies as well as some looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Guidelines (8).

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit (13). It should be remembered that the trials have tended to be of short duration, showing only moderate benefit. There are side effects; some of which may be serious. With more recently developed agents becoming available, with fewer serious side effects, carbamazepine is no longer a first-choice agent.

Gabapentin is commonly used for neuropathic pain and has been systematically reviewed (14). It provides good quality relief with NNT of approximately six. This is a more conservative estimate than in previous reports. Side effects are common, notably drowsiness, dizziness and peripheral oedema. These effects do limit compliance but are often tolerated by patients. The doses involved were all greater than 1.2 g/day. For upper dose levels, reference should be made to local formularies, and many clinicians do not routinely exceed 2.4 g/day in divided doses (most commonly three times daily).

One study of women with CPP has suggested that gabapentin alone or in combination with amitriptyline provides better analgesia than amitriptyline alone (15).

Pregabalin is another commonly used neuromodulator. There is good evidence for its efficacy in some neuropathic conditions but the NNT varies depending on the condition (16). The dose for benefit is in the range of 300 to 600 mg/day. The same systematic review has found that doses less than 150 mg/day are unlikely to provide benefit. As with gabapentin, side effects are relatively common and may not be tolerated by patients.

Other anticonvulsants are available but not commonly used for managing pain.

10.2.3 Other agents

Other agents can be used in the management of neuropathic pain but are best limited to those that are specialists in the management of pain and familiar with their use. They tend to be considered after the standard options have been exhausted. As with all good pain management, they are used as part of a comprehensive management plan.

Topical capsaicin has been used for neuropathic pain either by repeated low-dose (0.075%) administration or more recently as a single high dose (8%). Topical application (usually to an area of hyperaesthesia or allodynia) is more inconvenient than for other medications, and capsaicin does cause initial heat on application. Skin sensitivity is a limiting factor and may not be well tolerated. A systematic review has suggested there may be benefit in some patients (17). Care should be taken to ensure that unused cream or that washed off the hands following application is not inadvertently transferred to other areas of skin or mucous membranes.

Antipsychotics have been used and despite limited research, a systematic review has suggested that further research should be undertaken on the atypical antipsychotics, which have fewer side effects and are better tolerated than the older antipsychotics (18).

10.3 Opioids

Opioids are used for chronic non-malignant pain and may be beneficial for a small number of patients. Often patients will stop taking oral opioids due to side effects or insufficient analgesia (19).

They should only be used in conjunction with a management plan and with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician.

There are well established guidelines for the use of opioids in pain management as well as considering the potential risks (20). There is also information available online for patients (21,22).

Opioid rotation is used in palliative care and to some extent in non-cancer pain. The evidence is clinical, largely anecdotal, or from small trials and is not convincing (23). The rational is that if a patient has significant side effects and inadequate analgesia to one opioid then swapping to another agent may be better tolerated.
There are several agents available in the group. They can be divided into weak (e.g., codeine, dihydrocodeine and tramadol) or strong opioids (e.g., morphine, oxycodone, fentanyl and hydromorphone).

Oral administration is preferable, but if poorly tolerated, a percutaneous (patch) route may have advantages. More invasive approaches are less commonly used and within the realms of specialist units. Side effects are common and require active management. This is particularly true of constipation with some interesting developments on methods for managing it.

There is a growing understanding of opioid-induced hyperalgesia; a situation in which patients taking opioids, paradoxically, become more sensitive to painful stimuli (24). This is another reason for these drugs to be used in a controlled fashion for long-term management of non-malignant pain.

### 10.3.1 Recommendations for use of opioids in chronic/non-acute urogenital pain

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>All other reasonable treatments must have been tried and failed.</td>
</tr>
<tr>
<td>The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (including the patients and their family doctor).</td>
</tr>
<tr>
<td>Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.</td>
</tr>
<tr>
<td>The patient should undergo a trial of opioids.</td>
</tr>
<tr>
<td>The dose required needs to be calculated by careful titration.</td>
</tr>
<tr>
<td>The patient should be made aware (and possibly give written consent):</td>
</tr>
<tr>
<td>• That opioids are strong drugs and associated with addiction and dependency.</td>
</tr>
<tr>
<td>• Opioids will normally only be prescribed from one source (preferably the family doctor).</td>
</tr>
<tr>
<td>• The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period.</td>
</tr>
<tr>
<td>• The patient may be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed, and that non-prescribed drugs are not being taken.</td>
</tr>
<tr>
<td>• Inappropriate aggressive behaviour associated with demanding the drug will not be accepted.</td>
</tr>
<tr>
<td>• Hospital specialist review will normally occur at least once a year.</td>
</tr>
<tr>
<td>• The patient may be requested to attend a psychiatric/psychological review.</td>
</tr>
<tr>
<td>Failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.</td>
</tr>
</tbody>
</table>

Morphine is the first-line opioid, unless there are contraindications to morphine or special indications for another drug.

- The drug should be prescribed in a slow-release/modified release form.
- Short-acting preparations are undesirable and should be avoided where possible.
- Parenteral dosing is undesirable and should be avoided where possible.

### 10.3.2 Morphine

There is no compelling evidence that one opioid is better than another. Morphine is the traditional gold standard and the opioid with which many physicians are most familiar. The aim is to use a slow or sustained release preparation starting with a low dose and titrating the dose every 3 days to 1 week against improvement in both function and pain. Side effects should also be monitored and managed accordingly. Particular attention should be paid to the management of constipation.

### 10.3.3 Other opioid agents

There are a variety of agents available and some are mentioned below, giving an idea of the options available.

**Transdermal fentanyl** may be considered when oral preparations are restricted (e.g., ileostomy). It may also be beneficial when there are intolerable side effects from other opioids.

**Methadone** has a long record of use as an opioid. There is a theoretical advantage of benefit with its N-methyl-D-aspartate receptor (NMDA) antagonist activity. This may be particularly relevant in neuropathic pain (25).

**Oxycodone** may have greater efficacy than morphine in some situations, such as hyperalgesic states including visceral pain (26).
Analgesics with a dual mode of action may have a role in the management of chronic pain. Tramadol is an established analgesic with dual effects on opioid receptors and serotonin release. More recently, a new agent, tapentadol, has been released with opioid action and noradrenaline reuptake inhibition. It is too early to assess its real value in the armamentarium for pain management.

10.4  **Nerve blocks**  
Nerve blocks for pain management are usually carried out by specialists in pain medicine and as part of a broader management plan (27). They may have a diagnostic or therapeutic role.

Textbooks have been written on the subject and practitioners using them should be trained in appropriate patient selection, indications, risks and benefits. Many such interventions also require understanding and expertise in using imaging techniques to perform the blocks accurately.

Diagnostic blocks can be difficult to interpret due to the complex nature of the mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g., neurolytic block or radiofrequency procedures). Neurolytic blocks in particular should only be considered by practitioners experienced in their use and with the full understanding of the patient because complications can be disastrous.

There is a weak evidence base for these interventions for chronic non-malignant pain.

10.5  **Transcutaneous electrical nerve stimulation (TENS)**  
Despite the popularity of TENS and the number of trials undertaken, a systematic review has been unable to provide good evidence for or against its use in the management of chronic pain (28). It is clear that further more rigorous trials should be undertaken to provide some clarity for a commonly used intervention.

10.6  **Neuromodulation in pelvic pain syndromes**  
The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are only used as part of a broader management plan and require regular follow-up.

The research base is developing and the techniques broadening [e.g., spinal cord stimulation (SCS), sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation]. These are expensive interventions and thus many of the patients involved are refractory to other therapies. It is thus inappropriate to provide a detailed review of these techniques for this publication.

In the UK, guidance has been published for SCS in neuropathic pain (29). This emphasises the comments above. This guidance suggests a trial period of stimulation before full implementation.

Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence in small case series or pilot studies, but more detailed research is required (30). Its role in overactive bladder and faecal incontinence is more robust but is limited for pain.

10.7  **Summary**  
Chronic pelvic pain is a common complaint that is well defined and involves multiple mechanisms. Some of the conditions have clear management pathways but many do not. In these CPP syndromes, a holistic multidisciplinary team approach is required with active patient involvement.

This chapter focuses on general treatment of CPP, mainly drug therapy, and comments on other more invasive techniques. The latter are used in combination with other modalities. Many are aimed at management of neuropathic pain or conditions in which central mechanisms are implicated.

At this stage in management, the involvement of trained clinicians with expertise in chronic pain management should be considered. Centres with a particular interest in pelvic pain do exist and involve clinicians from several specialties along with other health care professionals (e.g., physiotherapy, psychology, nursing and occupational therapy).

With any of the agents above, the aim is to assess pain relief, improvement in function, and side effects. This should be done regularly while titrating and optimising drug dose. If there is no benefit, then the drug should be withdrawn.
Neuropathic agents are frequently used and often in combination. There is significant inter-patient variability in effect. Use is often limited by side effects that may be worse than any pain reduction.

Opioid drugs are used in this group of patients. Their role is limited and they should only be started in consultation with all parties involved (including the patient’s family practitioner). National guidelines exist and should be followed. There is growing understanding of the limitations of opioid use, and more recently, the paradoxical situation of opioid-induced hyperalgesia.

10.8 Recommendations for the medical and interventional treatment of CPP

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pain Type</th>
<th>LE</th>
<th>GR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Somatic pain</td>
<td>1a</td>
<td>A</td>
<td>Evidence based on arthritic pain with good benefit</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Pelvic pain with inflammatory process (e.g. dysmenorrhoea)</td>
<td>1a</td>
<td>A</td>
<td>Good evidence for their use</td>
</tr>
<tr>
<td>Antidepressants including tricyclic antidepressants, duloxetine and venlafaxine</td>
<td>Neuropathic pain</td>
<td>1a</td>
<td>A</td>
<td>Effective. No specific evidence for CPP</td>
</tr>
<tr>
<td>Anticonvulsants gabapentin, pregabalin</td>
<td>Neuropathic pain, fibromyalgia</td>
<td>1a</td>
<td>A</td>
<td>Effective</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Women with CPP</td>
<td>2b</td>
<td>B</td>
<td>Effective</td>
</tr>
<tr>
<td>Topical capsaicin</td>
<td>Neuropathic pain</td>
<td>1a</td>
<td>A</td>
<td>Some evidence of benefit</td>
</tr>
<tr>
<td>Opioids</td>
<td>Chronic non-malignant pain</td>
<td>1a</td>
<td>A</td>
<td>Beneficial in a small number of patients</td>
</tr>
<tr>
<td>Nerve blocks</td>
<td></td>
<td>3</td>
<td>C</td>
<td>Have a role as part of a broad management plan</td>
</tr>
<tr>
<td>TENS</td>
<td></td>
<td>1b</td>
<td>B</td>
<td>There is no good evidence for or against the use of TENS. Data covered chronic pain not just CPP and was insufficient regarding long-term treatment effects.</td>
</tr>
<tr>
<td>Neuromodulation</td>
<td>Pelvic pain</td>
<td>3</td>
<td>C</td>
<td>Role developing with increasing research</td>
</tr>
</tbody>
</table>

**TENS = transcutaneous electrical nerve stimulation; CPP = chronic pelvic pain**

**Figure 18: Algorithm for general analgesic treatment of chronic pelvic pain**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>General history</td>
<td>Grade A recommended</td>
</tr>
<tr>
<td>Medications used</td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td></td>
</tr>
<tr>
<td>Use of alcohol</td>
<td></td>
</tr>
<tr>
<td>Daily activities that will be affected</td>
<td>Grade B recommended</td>
</tr>
<tr>
<td></td>
<td>Other comments</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 19: General management algorithm

Pain described in neuropathic or central pain terms

yes

First-line management trial using
1. Amitriptyline
2. Gabapentin

Alternatives:
1. Nortriptyline or Imipramine
2. Pregabalin

Review

Adequate analgesia:
• review regularly
• sustained effect: consider dose reduction

Inadequate response:
• consider adding another first line agent
• rotate agents

Still inadequate:
• refer to specialist pain management unit

no

Simple analgesics

Review

Adequate analgesia:
• discharge back to primary care physician

Inadequate response:
• refer to specialist pain management unit

10.9 References


29. NICE technology appraisal guidance 159. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. 
http://guidance.nice.org.uk/TA159

## 11. Abbreviations Used in the Text

This list is not comprehensive for the most common abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPA</td>
<td>Amino-methylene-phosphonic acid</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosinetriphosphate</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette Guérin</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>BPS</td>
<td>Bladder pain syndrome</td>
</tr>
<tr>
<td>BTX-A</td>
<td>Botulinum toxin A</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive behavioural therapy</td>
</tr>
<tr>
<td>CFS</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonin gene-related peptide</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CPP</td>
<td>Chronic pelvic pain</td>
</tr>
<tr>
<td>CPPS</td>
<td>Chronic pelvic pain syndrome</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotrophin-releasing hormone</td>
</tr>
<tr>
<td>CyA</td>
<td>Cyclosporin A</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNIC</td>
<td>Diffuse noxious inhibitory control</td>
</tr>
<tr>
<td>DRG</td>
<td>Dorsal root ganglion</td>
</tr>
<tr>
<td>EH</td>
<td>Excisional haemorrhoidectomy</td>
</tr>
<tr>
<td>ESSIC</td>
<td>European Society for the Study of BPS</td>
</tr>
<tr>
<td>FM</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>FSSs</td>
<td>Functional somatic syndromes</td>
</tr>
<tr>
<td>GAG</td>
<td>Glycosaminoglycan</td>
</tr>
<tr>
<td>HBO</td>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>HIF</td>
<td>Hypoxia inducible factor</td>
</tr>
<tr>
<td>IASP</td>
<td>Association for the Study of Pain</td>
</tr>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>ICDB</td>
<td>Interstitial Cystitis Data Base</td>
</tr>
<tr>
<td>ICPSI</td>
<td>Interstitial Cystitis Symptom Index</td>
</tr>
<tr>
<td>I-PPS</td>
<td>International Prostate Symptom Score</td>
</tr>
<tr>
<td>ISSVD</td>
<td>Society for the Study of Vulvovaginal Disease</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>MAPPP</td>
<td>Multi-disciplinary Approach to the study of chronic Pelvic Pain research</td>
</tr>
<tr>
<td>MPA</td>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NBSs</td>
<td>Non-bladder syndromes</td>
</tr>
<tr>
<td>NGF</td>
<td>Nerve growth factor</td>
</tr>
<tr>
<td>NIDDK</td>
<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NIH-CPSI</td>
<td>NIH Prostatitis Symptom Index</td>
</tr>
<tr>
<td>NMADA</td>
<td>N-Methyl-D-aspartate</td>
</tr>
<tr>
<td>NNT</td>
<td>Numbers needed to treat</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>PAG</td>
<td>Periaqueductal grey</td>
</tr>
<tr>
<td>PID</td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>PNS</td>
<td>Pudendal nerve stimulation</td>
</tr>
<tr>
<td>PNS</td>
<td>Peripheral nervous system</td>
</tr>
<tr>
<td>PPMT</td>
<td>Pre-post-massage test</td>
</tr>
<tr>
<td>PPS</td>
<td>Prostate pain syndrome</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RBL</td>
<td>Rubber band ligation</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RTX</td>
<td>Resiniferatoxin</td>
</tr>
<tr>
<td>TUNA</td>
<td>Transurethral needle ablation</td>
</tr>
<tr>
<td>TUR</td>
<td>Transurethral resection</td>
</tr>
<tr>
<td>VAPS</td>
<td>Visual analogue pain scale</td>
</tr>
</tbody>
</table>
Conflict of interest

All members of the Chronic Pelvic Pain Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
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1. INTRODUCTION

Most renal transplantation centres in Europe were founded by urologists. However, many of them are becoming part of transplant centres run by general transplant surgeons. This is the main reason why it is important to present current knowledge about renal transplantation in these European Association of Urology (EAU) guidelines.

As renal transplantation is very much an interdisciplinary field, the guidelines group, hereafter referred to as the panel, contains not only urologists but also an immunologist (Prof. Dr. Süsal) and a nephrologist (Prof. Dr. Budde). Besides medical and technical aspects, the panel has also considered ethical, social, and political aspects. This was necessary because of the still-increasing gap between ‘supply’ and ‘demand’ for kidney transplants, and the large differences in organ donation rates between European countries, suggesting European countries can learn from each other on how to increase organ donation rates.

Methodology

There are few prospective randomised studies for most sections of the guidelines, and sometimes none. Thus, the grades of recommendation, which are evidence-based, seldom exceed grade C (see Table 2). Instead, the guidelines are well supported by a wealth of clinical experience based on several decades of work in renal transplantation, as in, for example, technical aspects of transplantation and explantation.

A level of evidence (LE) and/or grade of recommendation (GR) have been assigned where possible (1). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Publication:

The EAU Guidelines on Renal Transplantation were first published in 2003, with a partial update in 2004 followed by this full text update in 2009. Additionally, a quick reference guide is available. All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/guidelines/online-guidelines/.

Levels of evidence and grade of guideline recommendations*

Table 1: Level of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

Table 2: Grade of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*modified from Sackett et al. (1)

1.1 Reference


2. **KIDNEY DONATION**

2.1 **Ethical issues in transplantation**

2.1.1 **Primary ethical principles**
A number of primary principles are widely accepted as forming the bedrock of medical ethics (1-3). Conflict in an individual case often arises when trying to adhere to all these principles at the same time.

2.1.1.1 **Beneficence: doing good, avoiding harm, autonomy, fairness**
A central tenet of medical ethics is the obligation to strive at all times to do good for the patient. Although no physical good will accrue to a donor, it is generally accepted that the psychosocial benefits to the living donor justify the risks involved (4).

Making sure that there is an appropriate balance between benefit and harm is an important clinical judgment. A high standard of donor assessment and risk limitation is therefore of paramount importance before living kidney donation can take place (5).

Individuals are said to have ‘decision-making capacity’ if they can understand relevant information, consider its implications, and come to a communicable decision. A donor’s decision to donate should be respected.

The principle of justice is very important in kidney distribution, where demand far outstrips supply. This means there must be a ranking system for allocating organs in an order of priority that can be morally justified. In transplantation, scarce resources usually have to be carefully allocated to recipients chosen from a larger pool of the population.

2.1.2 **Deceased donor organ donation**
There has been an increase in living-donor organ procurement in recent years. Most organs still come from deceased donors, brain-dead donors, and from the non-heart-beating donor (NHBD) procurement programme, which is now used by several transplant centres. However, this resource base is shrinking. Together with an ever-increasing rise in potential recipients, this causes considerable pressure on the transplantation programme.

2.1.2.1 **Deceased organ donor**
In most countries, obtaining consent to proceed with organ donation is a major challenge. The process of gaining formal consent from relatives or from the patient during life can be defined as ‘opting in’ to a donor scheme. Unless consent is expressly given, the presumption is that consent is withheld. In some European countries, the opposite situation applies. Consent is presumed unless the patient has specifically opted out before death. This type of legislation can increase organ donation. For example, in Spain, this approach has produced a national network of medical teams dedicated to obtaining the maximum number of donors and greatly increasing organ transplantation (6).

2.1.2.2 **Allocation of deceased donor organs**
Who ‘owns’ deceased donor organs and who makes the decision regarding allocation are both issues needing clarification (7-9). However, there is a general presumption that the State holds the responsibility for allocation or disposal of donated organs, which is then delegated to the appropriate transplant team (10). It is considered unacceptable that deceased donor donation and allocation should depend upon the personal attributes of the recipient, e.g. race, religion or wealth. In kidney transplantation, the European healthcare systems attempt to maximise benefits by distributing kidneys on the basis of HLA matching. Potential recipients are allocated points for waiting time, matchability and sensitisation. Kidney distribution systems should be transparent and regularly audited.

2.1.3 **Living-organ donors**
The ethical approach to organ donation is guided mainly by those rules that seek to be charitable. Living-donor transplant has been regarded as a regrettable necessity because of the success of living-donor transplant (as judged by graft and patient survival) and the scarcity of deceased donor organs (11). The chronic shortage of deceased donor organs has led to a more general acceptance of living-donor transplants. The physical and psychosocial well-being of the donor are of primary importance. Each donor should have an advocate (i.e. a psychiatrist and nephrologist from the donor evaluation team) to provide unbiased advice on the donation process and there should be separation of the recipient and donor teams.

Kidneys can be accepted from related and unrelated donors, including spouses, friends and acquaintances, or altruistic donors (anonymous donors) or paired kidney donation (see Section 2.3.3.1). The donor must be given a psychosocial evaluation by a mental health professional, who has no relationship with the recipient, to assess
the donor’s ability to make the decision. The donor’s confidentiality must be protected and the evaluation must be carried out in the absence of the recipient. If a translator is necessary, the translator must be unknown to both the recipient and donor. The donor should be told about the benefits to the recipient’s health (physical and mental) and the risks to the donor’s health (physical and mental).

The donor’s motivation should be assessed. Coercion and secondary gain (monetary or other personal gain) should be excluded. Outcomes should be discussed: psychological benefits after a successful transplantation (increased self-esteem), and resentment or depression after an unsuccessful transplantation.

### Recommendations

<table>
<thead>
<tr>
<th>It is the right of individuals to donate as well as to receive an organ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercially motivated renal transplantation is unacceptable. It has been widely prohibited by law and is strongly opposed by the International Society of Transplantation.</td>
</tr>
<tr>
<td>With the increasing success of living-donor transplants, as judged by graft and patient survival, and with the scarcity of deceased donor organs, living-donor transplants should be encouraged. The appeal of using living donors in renal transplantation is partly due to the ongoing shortage of deceased donors.</td>
</tr>
<tr>
<td>The altruistic living donor must give informed consent, which can only be obtained if he or she has a proper understanding of the risks involved.</td>
</tr>
<tr>
<td>A patient should be treated as an ‘end’, and not as a ‘means’. Respect for dignity, integrity and authenticity of the person are basic human rights.</td>
</tr>
<tr>
<td>Living unrelated donors should only be accepted after the local ethical committee has given permission according to the rules of the country in which the donation is taking place.</td>
</tr>
</tbody>
</table>

Because ethical values cannot be measured using the ‘scientific’ basis of levels of evidence, grades of recommendation are not given.

### References


### Policies to increase the supply and use of deceased donors

Generally, the gap between the supply and demand of kidneys has tended to stabilise in countries with a donation rate greater than 40 kidneys per million population (pmp), but has increased in countries with a lower donation rate. This is in spite of the trend for donation rates to increase (or stabilise) in Europe since 2001. Table 3 lists recent kidney transplantation rates in different European countries (1).
The data suggest that a donation rate of 40 pmp per year should be achievable by any single country in Europe, especially with so many sociocultural similarities. However, the act of donation is complex, depending on many factors and interactions, few of which have been proven useful individually or are generally applicable throughout the European Union. Although it is relatively easy to set a minimum standard for organ donation, it is more difficult to recommend specific, donor-promoting activities for individual countries and professional organisations. However, a few options are described below.

### 2.2.1 Donor cards

Some countries such as the UK require donors to ‘opt in’. Others, such as Belgium and Denmark, ‘presume consent’ and allow individuals who do not want to be donors to ‘opt out’.

Many countries have publicity schemes encouraging the general population to carry donor cards or register their wish to donate (opting-in) on a computerised donor register. This helps to reduce the risk of donation being refused by the family. In the UK, 15.1 million individuals are registered on the ‘opting in’ computer, while 5-10% of the population prefer to carry donor cards (2). However, the efficiency of this ‘opt-in’ system in creating donors is lower than in countries with a presumed consent. Opt-in systems require continuous publicity to increase the number of opted-in donors and transplant centres. Intensive

---

**Table 3: Kidney transplant rates in 2010 (1)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Deceased donor kidneys (pmp)</th>
<th>Living-donor kidney (pmp)</th>
<th>Total kidneys (pmp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria (ET)*</td>
<td>38.1</td>
<td>6.9</td>
<td>45</td>
</tr>
<tr>
<td>Belgium (ET) (2008)</td>
<td>38.6</td>
<td>4.2</td>
<td>42.8</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>5.14</td>
<td>1.71</td>
<td>6.85</td>
</tr>
<tr>
<td>Croatia (ET)*</td>
<td>49.8</td>
<td>4.51</td>
<td>54.31</td>
</tr>
<tr>
<td>Cyprus (2008)</td>
<td>34</td>
<td>49</td>
<td>83</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>31.1</td>
<td>1.6</td>
<td>32.7</td>
</tr>
<tr>
<td>Denmark (ST)**</td>
<td>23</td>
<td>18.1</td>
<td>41.1</td>
</tr>
<tr>
<td>Estonia</td>
<td>26.1</td>
<td>3</td>
<td>29.1</td>
</tr>
<tr>
<td>Finland (ST)**</td>
<td>30.7</td>
<td>2.06</td>
<td>32.76</td>
</tr>
<tr>
<td>France (2007)</td>
<td>42.03</td>
<td>3.5</td>
<td>45.8</td>
</tr>
<tr>
<td>Georgia (2008)</td>
<td>0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Germany (ET)*</td>
<td>27.8</td>
<td>8.1</td>
<td>35.9</td>
</tr>
<tr>
<td>Greece (2009)</td>
<td>10.6</td>
<td>3.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Hungary</td>
<td>26.4</td>
<td>4.19</td>
<td>30.59</td>
</tr>
<tr>
<td>Iceland (ST)**</td>
<td>No data</td>
<td>15.74</td>
<td>15.74</td>
</tr>
<tr>
<td>Ireland (2007)</td>
<td>32.6</td>
<td>1.2</td>
<td>33.8</td>
</tr>
<tr>
<td>Italy</td>
<td>25.1</td>
<td>3</td>
<td>28.1</td>
</tr>
<tr>
<td>Latvia</td>
<td>27.8</td>
<td>0.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Lithuania</td>
<td>19.1</td>
<td>2.4</td>
<td>21.5</td>
</tr>
<tr>
<td>Luxembourg (ET)*</td>
<td>12.05</td>
<td>No data</td>
<td>12.05</td>
</tr>
<tr>
<td>Malta (2009)</td>
<td>15</td>
<td>12.5</td>
<td>27.5</td>
</tr>
<tr>
<td>Moldova (2007)</td>
<td>0</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Netherlands (ET)*</td>
<td>22.7</td>
<td>28.5</td>
<td>51.2</td>
</tr>
<tr>
<td>Norway (ST)**</td>
<td>36.9</td>
<td>16.9</td>
<td>53.8</td>
</tr>
<tr>
<td>Poland</td>
<td>24.85</td>
<td>1.3</td>
<td>26.15</td>
</tr>
<tr>
<td>Portugal</td>
<td>49.1</td>
<td>4.8</td>
<td>53.9</td>
</tr>
<tr>
<td>Romania</td>
<td>5.68</td>
<td>4</td>
<td>9.68</td>
</tr>
<tr>
<td>Slovak Republic (08)</td>
<td>27.4</td>
<td>3.6</td>
<td>31</td>
</tr>
<tr>
<td>Slovenia (ET)*</td>
<td>30.5</td>
<td>0</td>
<td>30.5</td>
</tr>
<tr>
<td>Spain (2009)</td>
<td>45.2</td>
<td>5</td>
<td>48.2</td>
</tr>
<tr>
<td>Sweden (ST)**</td>
<td>21.6</td>
<td>17.9</td>
<td>39.5</td>
</tr>
<tr>
<td>Switzerland</td>
<td>23.1</td>
<td>14.7</td>
<td>37.8</td>
</tr>
<tr>
<td>Ukraine (2009)</td>
<td>0.5</td>
<td>1.9</td>
<td>2.4</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>23</td>
<td>16.6</td>
<td>39.6</td>
</tr>
</tbody>
</table>

\[pmp = \text{per million population.}\]

* ET = Country member of the Eurotransplant.

** ST = Country member of the Scandia Transplant.
care physicians and transplant co-ordinators also need to access the register routinely to identify potential deceased donors.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all countries without presumed consent law, efforts should be increased to recruit donors through an opting-in register or by carrying donor cards.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.2.2 Improved organisation and resources

Services must be better organised and resourced to increase deceased donor donation. The ability to achieve more than 25 donors pmp increases with the number of intensive care beds. High-donating countries with better-resourced intensive care units (e.g. Spain, France, Belgium) have increased the number of staff responsible for donation (transplant coordinators) and given them proper financial support. Successful education programmes, such as European Donor Hospital Education Programme (EDHEP) (3) or institutional audits, such as Donor Action, have increased and maintained the awareness of intensive care physicians for the need for deceased donor donation and supported them in approaching donor families to discuss donation. Transplant coordinators are responsible for liaising with coroners and public relations, particularly avoiding adverse publicity.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional organisations within countries should, where necessary, put pressure on government health departments to maintain enough intensive care beds, create a cadre of national transplant coordinators, and fund and deploy educational programmes for intensive care physicians.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.2.3 ‘Opting-out’ legislation

The introduction of opting-out legislation results in increased rates of deceased donor donation. All European countries with more than 30 kidney donors pmp per annum (see Table 3) have opting-out legislation. Adverse publicity results in a ‘soft’ presumed consent in most countries, which also takes the family’s views into account. Countries with informed consent do not usually perform as well, with the USA producing the highest kidney donation rate of 24 donors pmp through the United Network for Organ Sharing/The Organ Procurement and Transplantation Network (UNOS/OPT) (4,5).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A recommendation cannot be made about something as fundamental as changing the law on deceased donor donation. However, presumed consent with an opting-out law is desirable.</td>
<td></td>
</tr>
</tbody>
</table>

2.2.4 Non-heart-beating donor

Non-heart-beating donors (NHBD) provide an important opportunity to decrease the deceased donor shortage of kidneys, even though NHBD kidneys are suboptimal organs due to the increased risk of delayed graft function and primary non-function. However, the long-term viability of NHBD kidneys in strictly selected donors has been improved by the use of a continuous perfusion machine on the cadaver before harvesting (6).

A continuous perfusion machine can be used to assess NBHD kidney viability. Flow measurements and urinary enzyme excretion (7) are predictors of viability. Presumed consent legislation would allow many more NHBD kidneys because rapid intra-arterial cold perfusion of a recently deceased person would normally be allowed before family members arrive at the hospital. However, under informed consent law, perfusion of a cadaver without relatives’ permission is an unwarranted assault. In contrast, under presumed consent, a coroner is able to give permission for perfusion without requiring the relatives’ consent, so allowing the use of NHBDs to be expanded significantly.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of non-heart-beating donors should be expanded significantly.</td>
<td>B</td>
</tr>
<tr>
<td>Transplant staff should create policies for recently dead admissions to casualty departments to be used as non-heart-beating donors.</td>
<td>B</td>
</tr>
</tbody>
</table>

2.2.5 Elderly donors

The use of kidneys from elderly donors (> 60 years) is increasing. In countries such as Spain, it represents 40% of total kidney transplants. Long-term survival of kidneys is similar to the transplants performed with non-expanded criteria donors (8). After 6 months’ post transplant, patients who have been transplanted have a better survival rate than patients remaining on dialysis. Kidney transplants from donors older than 70 years
carry a higher risk of graft loss and mortality, especially when transplanted to recipients under 60 years (9).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of carefully selected donors over 60 years of age should be maintained and encouraged as a continuing source of deceased donor kidneys.</td>
<td>B</td>
</tr>
<tr>
<td>Donors over 70 should be evaluated on an individual basis, taking into account that better results are obtained when transplanted to patients older than 60 years.</td>
<td>B</td>
</tr>
</tbody>
</table>

2.2.6  References
1. Transplant Procurement Management. Family approach for organ donation.  
   www.tpm.org
2. NHS Organ Donor Register.  
   http://www.unos.org
5. The Organ Procurement and Transplantation Network.  
   http://optn.transplant.hrsa.gov

2.3  Policies to enhance living donation
Kidney transplants from living donors offer a better graft and patient survival than those from deceased donors (1). Two major recent developments have led to the increased acceptance of living kidney donation:
• Kidney transplant results have improved so that more patients with end stage renal disease (ESRD) have opted for transplant rather than dialysis.
• As the number of deceased donor kidneys has not increased, the number of living donors has increased.

It is also likely that laparoscopic donor nephrectomy (less time off work, shorter hospital stay) has helped recruit living donors.

The USA have greatly improved the supply of kidney transplants by recruiting more than 50% of total donations from consanguineous and non-consanguineous donors (i.e. living unrelated donors, which comprise 40% of transplants from living donors) (2,3). In contrast, in Europe, living-donor transplants comprise only 15% of transplantations. However, there is a clear trend for an increase in the living-donor rate, especially in the Scandinavian countries, The Netherlands, and Cyprus (see Table 3). Living-donor rates can be improved at different stages in the referral process and in more general ways (Table 4).
Table 4: Ways of improving the living donation rate

<table>
<thead>
<tr>
<th>During referral process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrologists, at non-transplanting as well as transplanting centres, should be encouraged to discuss openly living donation with families of patients suffering from endstage renal disease, preferably before the patient begins dialysis. This results in pre-dialysis transplantation, increased transplant rates and better use of dialysis resources.</td>
</tr>
<tr>
<td>Counselling (e.g. by senior nurse practitioners or living-donor co-ordinators) should be available to discuss screening tests, provide information packs, and arrange reimbursement of necessary donor expenses allowed in law.</td>
</tr>
<tr>
<td>If legally permitted, living unrelated donors should be encouraged.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>More general methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical methods, such as laparoscopic harvesting, paired kidney exchange, transplantation of grafts with anatomical abnormalities (vascular, urinary tract fusion), reversal of a positive cross-match by treatment with plasmapheresis, and intravenous immunoglobulin administration.</td>
</tr>
<tr>
<td>Ethical methods, such as showing appreciation for organ donation.</td>
</tr>
<tr>
<td>Organisational methods, such as medical leave for organ donation and reimbursement of all costs to the donor.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living donation in Europe should be encouraged. There is a widening gap between donation and demand for kidney transplants, with not enough deceased donors. There is, however, an increase in living donors. In the USA, the number of kidneys from living donors is nearly the number of kidneys from deceased donors.</td>
<td>C</td>
</tr>
<tr>
<td>Organ donation should be considered a charitable gift. Society can express gratitude to organ donors for their gift as with charitable contributions, without jeopardising its altruistic basis (e.g. ‘Medal of Honour’, limited reimbursement, medical leave, priority access to organ for transplant, donor insurance).</td>
<td>C</td>
</tr>
<tr>
<td>All nephrologists who care for ESRD patients should explore the living donor option with the family when a patient first presents with ESRD.</td>
<td></td>
</tr>
</tbody>
</table>

ESRD = endstage renal disease.

2.3.1 Medical methods to increase number of living donations

2.3.1.1 Acceptance of grafts with anatomical anomalies

The use of grafts with anatomical anomalies is considered a relative contraindication by most experienced transplantation centres because of the shortage of living donors. Anatomical anomalies include renal cysts, uretero-pelvic junction obstruction, solitary stones > 1 cm, duplex ureteral system, and multiple arteries and veins. However, retrospective reports have suggested that grafts with multiple renal artery or vein anomalies, such as circumaortic or retroaortic renal vein, do not carry an increased risk of complications in experienced hands (4).

If the donor has a good immunological correspondence with the recipient, but an abnormal kidney, which is the only kidney available, and if the recipient on haemodialysis has a poor status, the abnormal kidney should be transplanted leaving the donor with the best one.

A laparoscopic right kidney donor nephrectomy is as safe as a left nephrectomy. A recent prospective trial showed no differences in complication rates and graft survival between left- and right-sided donor nephrectomy (5).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Multiple renal artery or grafts with anatomical anomalies are not absolute contraindications. Decisions should be made on an individual basis.</td>
<td>C</td>
</tr>
<tr>
<td>Laparoscopic right kidney nephrectomy is as safe as left kidney nephrectomy in terms of complications and graft survival.</td>
<td>A</td>
</tr>
</tbody>
</table>
2.3.1.2 Laparoscopic living-donor nephrectomy

Laparoscopic living-donor nephrectomy (LLDN) is an alternative surgical method that has increased the rate of living donations. It is becoming the preferred technique for living-donor renal transplantation. In the USA, laparoscopic donor nephrectomies are more common than open surgery donor nephrectomies. In Europe, although the number of nephrectomies are increasing, fewer laparoscopic nephrectomies are performed than open procedures (6).

There is a good evidence base for LLDN, including three systematic reviews, which have compared its safety and efficacy to the ‘gold standard’ of open donor nephrectomy, at least seven randomised control trials (LE: 1-2), five prospective non-randomised studies (LE: 2) and several retrospective studies (7-9). Compared to open live donor nephrectomy (OLDN), LLDN shows similar rates for graft function, rejection rate, urological complications, and patient and graft survival. However, measures for analgesic requirements, pain, hospital stay, and time to return to work are significantly better for a laparoscopic procedure.

In terms of donor safety, the historical mortality rate is 0.03% with open donor nephrectomy, a rate that remains unchanged by the introduction of LLDN (10,11). The data about potential mortality should be included in all informed consent. In addition, LLDN does not affect the long-term risk of developing ESRD (12). However, the laparoscopic approach takes longer and requires additional resources. Nevertheless, the shorter hospital stay and a more rapid return to work may compensate for the initial higher costs. In addition, the number of live kidney donations has increased by more than 100% in many institutions since the introduction of the laparoscopic approach.

Overall, laparoscopic nephrectomy offers donors less post-operative pain, shorter convalescence and better cosmetic results compared to traditional open donation. In experienced hands, this procedure is accomplished without increased risk to the donor’s safety or allograft function. As with OLDN, LLDN should be considered the gold standard of treatment.

Recently introduced, LESS transumbilical nephrectomy allows the surgeon to work through the umbilicus using a multientry port. The same incision is then used for kidney withdrawal. Increasing experience in selected centres suggest that it is a promising technique with better cosmetic results. NOTES-assisted transvaginal nephrectomy is a technique that also allows avoiding the extraction abdominal scar. Both LESS transumbilical nephrectomy and NOTES-assisted transvaginal nephrectomy are experimental and should be used only in highly specialised centres (13).

Table 5: Laparoscopic live donor nephrectomy: advantages and disadvantages

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less post-operative pain</td>
<td>Graft loss or damage during ‘learning curve’</td>
</tr>
<tr>
<td>Minimal surgical scarring</td>
<td>Pneumoperitoneum may compromise renal blood flow</td>
</tr>
<tr>
<td>Rapid return to full activities</td>
<td>Longer operative time and work (about 4 weeks)</td>
</tr>
<tr>
<td>Shorter hospital stay</td>
<td></td>
</tr>
<tr>
<td>Magnified view of renal vessels</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations

Laparoscopic nephrectomy offers equal urological complications, graft function and graft survival to open nephrectomy, with less post-operative morbidity, shorter convalescence, and better cosmetic results.

Laparoscopic nephrectomy increases the number of individuals willing to donate. It should be used only by appropriately trained and experienced surgeons.

2.3.1.3 References

2.3.1.4 ABO-incompatible donors

ABO incompatibility was once a contraindication for renal transplantation, but this is no longer the case because of new techniques (antibody adsorption columns) (1) and new immunosuppressive tools (e.g. anti-CD20 monoclonal antibody, rituximab) (2). This has increased the opportunities for organ donation. Successful transplantation case studies have been reported in living donors against a blood group barrier, with retrospective studies showing similar outcomes to those of blood-group-compatible transplants (3,4). Limitations of the current reports are the small patient numbers, relatively short follow-up periods and differences in treatment protocols (5,6). Further investigation is ongoing (7-10). Current reports indicate that ABO-incompatible transplantation require a more intense and more costly immunosuppressive therapy (11-13) (LE: 3).

Until more long-term data are available, and key issues of the treatment protocol are solved, this procedure remains experimental and should only be performed as part of a scientific trial. Patients should be counselled on the potential risks (more intense immunosuppression, lack of long-term outcome data) and benefits (immediate availability of a living donor). Other transplantation methods should be considered, such as cross-over transplantation, which allows timely transplantation using standard immunosuppressive protocols (LE: 3).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO-incompatible transplantation is a promising procedure undergoing clinical evaluation.</td>
<td>C</td>
</tr>
<tr>
<td>Due to its experimental nature, it should be performed in experienced centres under scientific documentation.</td>
<td>C</td>
</tr>
<tr>
<td>Patients should be counselled about potential risks and alternatives.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.3.1.5 Cross-match-positive living-donor kidney transplants

This was previously thought to be a contraindication. However, several pilot studies (11-14) have reported successful transplantation with acceptable short-term results, using extensive antibody elimination strategies (e.g. plasmapheresis), intravenous application of immunoglobulins, and a more intense immunosuppression with antibody induction and the use of B-cell depleting agents (e.g. anti-CD20 antibody rituximab) (LE: 3).

Due to a lack of standardised treatment protocols and the lack of long-term results from larger
cohorts, this procedure remains experimental and should only be performed as part of a scientific trial. Patients should be counselled adequately on the potential risks. Alternative ways for transplanting highly immunised patients (e.g. Eurotransplant Acceptable Mismatch programme, cross-over transplantation) should be considered to allow a timely transplantation of these patients with standard immunosuppressive protocols (15) (LE: 4).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplantation of cross-match positive living donors is an experimental procedure, which should only be performed in scientific trials. Patients should be counselled about risks and potential alternatives.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.3.1.6 Living unrelated kidney donation
In many countries in Europe, altruistic non-consanguineous kidney donation is allowed legally, provided checks are made for altruistic motivation and financial gain excluded (15,16). The results are comparable to related living donation (LE: 3).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living related and unrelated donation should be encouraged within national laws.</td>
<td>B</td>
</tr>
</tbody>
</table>

2.3.1.7 ‘Non-directed’ living-donor transplantation
‘Non-directed’ living-donor transplantation between an altruistic donor and a recipient unknown to the donor is being performed in a few centres worldwide (17-19). Although controversial, there seem to be no moral or social reasons to exclude such truly altruistic donors (16,20). However, there are ethical and legal concerns about this type of donation (21), which at the moment make it difficult to recommend in these guidelines.

2.3.1.8 Payment to living donors from a central organisation
Although paying living donors to donate organs from a central organisation would be a potential way of increasing organ availability in an era of organ shortage (22), it is generally agreed that the payment of living donors to donate organs is ethically unjustifiable (23,24). It is strongly recommended that all organ donors have adequate lifelong access to medical care for the prevention of renal failure and potential side effects of organ donation (15,16).

The cornerstone of clinical transplantation has been the altruistic donation of kidneys from living relatives. The gift of a transplant is priceless and societies that support transplantation have generally refused to give a monetary value to a transplantable organ or tissue. In Europe, it is illegal to make a payment for living related organs and The World Health Organization (WHO) has stated that the body and its parts cannot be the subject of commercial transactions, and all giving and receiving of payments should be prohibited (24) (LE: 4).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legislation in every European country forbids payment for organs.</td>
<td></td>
</tr>
<tr>
<td>Donation of an organ should remain a gift of live without any financial impetus.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.3.1.9 References


2.3.2 Ethical ways of showing appreciation for organ donation

2.3.2.1 Donor ‘medal of honour’
Organ procurement organisations could have ceremonies which recognise and honour organ donation. A donor ‘medal of honour’, given by a top official of a country, would effectively express appreciation and gratitude on behalf of the whole community to the living donors and families of deceased donors (1,2). Policymakers, ethicists and the transplant community cannot agree on whether giving benefits to the families of organ donors would increase organ availability (3) (LE: 4). Because of the lack of evidence, no general recommendation can be made on whether or not to provide incentives for living donors or families of deceased donors.

2.3.3 Organisational ways to encourage organ donation

2.3.3.1 Cross-over transplantation or paired organ exchange
A cross-over renal transplantation or a paired kidney exchange transplant is an exchange between two or more couples, who are prevented by ABO incompatibility or positive cross-match from donating their kidneys to their preferred recipients. The problem may be solved by exchanging the living donor kidneys between pairs of couples to achieve a cross-match negative or ABO-compatible combination.

The inclusion criteria should favour the exchange of equivalent kidneys in size and age. A programme of cross-over kidney transplantation allows an exchange of organs between two living donors (4), or in some countries, from one living donor and one deceased donor (5). By using paired kidney exchange, the recipients are able to benefit from living donation. Paired kidney exchange also reduces the duration of dialysis before transplantation and expands the pool of living donors (6). Graft survival rates of paired kidney exchange are similar to directed, compatible live donor transplants (7) (LE: 3).

<table>
<thead>
<tr>
<th>Recommendation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Paired kidney exchange and cross-over renal transplantation if permitted by national law is a way of increasing the number of kidney transplants.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.3.3.2 Medical leave for organ donation
No-one should have to incur a personal expense for donating an organ (8). Many countries legally provide 30-days’ paid medical leave to all employees who donate an organ for transplantation (9). The American Society of Transplantation has recommended living donors should be given leave from employment similar to parental leave granted for a new baby (LE: 3).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The health and well-being of living donors should be monitored in a follow-up register to document any long-term medical problems due to donation.</td>
<td>B</td>
</tr>
<tr>
<td>There should be a national insurance plan that provides life and disability insurance for all living donors.</td>
<td>B</td>
</tr>
</tbody>
</table>

2.3.4 References


2.4 Kidney donor selection and refusal criteria

2.4.1 Introduction

A diagnosis of brain death is required in a comatose subject who may potentially be a deceased organ donor. The potential donor must be evaluated for any transmissible pathological condition and the quality of any organ(s) being considered for transplantation.

The short-term results of transplants with kidneys from donors over 65 years old are almost similar to those with younger organs. However, long-term graft survival is lower (1). In addition, the main physiological risk factor in ‘older’ kidneys is a prolonged cold ischaemia time (2,3). In keeping with these observations, the modern definition of a suitable donor places less emphasis on age and more on the physical condition of the donor, especially of the organ to be donated. The aim is to reduce the possibility of discarding usable organs. Thus, there are now no absolute age limits to donation. However, a short ischaemia time is mandatory, as well as careful donor selection, particularly because older donors have more co-morbidity. There is a similar trend towards extending the upper age donation limit in living donors to over 55 years old (4).

2.4.2 Infections

The potential donor must be checked for infectious diseases (Table 6).

Table 6: Infections to be checked for in potential donor

<table>
<thead>
<tr>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus-1, -2 (HIV-1, HIV-2)</td>
</tr>
<tr>
<td>Hepatitis C (HCV)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen (HBsAg), anti-HBc; acute hepatitis (liver enzymes)</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV), only in paediatric recipients</td>
</tr>
<tr>
<td>Active syphilis</td>
</tr>
<tr>
<td>Viral infection, sepsis, tuberculosis, infections of unknown aetiology</td>
</tr>
<tr>
<td>Family history of (or clinical signs that may be caused by) Creutzfeldt-Jacob disease</td>
</tr>
</tbody>
</table>

There is a high risk of HIV transmission from potential donors with suspected intravenous drug abuse. In addition, serology tests during the incubation period of HIV (2 months) or hepatitis (up to 6 months) may be negative, while large amounts of fluids administered during a resuscitation attempt can result in a normal serology due to dilution effects (5). Serological tests must therefore be repeated and additional tests done (e.g. polymerase chain reaction) to rule out infection.

2.4.3 Special exceptions for infections

Different circumstances apply when an organ recipient is already infected with HIV or hepatitis (Table 7).

Table 7: Exceptions for organ recipients who already have infections

<table>
<thead>
<tr>
<th>Infections</th>
<th>Acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-positive donor</td>
<td>In an HCV-positive recipient, transplant is allowed following informed consent.</td>
</tr>
<tr>
<td></td>
<td>In an HCV-negative recipient, there is a high risk of disease transmission. However, transplant may be possible in emergency situations following informed consent.</td>
</tr>
<tr>
<td>HBsAg-positive donor</td>
<td>In an HBsAg-positive recipient (if HDV antigen is negative), transplant is allowed after informed consent.</td>
</tr>
<tr>
<td></td>
<td>In an HBsAg-negative recipient with high anti-HBs antibody titre and HBC positivity, transplant is allowed after informed consent.</td>
</tr>
</tbody>
</table>
In an HBsAg-negative recipient with intermediate/high anti-HBs antibody titre alone (Hbc-antibody negative), transplantation may carry a higher risk but is allowed after informed consent.

In an HBsAg-negative recipient with undetectable anti-Hbs antibody, transplant is allowed only in a life-saving situation, when HDV antigen is negative and following informed consent.

**HBc-antibody-positive donor**

In liver transplantation, there is a high risk (50%) of transmitting hepatitis B from an anti-HBc antibody-positive donor to the recipient. In this situation, liver transplantation is allowed after informed consent. Kidneys, heart and lungs carry a low, but not absent, risk of hepatitis B transmission, so kidney transplant is allowed in an HBsAg-positive recipient, or an HBsAg-negative recipient with anti-HBs antibody titre $\geq 10$ mIU/mL, following informed consent.

In an HBsAg-negative recipient with no anti-HBsAg antibody, only life-saving transplants are allowed, after informed consent.

### 2.4.4 Malignant tumours

A previous history of malignancy is not usually a contraindication for organ donation. However, there are some absolute contraindications that make a donor unsuitable for transplant. These are active cancer or a history of metastatic cancer (with a few exceptions, such as testicular cancer) and cancers with high recurrence rates, such as advanced breast carcinoma, melanoma, leukaemia, or lymphoma. In addition, when a potential donor has experienced a brain haemorrhage of unknown aetiology, metastasis must be excluded as a cause of intracranial bleeding. For example, the serum level of human chorionic gonadotrophin (hCG) must be measured to exclude choriocarcinoma in female donors.

With other cancers, if less than 10 years has elapsed since completion of treatment, a careful risk-benefit assessment must be done of the risk of disease transmission versus mortality on the waiting list. The donor shortage has led to many transplant programmes accepting donors after only 5 years’ absence of recurrent malignancy. So far, only a low incidence of donor-transmitted malignancies has been observed (6). Successful renal transplants have been performed with kidneys affected by small, low-grade renal carcinomas that were completely excised. Recipients of organs from donors with a history of malignancy must be informed and carefully monitored (7).

### 2.4.5 Special exceptions for malignant tumours

For special exceptions in malignant tumours, see Section 8.1.

### 2.4.6 Vascular conditions and renal function

Important risk factors for organ failure are a prolonged history of diabetes mellitus or serious hypertension with retinal vascular damage. Factors for excluding potential donors or for considering a donor as a single- rather than a multi-organ donor include:

- previous myocardial infarction
- coronary bypass and angina
- severe systemic vascular disease
- events of long-lasting hypotension
- oliguria
- long-lasting intensive care stay.

A donor’s renal function should be evaluated at admission using creatinine clearance (Cockcroft-Gault formula), which corrects the serum creatinine value for age, body weight, and sex (8). The urinary tract can also be assessed by 24-h proteinuria and ultrasound (US) kidney imaging, particularly in elderly donors. In many transplant centres, a calculated creatinine clearance level of 50 mL/min is at the lower range for kidneys usable for two recipients, independent of the histology of the organ, but according to the history of the donor, while other centres evaluate glomerular sclerosis and arteriolar sclerosis from renal biopsy (9).

Acute renal failure is not itself a contraindication. The kidneys may be used after careful assessment (LE: 3).

### 2.4.7 Marginal donors

The following criteria need to be considered in a marginal organ (10) (LE: 3):

- Age over 70 years without other risk factors.
- Age between 60 and 70 years, with a history of diabetes mellitus, hypertension, clinical proteinuria up to 1 g/24 h, or retinal vascular changes.
- Calculated creatinine clearance of 50 mL/min – the organs are still valuable for a single graft.
- Calculated creatinine clearance $<$ 50 mL/min – the organs should be used as dual graft or discarded if histologically abnormal.
• Approximately 5-20% of glomerulosclerosis at biopsy with at least 25 glomeruli taken from both kidneys – the organs are still valuable for a single or double graft.
• More than 20% glomerulosclerosis – an individual decision has to be made based on renal function.

The true clinical meaning of each criterion is unknown because none of them have been rigorously validated and opinions differ over their individual value, as for example with pre-transplant renal biopsy (11,12).

2.4.8 One graft or two grafts per recipient

The rationale for dual marginal kidney transplantation is based on two conflicting concepts. Firstly, kidneys with a small nephron mass undergo hyperfiltration and glomerular hypertension, which causes progressive glomerulosclerosis (13). A single marginal kidney has a reduced renal mass and a suboptimal number of nephrons, which are further reduced by cold ischaemia time, transplant trauma, and the potential nephrotoxicity of immunosuppressive therapy. Simultaneous transplantation of both kidneys to the same recipient may increase nephron mass and prevent kidney damage.

Secondly, marginal kidneys have a functional reserve only verifiable after transplantation. In addition, the glomerular filtration rate of a transplanted kidney often increases post transplant (14-16). Dual transplantation is redundant because it shortens the organ pool.

These two opposing concepts would seem to suggest that kidneys judged unsuitable based on function or histology should either both be transplanted into a single recipient or both be discarded (17). However, a prospective multicentre study (18) concluded that double-kidney transplants are safe, well tolerated, and result in no more surgical complications than single-graft operations.

To date, the surgical technique for dual renal grafting has not been standardised (19,20) (LE: 3).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any brain death comatose subject should be considered a potential organ donor, without age limits.</td>
<td>C</td>
</tr>
<tr>
<td>Consensus for organ harvesting should be obtained from relatives or significant others according to local law and policies. Authorisation for explantation by the donor's close relatives is always recommended, even if local legislation on organ donation presumes consent.</td>
<td></td>
</tr>
<tr>
<td>- Contact between relatives and a well-trained, sensitive professional is very important in establishing favourable public opinion on organ donation.</td>
<td></td>
</tr>
<tr>
<td>- Individuals who objected to donation during life must always be excluded.</td>
<td></td>
</tr>
<tr>
<td>Any donor organ affected by a potentially transmittable pathology (infections, neoplasias) must be carefully evaluated considering the risk-benefit ratio for the recipient.</td>
<td>B</td>
</tr>
<tr>
<td>A good-quality organ must be guaranteed to the recipient and every transplant centre must establish its own guidelines on organ acceptability. Organs from marginal donors can only be used after thorough assessment. The recipients need to be informed and must confirm their acceptance.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.4.9 References


11. Andrés A, Herrero JC, Morales E, et al. The double or single renal graft depending on the percentage of glomerulosclerosis in the preimplant biopsy reduces the number of discarded kidneys from donors older than 60 years. Transplant Proc 1999 Sep;31(6):2285-6.  


2.5 **Explantation technique**

2.5.1 **Technique of deceased donor organ recovery**

Each solid organ should be procured as quickly as possible to minimise ischaemic injury. Removal of the heart, lungs, liver, and pancreas (Table 8) usually takes place before kidney retrieval (Table 9) (1-10) (LE: 3). Continuous machine perfusion reduces injuries due to ischaemia or reperfusion and improves the immediate post-operative graft outcome (8-10) (LE: 3).
Table 8: Important considerations during removal of heart, lungs, liver, and pancreas

<table>
<thead>
<tr>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infuse 3L of University of Wisconsin (UW) solution into the aorta before organ recovery.</td>
</tr>
<tr>
<td>Open Gerota’s fascia to expose the kidneys for surface cooling. While the heart is being removed and the cold perfusate is being infused, place ice slush into the abdominal cavity to provide surface cooling for the liver, kidneys, and pancreas.</td>
</tr>
<tr>
<td>After the heart is removed and the liver is to be retrieved, careful attention should be given to ensure the following:</td>
</tr>
<tr>
<td>• Do not extend the aortic cannula beyond the ostia of the renal arteries. This will avoid the risk of inadequate flushing of the kidneys, leading to unnecessary and harmful warm ischaemia.</td>
</tr>
<tr>
<td>• If the superior mesenteric artery is not being taken along the coeliac artery for the liver, the upper portion of the remaining aorta can be reclamped to allow continued perfusion of the kidneys and cooling during removal of the liver.</td>
</tr>
<tr>
<td>• If the superior mesenteric artery is taken with the liver and removed, it may not be possible to place a curved forceps in a tangential manner on the remaining segment of aorta. Although this would allow continued flushing of the kidneys, there is a risk of occluding the renal artery orifices, especially on the right side.</td>
</tr>
<tr>
<td>During transection of the vena cava between the liver and the kidneys, take care to avoid injury to the right renal vein. The right renal vein can often extend superiorly before entering the vena cava and may be accidentally transected. Because a segment of infrahepatic vena cava is needed in liver transplantation, the kidney retrieval team must be instructed to leave an optimal amount of venal caval cuff to go with the liver to prevent injury to the right renal vein.</td>
</tr>
<tr>
<td>The pancreas, if being retrieved, should be removed before the kidney. Again, injury to the left renal artery or vein can occur while the pancreas is dissected. Often the pancreas, and occasionally the kidneys, are recovered en bloc with the liver and then separated on the back table.</td>
</tr>
<tr>
<td>It is unnecessary to perform extensive kidney mobilisation prior to kidney removal, especially in multiple organ recovery. Such retroperitoneal dissection may cause accidental injury to aberrant renal arteries, so causing incomplete perfusion and warm ischaemia of the kidneys (2-4) (LE: 2a).</td>
</tr>
</tbody>
</table>

Table 9: Important considerations in kidney retrieval

<table>
<thead>
<tr>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection is carried cephalad and kept as far posterior as possible; the line of dissection is maintained at the level of the paraspinal muscles. Gerota’s fascia is kept attached to the kidneys. At the superior poles of the kidneys, the adrenal glands are left intact attached to the kidneys. The kidneys are removed en bloc without identification of the hilar structures.</td>
</tr>
<tr>
<td>On the back table, care must be taken to identify aberrant renal arteries, which may originate from the iliac arteries or distal or superior aorta. The aortic segment is left intact. The ureters are examined for length, numbers, and size.</td>
</tr>
<tr>
<td>It is useful to rewash each kidney until the effluent is free of blood before packaging.</td>
</tr>
<tr>
<td>If the liver is not to be recovered, a double balloon perfusion cannula can be placed in the aorta for selective renal perfusion and a venting catheter is inserted into the lower vena cava to allow venous blood to be washed out.</td>
</tr>
<tr>
<td>Dissection of the kidneys can then proceed with mobilisation of the right colon, exposing the right kidney, the inferior vena cava, and lower aorta. Identification and ligation of the inferior mesenteric artery and vein are performed, and the splanchnic nerves are divided, allowing mobilisation of the left mesocolon and exposure of the left kidney. The coeliac axis is identified, ligated and divided.</td>
</tr>
<tr>
<td>Mass clamping of the hepatoduodenal ligament can be performed to minimise flushing of the liver. In a donor &lt; 3-4 years, the surgeon must make sure the aortic cannula does not occlude the renal artery orifices.</td>
</tr>
</tbody>
</table>

Improvements in techniques for harvesting organs from non-heart-beating donors (NBHDs) has allowed the use of organs that would otherwise not have been considered for transplantation. Reports of the satisfactory function of organs retrieved in this manner have been followed by the development of adequate methods of aortic infusion techniques (11-13). Non-heart-beating donors accounted for 11.06% in EUROTRANSPLANT and for 6.5% in USA (12-18).  
With the development of multiple organ recovery techniques (19), good co-ordination and co-operation between the various surgical teams involved are essential for the successful retrieval of
transplantable organs (2,19-21). Logistics and programming of organ explantation should routinely be done by the local transplant coordinator.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys are the last organs to be recovered in multiple organ recovery. Appropriate placement of the aortic cannula for the cold ‘in-situ’ flush is essential.</td>
<td>C</td>
</tr>
<tr>
<td>After retrieval of the thoracic organs and liver, and if the pancreas is to be removed, the liver and pancreas should be recovered en bloc and separated on the back table.</td>
<td>B</td>
</tr>
<tr>
<td>In multiple organ recovery, it is essential there is good co-ordination and co-operation between the surgical teams.</td>
<td>C</td>
</tr>
</tbody>
</table>

2.5.2 **The living donor**

At present, 20% in EUROTRANSPLANT and 40% in USA of all kidney transplants are performed with living donors (14,16) (LE: 2a). In countries with low deceased donor rates, over 75% of kidney transplants are with living donors (22).

Most living donors are family members, but there is an increasing number of genetically unrelated donors, who are ‘emotionally related’, such as spouses or friends. In 2005, in EUROTRANSPLANT, nearly 50% of living donors were not genetically related (42.2%). In the USA, 37.2% were unrelated living donors (14,16) (LE: 2a).

Ethical guidelines mandate that the living donors have not been coerced and not been paid for their donation. Living donation should be considered a gift of extraordinary value and should be facilitated wherever a suitable donor is available (Table 10) (23-26) (LE: 2b).

**Table 10: Advantages of living donation**

<table>
<thead>
<tr>
<th>Better results (both long- and short-term) compared to deceased donor grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent early function and easier management</td>
</tr>
<tr>
<td>Avoidance of long waiting time for transplantation</td>
</tr>
<tr>
<td>Less aggressive immunosuppressive regimens</td>
</tr>
<tr>
<td>Emotional gain to donor</td>
</tr>
<tr>
<td>Global increase of the kidney transplant rate</td>
</tr>
</tbody>
</table>

2.5.2.1 **Evaluation**

Evaluation of a potential donor may be performed by an independent physician and consists of a complete history and physical examination, routine laboratory testing, and serological evaluation for EBV, herpes virus, CMV, HIV, HCV, and hepatitis B virus (HBV). Routine evaluation should also include urinalysis and culture, together with 24-h urine collection for creatinine clearance and protein excretion. A borderline hypertensive blood pressure should be measured on at least three, and as many as 10, separate occasions. Renal angiography is indicated only if spiral computed tomography (CT) scan with three-dimensional reconstruction or magnetic resonance imaging (MRI) angiography with reconstruction are not available.

Donors are unsuitable for a variety of reasons (Table 11). Potential donors for siblings with diabetes should routinely undergo a 5-h glucose tolerance test and the 24-h urine specimen must be free of proteinuria. Unexplained microscopic haematuria may indicate underlying renal disease. A history of thromboembolism or thrombophlebitis places a potential donor at increased risk of pulmonary embolism and contraindicates donation, as does advanced heart disease or a history of malignant neoplasia. Obesity is a relative contraindication for any potential donor > 30% above ideal body weight.

**Table 11: Exclusion criteria for living donors**

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 18 years</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (&gt; 300 mg/24 h)</td>
<td></td>
</tr>
<tr>
<td>Abnormal GFR for age</td>
<td></td>
</tr>
</tbody>
</table>
Microscopic haematuria
High risk of thromboembolism
Medically significant illness (chronic lung disease, recent malignant tumour, heart disease)
History of bilateral kidney stones
HIV positive

Relative contraindications
Active chronic infection (e.g. tuberculosis, hepatitis B/C, parasites)
Obesity
Psychiatric disorders

GFR = glomerular filtration rate; HIV = human immunodeficiency virus.

Patients with psychiatric disorders should be fully evaluated by a psychiatrist to establish that the donor understands and agrees to the procedure.

2.5.2.2 Choice of kidney
If examination of the donor’s vascular supply and drainage system reveals an abnormality, it must be decided whether the risks imposed on the donor or the recipient are too great. When one kidney is smaller or has a minor abnormality, the donor should always be left with the ‘better’ kidney.

2.5.2.3 Pre-operative management
Pre-operative assessment by the anaesthesiologist and the pain management team is mandatory.

2.5.2.4 Surgical alternatives in live-donor nephrectomy
There are several ways of harvesting kidneys from living donors (Table 12) (11-13,21,27-35). The method chosen will depend on the surgeon’s experience and preferred choice of operation.

Table 12: Approaches for harvesting kidneys from living donors

<table>
<thead>
<tr>
<th>Approach</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic transperitoneal</td>
<td>Through a midline or through a left or right subcostal incision.</td>
</tr>
<tr>
<td>Sub- or supra-costal</td>
<td>Perform incision either underneath the 12th rib, resecting the 12th rib, or above the 12th rib (extraperitoneal, extrapleural).</td>
</tr>
<tr>
<td>extraperitoneal</td>
<td></td>
</tr>
<tr>
<td>Dorsal lumbar</td>
<td>Can be either left- or right-sided.</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>Can be transperitoneal or retroperitoneoscopic. The transperitoneal approach is more common in the USA and Scandinavia.</td>
</tr>
</tbody>
</table>

The operative stages are similar to those in transperitoneal nephrectomy performed for malignant or benign conditions of the kidney. In 2.3% of cases, concomitant splenectomy is needed (11-13,21,28-35), due to injuries of the spleen that occur during colon dissection. In addition, the transperitoneal approach is accompanied by a significantly higher rate of intestinal complications, such as ileus (functional or even obstructive).

Removal of the left kidney from a living donor is recommended because of the longer length of the left renal vein (36-38).

Before starting the incision, the donor’s diuresis is increased, usually by giving mannitol, 25 g. Arterial spasm may be prevented with externally applied papaverine (39).

Laparoscopic kidney removal (Table 13) is a less traumatic technique, entails less pain, a shorter hospital stay and may encourage more people to consider donation.

Table 13: Special considerations during a laparoscopic procedure

<table>
<thead>
<tr>
<th>Patient’s preparation</th>
<th>During organ harvesting, especially during dissection of the renal pedicle, the patient requires appropriate fluids and a mannitol infusion to maximise renal function during surgery and after transplantation (15-17,40,41).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s position on the operative table</td>
<td>Place the patient on the operative table in a left or right position with the kidney bridge. The left kidney is preferred for laparoscopic removal because it has a longer renal vein. On the right side, the liver may make dissection difficult in a transperitoneal approach.</td>
</tr>
</tbody>
</table>
Transperitoneal laparoscopic approach
The transperitoneal approach offers more working space. The kidney is approached by dissecting the colon and peritoneum on different lengths. The approach to the renal artery is more complicated due to its position behind the renal vein. However, after detachment from vascular connections, the kidney can be more easily extracted through a lower umbilical incision.

Retroperitoneoscopic approach
The retroperitoneal approach allows an easy, initial identification of the renal artery and a direct approach to the branches of renal vein. Its main drawback is the limited space for manoeuvre, which also makes it difficult to use endobags for a quick kidney extraction.

2.5.2.5 Post-operative care
Adequate post-operative analgesia is crucial in preventing post-operative complications, such as atelectasis and pneumonia (20,21). Antibiotic prophylaxis should also be given. Subcutaneous heparin, the continuous use of leg stockings and sequential compression devices should be prescribed to prevent deep venous thrombosis of the lower limbs. Most patients tolerate oral feeding by post-operative day 2 or 3, and the donor can be discharged between post-operative days 2 to 6. Renal function should be assessed periodically after operation. Although donors experience a 25% increase in serum creatinine level, the creatinine level should return to near baseline within 3 months.

There are no convincing data to suggest that living donors are at increased long-term risk because of kidney donation. Nevertheless, ongoing periodic long-term follow-up evaluation is recommended for donors. This can be performed by the donor’s personal physician (14-17,40-43) (LE: 2a).

2.5.3 References


2.6 Organ preservation

2.6.1 Kidney storage solutions

There is no agreement on which of the mechanisms listed in Table 14 is most important for post-ischaemic renal graft function (1-6). No storage solution combines all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended. Today, Celsior-solution, UW-, and HTK- (histidine-tryptophane-ketoglutarate) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures (7-10) (LE: 1b). For living donors, in whom a long cold ischaemia time is not expected, perfusion with crystalloid solution (e.g. Ringer-lactate) is sufficient.

Table 14: Aims of modern kidney storage solutions (1-6)

<table>
<thead>
<tr>
<th>Aim</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of cell-swelling during hypothermic ischaemia</td>
<td></td>
</tr>
<tr>
<td>Maintenance of intra- and extra-cellular electrolyte gradient during ischaemia</td>
<td></td>
</tr>
<tr>
<td>Buffering acidosis</td>
<td></td>
</tr>
<tr>
<td>Providing energy reserve</td>
<td></td>
</tr>
<tr>
<td>Minimising oxidative reperfusion injury</td>
<td></td>
</tr>
</tbody>
</table>

2.6.2 Methods of kidney preservation

There are two methods of kidney preservation:
- Initial flushing with cold preservation solution followed by ice storage.
- Continuous pulsatile hypothermic machine-perfusion (clinical relevance for non heart-beating donors and marginal donors).

2.6.3 Duration of organ preservation

The duration of cold ischaemia should be as short as possible. Kidneys from the elderly (> 55 years) and marginal donors are more sensitive to ischaemia than young kidneys (LE: 1b). Organ preservation relies mainly on hypothermia, which lowers the metabolic rate, conserves stores of adenosine triphosphate, and prevents formation of oxygen-free radicals during the reperfusion phase.

Recommendations | GR |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UW-solution and HTK-solution are standard storage solutions and equally effective for both multiorgan-donors and kidney-only donors.</td>
<td>A</td>
</tr>
<tr>
<td>Celsior-solution seems to be equally effective.</td>
<td>B</td>
</tr>
<tr>
<td>Keep cold and warm ischaemia times as short as possible for any renal transplant.</td>
<td>A</td>
</tr>
</tbody>
</table>

UW = University of Wisconsin; HTK = histidine tryptophane ketoglutarate

2.6.4 References

3. KIDNEY RECIPIENT

Kidney transplantation prolongs life, reduces morbidity, improves quality of life, enables social and medical rehabilitation, and reduces the costs associated with the medical care of patients with ESRD. Kidney transplantation is a surgical procedure, with inherent risks due to anaesthesia and the surgical procedure itself. In addition, the need for continuous immunosuppressive therapy may lead to immunosuppression-related side-effects.

The pre-transplant evaluation evaluates potential contraindications and risk factors for transplantation (e.g. malignancy, ongoing infection) (LE: 2b).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careful pre-operative work-up of all transplant candidates is mandatory to improve organ and patient survival in the post-transplant period. The work-up should be repeated regularly.</td>
<td>B</td>
</tr>
</tbody>
</table>

3.1 Pre-transplant therapy

3.1.1 Abnormal urogenital tract

In patients, whose ESRD is caused by either a congenital (i.e. posterior urethral valve, spina bifida, prune belly syndrome, vesico-renal reflux, bladder extrophy, VATER syndrome) or an acquired malformation (shrunken or neurogenic bladder) of the lower urinary tract, the abnormality should be corrected before transplantation (1-4).

Avoid ureteral implantation in a fibrotic, thickened bladder wall (e.g. following a urethral valve) because of the high risk of surgical complications and/or graft loss (1). In low-compliance bladders, pharmacological therapy (e.g. parasympathicolysis), with or without intermittent self-catheterisation, is necessary. If these methods fail, bladder augmentation is recommended. If catheterisation is not possible, supravesical urinary diversion is crucial.

Anatomical or functional urological disorders do not seem to change the outcome of renal transplantation (LE: 3).

3.1.2 Urinary diversion

In patients with sphincter insufficiency (e.g. neurogenic bladder) or absent bladder, supravesical urinary diversions must be performed, such as conduits or continent catheterisable pouches. Artificial sphincters may be an alternative. In low-compliance bladders with intact sphincters, both bladder augmentation and continence pouches are successful alternatives (4-9).

Most urologists prefer to perform a supravesical urinary diversion at least 10-12 weeks before transplantation (6, 8). Bladder augmentation or conduit is possible following transplantation (6). Patients with conduits, augmented or abnormal bladders have an increased risk of urinary infection (1,4-6).

Results can be similar to those in the general population (7,9-12) (LE: 3).
3.1.3  **Indications for pre-transplant nephrectomy**

Depending on the indication (Table 15), nephrectomy can be done by either an open or laparoscopic approach (LE: 3-4).

**Table 15: Indications for pre-transplant nephrectomy**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal-dominant polycystic kidney disease (ADPKD)</td>
<td>Unilateral or bilateral nephrectomy is necessary if there is not enough space for the transplant kidney, or if there are complications, such as cyst infection, cyst rupture with/without haematuria, pain, or abdominal girth. Nephrectomy can be done before transplantation or simultaneously with similar complication rates and outcomes (2,13,14).</td>
</tr>
</tbody>
</table>

| Medically refractory hypertension              | Bilateral nephrectomy usually results in less antihypertensive medications (15). It has become rare due to improved control of hypertension with better dialysis and drugs. |
| Chronically infected kidneys                   | No strong evidence for removal of native kidneys in urolithiasis.        |
| Suspected renal or urothelial cancer           | Nephrectomy is necessary if there is a possible risk of infection due to stones. |

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In abnormal urogenital tract, meticulous pre-transplant work-up is necessary, with urodynamics being the key investigation.</td>
<td>B/C</td>
</tr>
<tr>
<td>If pharmacological therapy or intermittent catheterisation fails or is not possible, urinary diversion is necessary using catheterisable pouches, conduits or cystoplasties.</td>
<td>B/C</td>
</tr>
<tr>
<td>ADPKD with insufficient space or complications, chronic infections, or kidneys with suspected tumour growth have to be removed either pre-operatively or concomitant with transplantation.</td>
<td>B/C</td>
</tr>
</tbody>
</table>

**ADPKD = autosomal dominant polycystic kidney disease**

3.1.4  **References**


3.2 Selection and refusal criteria

3.2.1 Contraindications

3.2.1.1 Malignancy

Active malignancy is a contraindication for transplantation because immunosuppressive therapy may aggravate underlying malignancy, jeopardising the patient’s life and long-term success of the transplant (1-3). Patients with a history of malignancy should be cured (see Chapter 8 - Malignancy).

3.2.1.2 Infection

Infections can be a major cause of morbidity and mortality in transplanted patients, especially under intense immunosuppressive therapy. As part of the pre-transplant work-up, carry out screening for infections to exclude any active infections, which might jeopardise the immediate outcome post transplant (1-3). In contrast, chronic infection does not cause an immediate post-operative risk. If chronic infection is detected, counsel the patient and treat it before transplantation or take prophylactic measures after transplantation. Screening for infections also documents the recipient’s infectious status in case of disease transmission from the donor. In cases of previous negative serology for CMV, HBV, HCV, and HIV recipients, serology should be repeated at the time of transplantation. A record of the viral status before transplantation enables graft transmission of disease to be firmly excluded. Finally, the recipient’s infectious status may have implications for the allocation of organs (LE: 3).

If the patient’s history or physical examination suggests an underlying infection, a thorough examination should be instituted, which may involve physicians from other subspecialties, such as an ear, nose, and throat specialist; dentist; dermatologist; urologist; and gynaecologist, to firmly rule out infectious foci (1-3) (LE: 3).

Important infections screened prior to transplantation are HBV, HCV, HIV, tuberculosis (TB), CMV, and Treponema pallidum (1-3). Testing of HBV and HCV serology is particularly important, because viral hepatitis is the major cause of liver disease after renal transplantation and contributes to post-transplant morbidity and mortality (4-6) (LE: 3). A liver biopsy may be needed to assess disease status in patients positive for HBV or HCV before transplantation. Consider antiviral therapy before transplantation according to current guidelines (7-9) (LE: 3).

The serological CMV status of all recipients should be determined (1-3) (LE: 3). Current immunosuppressive regimens are associated with a high incidence of potentially life-threatening CMV disease (4,10) that is, however, preventable with the appropriate prophylactic strategy (LE: 1a).

Human immunodeficiency virus screening is recommended because active HIV disease is a contraindication for transplantation (1-3). However, retrospective studies show that renal transplantation can be successful in well-controlled (no detectable viral load) and treated HIV-positive recipients (3) (LE: 3). A history of TB is important because adequate preventive measures (e.g. isoniazid prophylaxis; 11,12) will avoid reactivation of TB under heavy post-transplant immunosuppression (LE: 1a). Screening for TB requires a careful history and chest x-ray (1-3) (LE: 3).

Screening for T. pallidum has been previously recommended (1,2). However, due to the low
incidence of disease, it is not strongly recommended for all potential transplant candidates. A Treponema haemagglutination (TPHA)-test may be performed in populations with a higher risk for disease (LE: 3). Screening for Epstein-Barr virus (EBV) has been suggested in children and young adults (13), because of their higher risk for the development of EBV-related lymphoproliferative disease. General EBV screening is not recommended (LE: 3).

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active infection, which may exacerbate after transplantation causing life-threatening infection, is a contraindication to transplantation.</td>
<td>B</td>
</tr>
<tr>
<td>Carry out screening for viral and bacterial diseases in all transplant candidates. Screen all patients for HBV, HCV, HIV, CMV, and TB (history and chest x-ray).</td>
<td>B</td>
</tr>
<tr>
<td>Routine screening examination of all patients in all subspecialties is not necessary.</td>
<td>B</td>
</tr>
</tbody>
</table>

*HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; CMV = cytomegalovirus; TB = tuberculosis*

#### 3.2.1.3 Other contraindications for transplantation

Transplantation should be offered to patients with potential for long-term survival of the graft because of the scarcity of organs, the complexity of the transplant procedure, and increased mortality associated with the transplant procedure itself.

A short life expectancy and conditions that interfere with compliance (e.g. severe psychiatric disease) are not acceptable risks for long-term success of transplantation. If there is non-compliance, a careful psychological examination should try to identify the underlying cause (14) and if possible institute an adequate treatment (15). Non-compliance is not a lifelong determinant of a personality and re-evaluation may be needed.

### Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In severe co-morbidity or non-compliance, a thorough and individual assessment should be performed.</td>
<td>C</td>
</tr>
</tbody>
</table>

### 3.2.2 Co-morbidity

Due to the inherent risks of the surgical procedure, anaesthesia, and post transplant immunosuppressive therapy, a careful evaluation of potential transplant recipients is very important, particularly a cardiovascular work-up to reduce early graft failure due to technical problems and to improve patient survival in the post-transplant period (1-3).

#### 3.2.2.1 Cardiac disease

Death with a functioning kidney allograft occurs frequently in kidney-transplanted patients, with cardiac death being the most important cause (16). Nevertheless, uraemic patients with cardiovascular disease are more likely to survive with a renal transplant compared to dialysis (17,18). However, patients with cardiac disease have a higher peri-operative risk (19,20). All candidates should therefore be given a careful history and physical examination for cardiac disease, including an electrocardiogram and chest x-ray (21) (LE: 3).

An additional, extensive cardiac work-up is recommended for patients with a history of coronary heart disease, severe peripheral artery disease, or a history of stroke or severe occlusive cerebrovascular disease, and a long history of renal insufficiency/dialysis (22,23), as well as for elderly and/or diabetic patients (22,24,25) (LE: 3).

The work-up includes (22,23):

- Echocardiography to detect valvular disease, cardiomyopathy, and systolic and/or diastolic left ventricular dysfunction (26).
- Exercise electrocardiogram and/or exercise thallium scintigraphy or stress echocardiography in patients with a low exercise capacity (22,23).
- Coronary angiography in every suspicious case, especially in dialysis patients who are elderly and/or diabetic, or in patients with a long history of renal disease (27).

Revascularisation, either surgical or by coronary angioplasty, should be performed in every suitable transplant candidate (18,24) before transplantation (LE: 3).
Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-transplant work-up should focus on the presence of cardiac disease.</td>
<td>B</td>
</tr>
<tr>
<td>In patients with a high risk of cardiac disease, an extensive work-up is strongly recommended to firmly rule out coronary artery disease.</td>
<td>B</td>
</tr>
<tr>
<td>Perform any revascularisation before transplantation.</td>
<td>B</td>
</tr>
</tbody>
</table>

3.2.2.2  Peripheral artery disease, cerebral occlusive vascular disease

Peripheral artery disease is common in uraemic patients (28). In potential kidney transplant recipients, very severe pelvic vessel disease may prohibit transplantation, be a significant cause of technical graft failure, and may enhance the risk of amputation. Cerebral vascular occlusion may lead to post-operative morbidity and mortality (29,30).

Evaluate the patient carefully for signs and symptoms of vascular occlusive disease. Pelvic radiography should be done routinely before transplantation (31,32). If there is vascular calcification, signs and symptoms or risk factors (e.g. age, diabetes, length of time on dialysis) of vascular occlusive disease, perform a thorough work-up, including duplex ultrasonography of the peripheral and cerebral arteries (33), and/or non-contrast enhanced abdominal-pelvic CT scan. In selected patients, angiography and pre-transplant arterial repair can be indicated. Avoid contrast-enhanced MRI because of the risk of nephrogenic systemic fibrosis (34) (LE: 3).

Recommendation

| During pre-transplant work-up, special attention should be paid to iliacal, peripheral, and cerebrovascular disease. Appropriate diagnostic and therapeutic measures are recommended. | C  |

3.2.2.3  Diabetes mellitus

Patients with diabetes mellitus have an increased mortality and reduced long-term graft outcome compared to non-diabetic patients following kidney transplantation (35). Nevertheless, diabetes mellitus itself is not a contraindication for kidney transplant (1-3). Moreover, a kidney-only transplant or a combined kidney-pancreas transplant will reduce the long-term morbidity and mortality of uraemic diabetic patients compared to dialysis (36,37) (LE: 3).

Thus, kidney transplantation should be considered in every diabetic uraemic patient who has no other severe contraindication, especially cardiovascular disease. In patients with diabetes type I, a combined kidney-pancreas transplant is preferred because it improves blood glucose control and slows progression of cardiovascular disease (38,39) (LE: 3).

Because there is an exceptionally high incidence of cardiovascular disease in diabetic dialysis patients (21-23), it is usually necessary to exclude patients with a high vascular risk using peripheral angiography or non-invasive imaging procedures (e.g. CT scan) (27). Bladder neuropathy is a common complication in diabetic patients (40) and a urological clinical work-up should be performed. In selected patients, an urodynamic examination is needed (LE: 3).

Recommendation

| Patients with diabetes mellitus should be transplanted. They require an extensive pre-transplant work-up. | B  |

3.2.2.4  Obesity

Overweight patients have a higher incidence of surgical and non-surgical complications (41,42). Weight is a traditional risk factor for diabetes, hypertension, and cardiovascular disease. However, renal transplantation provides a better survival and better quality of life in overweight dialysis patients (43,44) (LE: 3). There is not enough evidence to recommend exclusion based on body mass index (BMI).

Recommendation

| Obesity itself is not a contraindication for transplantation. However, a thorough pre-transplant evaluation and attempt to reduce weight are recommended. | C  |

3.2.2.5  Coagulopathies

Coagulation disorders have a negative impact on post-transplant graft survival, leading to early graft thrombosis or post-transplant thrombotic complications (45,46). Early post-transplant anticoagulation may
prevent thrombosis and early graft loss (47,48). As a consequence, a pre-transplant work-up should include the diagnosis of coagulopathies, especially in patients with recurrent shunt thrombosis or with a history of thrombotic events. In these patients, a careful pre-transplant assessment is mandatory, including ATIII, protein C, activated protein C resistance (Factor V Leiden), protein S, and anti-phospholipid antibodies (LE: 3).

Patients on anticoagulant treatment, e.g. warfarin, acetylsalicylic acid, clopidogrel, are not excluded from transplantation. During surgery, special precautions for anticoagulant use are needed.

### Recommendation

A careful examination of coagulopathies in patients at risk in order to prevent early post-transplant thrombotic events is recommended.

#### 3.2.2.6 Other diseases with potential influence on post-transplant outcome

Some conditions or diseases may follow an aggravated clinical course after transplantation due to immunosuppressive therapy and/or may place the transplanted kidney at a higher risk for complications (1-3). Important examples are diverticulosis, with or without previous episodes of diverticulitis, cholecystolithiasis, and hyperparathyroidism. Decisions for pre-transplant treatment should be made by a multidisciplinary team on an individual basis with appropriate patient counselling (LE: 4).

Mental retardation and psychiatric diseases are not necessarily contraindications for transplantation (1-3). If the patient is able to understand the procedure and can adhere to the procedures and medication required, such patients are eligible for transplantation (LE: 4).

### Recommendation

Diseases that might influence post-transplant course should be identified during pre-transplant work-up and if possible treated before transplantation.

#### 3.2.3 Age

Although there is no controversy about the fact that a kidney transplant offers improved survival and quality of life in younger patients with ESRD, an ongoing debate exists about kidney transplants in the elderly.

Reduced mortality in patients over 65 years of age has been shown in transplanted patients compared to patients on the waiting list (35,36) and reasonable outcomes have been reported for elderly transplant recipients (49,50) (LE: 3). However, a prolonged waiting time in this patient subgroup significantly decreases the beneficial clinical outcome and socio-economic advantages of transplantation (51,52). Every effort should be taken to reduce waiting times in the elderly (> 65 years). Elderly transplant patients should be enrolled in special programmes such as the Eurotransplant (ET) Senior programme (50), as well as applying for living-donor transplantation (LE: 3).

In elderly dialysis patients selected for kidney transplantation, special attention must be paid to concomitant cardiovascular disease and possible pre-existing cancer (53). Patients should be informed about the potential hazards of transplantation, including a high fatality rate in the first year after transplantation and infection during the first year post-transplant (49,50,53-56) (LE: 3). If there are any signs of age-related dementia, a psychological evaluation should be instituted.

### Recommendation

Although age itself is not a contraindication for transplantation, a thorough pre-transplant evaluation is needed. A careful risk-benefit evaluation must be performed and the patient should be counselled on the increased risks associated with age.

#### 3.2.4 Recurrence risk (original renal disease)

A histological recurrence of original renal disease is common in a transplanted kidney. Despite high recurrence rates in some diseases, overall graft loss due to recurrence is less than 10% after 10 years (57,58). Higher recurrence rates have occurred in living related donors and living donation should therefore be critically discussed, especially in diseases with early and very high recurrence rates (LE: 3).

Some rare renal diseases with a high recurrence rate, which can lead to an immediate graft loss, are contraindications for transplant. They include light-chain deposit disease (LCDD), primary oxalosis, and anti-glomerular basement (anti-GBM) antibodies (1-3). However, transplants may still be possible in some circumstances:

- Patients with anti-GBM disease can be given a transplant after disappearance of anti-GBM antibodies (1-3) (LE: 3).
- In patients with primary oxalosis, combined liver-kidney transplantation is recommended (1-3) (LE: 3).
- In patients with amyloidosis or LCDD, no treatment guidelines exist. In this very rare group of patients, case reports and small case series describe successful chemotherapy or autologous stem cell transplantation, with or without kidney transplantation (59-61) (LE: 3).

In patients with systemic diseases (e.g. lupus, vasculitis, haemolytic uraemic syndrome), the underlying disease should be treated and the patient should be in remission before transplantation (1-3) (LE: 3).

For most patients with glomerulonephritis, no special precautions are recommended (1-3). Focal and segmental glomerulosclerosis (FSGS) may recur early after transplantation (62,63) and may be treated with plasmapheresis and/or with anti-CD20 antibody (rituximab) (64,65). When a previous graft has been lost because of recurrent glomerulonephritis, especially FSGS, the patient must be counselled on the higher risk of graft failure in a second transplant. However, successful long-term outcomes have occurred in these patients (62,63) (LE: 3).

### Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Recurrence of the original disease is common, but graft loss due to recurrence is infrequent.</td>
</tr>
<tr>
<td>C</td>
<td>Only a few rare diseases with a high recurrence rate leading to early graft loss are a contraindication for renal transplant.</td>
</tr>
<tr>
<td>C</td>
<td>Patients with the risk of recurrent diseases should be counselled before transplantation, especially before living related kidney transplant.</td>
</tr>
</tbody>
</table>

### 3.2.5 Patients with a previous transplant

Assess patients with a previous graft loss carefully for malignancy, cardiovascular disease (1-3), and for increased immunological risk because of the development of antibodies against the first graft (66). Gradually discontinue immunosuppression following graft failure, as continuous immunosuppressive therapy has a higher risk of complications under renal replacement therapy (67,68) (LE: 3). If the graft becomes symptomatic, perform graft nephrectomy immediately (69). Graft embolisation (70) may be an alternative. However, prophylactic transplantectomy does not seem to be beneficial (71-73). Take appropriate measures to avoid repeated alloantigen mismatches (LE: 3).

Patients with a previous non-renal organ transplant, who develop ESRD (74,75), also benefit from renal transplantation, as there is a high risk of severe complications with a combination of ESRD and continuous immunosuppressive therapy (76) (LE: 3). Work-up should pay special attention to malignancy, cardiovascular disease, potential immunisation, and potential graft dysfunction of the previously transplanted organ, which may therefore require a combined transplant procedure (LE: 3).

### Recommendation

Pre-transplant work-up for patients with retransplantation or previous non-renal transplantation should focus on the immunological risk, including a thorough analysis for the presence of anti-HLA antibodies.

### 3.2.6 References

1. EBPG (European Expert Group on Renal Transplantation); European Renal Association (ERA-EDTA); European Society for Organ Transplantation (ESOT). European Best Practice Guidelines for Renal Transplantation (part 1). Nephrol Dial Transplant 2000;15(Suppl 7):1-85.


3.3 Transplantation in pregnancy

3.3.1 Planning pregnancy

Chronic renal failure is often associated with sexual dysfunction and infertility. After kidney transplantation, sex life and fertility are improved (1). Both male and female patients should be counselled about the possibility of pregnancy. Ideally, pregnancy should be planned at a time of good general and graft health, usually not earlier or later than 1-2 years after transplant (2). In pregnancy occurring some years after transplantation, there is a risk that some chronic rejection and/or some deterioration of renal function may have developed.

If graft function and immunosuppressive therapy are stable, and there is no sign of rejection,
hypertension, proteinuria, hydronephrosis, or chronic infection, there is no significant difference in outcome between early, recommended, or late pregnancies (3) (LE: 2a). Hydronephrosis makes pregnancy riskier because of the increased possibility of infection and lithiasis, which may also worsen in the last trimester. Early detection of pregnancy is important so that monitoring and adjustment of immunosuppressive therapy can begin as soon as possible.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy should be planned at a time of good general and graft health, when renal function and immunosuppressive therapy are stable and there is no sign of rejection, hypertension, proteinuria, hydronephrosis, or chronic infection.</td>
<td>B</td>
</tr>
<tr>
<td>The second post-transplant year is the ideal period.</td>
<td>B</td>
</tr>
</tbody>
</table>

3.3.2 **Graft survival**
Recently, the pregnancy rate in the kidney-transplanted population has increased from 2% to 5%. Successful gestations are common in female organ transplant recipients (4) (Table 16).

**Table 16: Factors that may affect a kidney graft during pregnancy**

<table>
<thead>
<tr>
<th>Haemodynamic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Impairment of renal function (5-10) (LE: 2a)</td>
</tr>
<tr>
<td>Rejection (11)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
</tr>
</tbody>
</table>

Pregnancies in transplanted women are often unproblematic, but these patients should always be considered high risk and require shared care by an obstetrician, nephrologist, and a urologist.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>After kidney transplantation pregnancy is possible and well tolerated for most patients with normal graft function.</td>
<td>B</td>
</tr>
<tr>
<td>However, pregnant transplanted women always must be considered at high risk and their care requires the co-operation of the obstetrician, nephrologist, and urologist.</td>
<td>B</td>
</tr>
</tbody>
</table>

3.3.3 **Care during pregnancy**
The care of a pregnant transplanted patient should focus on the risk factors mentioned in Table 16. This includes checking for bacterial urinary tract infection with monthly urine cultures and always treating bacteriuria, whether symptomatic or asymptomatic. Antibiotics agents should be chosen from the penicillin and cephalosporine families to avoid foetal and renal toxicity. Every urological endoscopy requires antibiotic protection. Viral infections may be transmitted to offspring. If this is CMV, the baby may be mentally retarded. Amniotic culture will reveal any foetal infections (12).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Care during pregnancy should focus on control of proteinuria, hypertension (pre-eclampsia affects 30% of patients), renal function, rejection, and infection.</td>
<td>B</td>
</tr>
</tbody>
</table>

3.3.4 **Immunosuppressive treatment**
The common immunosuppressive treatment used during pregnancy is cyclosporine, with or without azathioprine and prednisone (6,13). These drugs pass the placental barrier but apparently do not increase the risk of teratogenicity. Blood cyclosporine levels may change, and usually decrease, especially during the third trimester because of increased volume distribution and pharmacokinetic changes. Its dosage should usually be augmented. Recent papers suggest that the new drug tacrolimus (14,15) (LE: 3, 2b) used in kidney, heart, and liver transplantation might also be safe. There are only sporadic reports on the effects of mycophenolate mofetil (MMF), which, like sirolimus, is contraindicated due to teratogenicity (16).
3.3.5 Follow-up
Rates of spontaneous (14%) or therapeutic (20%) abortions in transplanted women are similar to those in the general population. Although a vaginal delivery is not mechanically impaired by an abdominal graft, pre-term delivery and a high rate (50%) of Caesarean sections are observed, due to a high incidence of prematurity (uncontrolled hypertension, foetal distress, rupture of membranes weakened by steroid use). About 20% of babies have a low birthweight (mean birthweight 2.5 kg ± 0.67 vs normal birthweight 3.5 kg ± 0.53) (17,18), but congenital abnormalities are no higher than in the general population. Breastfeeding is not suggested because of the baby’s risk of ingesting immunosuppressive agents. A close follow-up of the mother in the first three post-partum months is recommended, including weekly renal function tests. Delay vaccinations until the infant is 6 months old.

There are few data on the growth, long-term outcome, or adult life of children born from kidney-transplanted mothers. Offspring are often born prematurely and have a reduced birthweight. Long-term studies on foetal exposure to immunosuppressive therapy have only recently begun. No other important data exist at present. Children of fathers in immunosuppressive treatment following kidney transplantation are clinically not different from those of the general population. They are aborted less often than foetuses of kidney-transplanted mothers. However, if the father is affected by hereditary disease, there is a higher risk of transmission.

3.3.6 References


4. TRANSPLANTATION TECHNIQUES

4.1 Transplant preparation and transplant techniques in adults

Transplant preparation is a crucial step in the transplantation process and should not be neglected. Key points of transplant preparation are listed in Table 17. The transplant procedure in adults, with special considerations, is detailed in Table 18.

Table 17: Transplant preparation

<table>
<thead>
<tr>
<th>Kidney</th>
<th>Place the kidney on a sterile iced bed.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Check for the absence of renal tumours.</td>
</tr>
<tr>
<td></td>
<td>Tie all that is cut near the hilus (lymphostasis).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vein</th>
<th>The right kidney should be removed, together with the infra renal vena cava for lengthening the renal vein on the back table (1).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Artery</th>
<th>Preserve the aortic patch and check the intima of the renal ostium.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In severe atheroma in the ostium, remove the aortic patch.</td>
</tr>
<tr>
<td></td>
<td>In multiple arteries, back table reconstruction could be necessary (2,3).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ureter</th>
<th>Preserve peri-pyelic and proximal peri-ureteral fat in the ‘golden triangle’.</th>
</tr>
</thead>
</table>
Check for double ureter.

**Transplant biopsies**

Systematic in some centres because it can be very important to follow the long-term histological modifications of the transplant.

**Table 18: Transplant technique**

**Transplant technique in adults**

**Approach**

Extra peritoneal approach of one iliac fossa.

Transplantation is possible either into the contralateral or ipsilateral iliac fossa.

Lymphostasis with clips or ligatures to avoid lymphocele is mandatory.

Total mobilisation of the external iliac vein may avoid traction on the venous anastomosis (sometimes ligation of the internal iliac vein is necessary particularly for right transplant with a short vein).

Minimal dissection of the iliac artery.

**Vascular anastomosis**

Generally external iliac vessels are used; avoid atheromatous plaques.

Choose the sites of vascular anastomosis according to the length of each vessel to avoid plication or traction.

Both anastomoses are performed with two halves of running non-absorbable monofil 6x0 or 5x0 sutures.

Internal iliac artery should not be used except in specific situations.

An orthotopic kidney transplant is possible to both the left and right iliac fossa (4).

**Ureteral anastomosis**

Extravesical implantation at the antero-lateral surface of the bladder is the method of choice. Suture the ureter to the bladder mucosa using two halves of running absorbable 6x0 or 5x0 sutures. This technique gives better results than open implantation to the bladder (5,6).

A double-J stent may be placed to protect the anastomosis, particularly in cases of tricky anastomoses.

Prophylactic double-J stenting prevents major urinary complications (7,8) (LE: 1a).

The uretero-ureteral anastomosis is an alternative to a very short or poorly vascularised transplant ureter. It is also used for a third transplant or in children (9). A JJ-stent is absolutely necessary in these cases (LE: 3).

Intravesical implantation is an alternative in experienced hands (low rate ureteral complications). There is no data discussing placement of a double-J stent in intravesical implantation.

**Special considerations**

**Kidneys taken from children weighing < 15 kg**

In adults, en-bloc transplantation should be performed, including the aorta and the inferior vena cava.

The two ureters are anastomosed in double pant using the extra-vesical technique.

**Vascular problems in the recipient**

If the iliac arteries do not allow clamping, endarterectomy or a simultaneous vascular prosthesis has to be performed (10).

If a prosthetic replacement has been previously carried out, implant the renal artery into the prosthesis using a punch perforator (11).

If iliac vein and/or vena cava are thrombosed, native renal vein or superior mesenteric vein can be used. However, in most cases, transplantation must be stopped.

Postoperative heparinisation is not routinely indicated in non-risky live-donor renal transplantation (12) (LE: 1b).

**Paediatric recipient**

Large kidneys must be placed in a higher position towards the lumbar fossa, using the aorta or the right common iliac artery and the inferior vena cava.

Iliac fossa is an option for young recipients (13,14) (LE: 3).

**Recommendations**

It is essential not to neglect transplant preparation. This is a crucial step in the transplantation process.  

**GR**  

C
Take care with lymphostasis into the recipient and during the graft preparation.  
Vascular anastomosis sites should take into account the differences in vessel length.  
JJ-stent may be used routinely.  
Check the arterial and venous status before transplant.  
Iliac fossa may be an alternative in children less than 20 kg provided the graft is small enough.

### 4.2 Early complications

#### 4.2.1 General complications

##### 4.2.1.1 Wall abscesses (5%)

These are more common when the recipients are obese or old. Risk factors include diabetes, haematoma, urine leak posttransplant, obesity, rejection, or over-immunosuppression (15,16). Abscesses can be prevented by minimising electrocoagulation and using subcutaneous aspirational drainage in obese patients. A superficial abscess can be treated with a simple opening of the wound, while a deep abscess requires surgical drainage. It is important to look for urinary fistulae (LE; 3).

##### 4.2.1.2 Haemorrhage

Risk factors include acetylsalicylic acid, poorly prepared transplant hilus, multiple renal arteries, renal biopsies and hyper-acute rejection (HAR) (17-19). A large haematoma or active bleeding requires surgical drainage. Following drainage, the uretero-vesical anastomosis must be checked and a JJ-stent may be inserted.

##### 4.2.1.3 Haematuria

After transplant biopsy, look for arterio-venous fistula (AVF) (20). Selective percutaneous embolisation is necessary for large AVF and for recurring haematuria. Clotting may cause ureteral obstruction, increasing the risk of haematuria. Dialysis may be necessary if ureteral stenting or percutaneous nephrostomy are ineffective.

##### 4.2.1.4 Incisional hernia (3-5%)

Risk factors include age, obesity, diabetes, haematoma, rejection, reoperation through transplant incision and finally m-TOR inhibitors (LE; 3). Treat in a similar way to a ‘classical’ incisional hernia with or without synthetic mesh (15,16,21,22).

#### 4.2.2 Urinary fistulae

Urinary fistulae are the most common early complication. They occur in 3-5% of cases in which a double J-stent has not been used (24,25). They can occur on the ureter, bladder, or parenchyma. The most frequent cause is ischaemic necrosis of the ureter (24,26).

##### 4.2.2.1 Management

If it is possible to localise the fistula, it is worth trying nephrostomy and/or a vesical catheter and double J-stent. Stented re-implantation is possible if necrosis is very distal and the ureter is long enough. Otherwise, uretero-ureteral anastomosis is performed using the patient’s original ureter (27). Vesical fistulae may be treated by suprapubic or transurethral catheter. Calyceal fistulae may be treated by JJ-stent and vesical catheter. In most cases, polar nephrectomy and omental plasty are necessary (28).

### Recommendations GR

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use a short ureter and keep the peri-ureteral fat around the hilus (29).</td>
<td>C</td>
</tr>
<tr>
<td>Avoid ligation of polar artery because of the risk of parenchymal and ureteral necrosis.</td>
<td>C</td>
</tr>
<tr>
<td>Prophylactic use of JJ-stent prevents major urinary complications (8).</td>
<td>A</td>
</tr>
</tbody>
</table>

#### 4.2.3 Arterial thrombosis

The incidence of arterial thrombosis is 0.5% in the first post-operative week. Risk factors include atherosclerosis, unidentified intimal rupture, poor suture technique, kinking if the artery is longer than the vein or the anastomosis is incorrectly sited, multiple arteries (30), and paediatric transplants (31-33). It should be suspected if there is primary non-function or sudden anuria. It is diagnosed by Doppler or technetium scan and confirmed by CT scan.

##### 4.2.3.1 Treatment

Surgery is always necessary. A radiological endovascular may be carried out successfully within the first 12 h. However, tolerance to warm ischaemia is poor and most transplants have to be removed.
Recommendations

<table>
<thead>
<tr>
<th>Importance of procurement technique quality.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preserve when possible the aortic patch; otherwise, use a punch perforator to create a large arterial opening.</td>
</tr>
<tr>
<td>Look for a possible intimal rupture before performing anastomosis.</td>
</tr>
<tr>
<td>Avoid plication of the artery.</td>
</tr>
<tr>
<td>Sudden anuria should lead to Doppler.</td>
</tr>
</tbody>
</table>

4.2.4 Venous thrombosis

Venous thrombosis is rare, occurring in 0.5% of kidney transplants in adults and in 2.5% in paediatric patients (33,34). It is suspected by primary non-function, haematuria, or anuria and is diagnosed by Doppler or technetium scan. Salvage thrombectomy has a very poor success rate and transplantectomy is often necessary.

Recommendations

| Lengthen the right renal vein with the infra renal vena cava. |
| Carry out a large venous anastomosis. |
| Avoid post-operative drop in blood pressure. |
| If there is a history of thrombosis, check for hypercoagulation or Leiden factor V mutation. |
| Sudden anuria should lead to Doppler. |

4.3 Late complications

4.3.1 Ureteral stenosis

The renal calyces and pelvis are dilated and there is often an elevated creatinine level. These stenoses occur in 5% (range, 2-7.5%) of transplants (35-37). They can present late between 1 and 10 years’ post transplant (38). There are three causes of ureteral dilatation:

- vesical high pressure with thickened bladder wall or urinary retention, which is treated by bladder drainage;
- vesicorenal reflux, which is not an obstruction;
- ureterovesical stenosis due to scar formation and/or poor surgical technique. These comprise 80% of ureteral stenoses. Most occur during the first year post transplant, although the risk of occurrence increases with time to 9% of transplant patients at 10 years.

Risk factors include multiple arteries, donor’s age, cold ischemia time, delayed graft function, and CMV infection (35).

Initial treatment involves percutaneous drainage and checking renal function to see if it has improved. Imaging should then be done to determine the level of stenosis, degree, and length. Further treatment depends on the level of stenosis, degree, and delay of occurrence. This can be endoscopic, either transurethral or percutaneous. The outcome of dilatation is better when the stenosis is early, distal, and short (39-43). Treatment can also be with open surgery using a uretero-ureteral anastomosis to the patient’s ureter or a vesicopyelostomy.

Recommendations

| Use a short and well-vascularised ureter, surrounded by peri-ureteral fat. |
| Preserve peri-pyelic and proximal peri-ureteral fat in the ‘golden triangle’. |
| Do not narrow the anastomosis and the antireflux tunnel. |
| Yearly routine echography. |

4.3.2 Reflux and acute pyelonephritis

Acute pyelonephritis is a rare complication (44,45). Reflux in the renal cavity is more common (46). Reflux is found in up to 30% of cases after Leadbetter and in 80% after Lich-Gregoire if the submucosal tunnel is short and in 10% if the tunnel is long. In lower urinary tract infections, the risk of acute pyelonephritis is 80% with reflux and 10% without reflux. Every reflux complicated by acute pyelonephritis should be treated with an endoscopic injection. This has a success rate of 30-78% (47,48). If this fails, try using a uretero-ureteral anastomosis if the native ureter is not refluxive, or a ureterovesical re-implantation with a long tunnel if the original ureter is refluxive or non-usable.
4.3.3 **Kidney stones**

Kidney stones may be transplanted with the kidney or may be acquired. The incidence is less than 1% of
transplants (49,50). The stones manifest themselves by haematuria, infection, or obstruction. Diagnosis
may require non-injected CT scan. Some stones are eliminated spontaneously, but if stones do need to be
removed, there are several options (51):

- The first step should be to try a JJ-catheter or echo-guided percutaneous nephrostomy.
- Calyceal and smaller renal stones should be treated by extracorporeal shock wave lithotripsy (ESWL).
- Larger stones should be removed by percutaneous (52) or open nephrolithotomy.
- Ureterolithiasis should be treated by ESWL (53) or by ureteroscopy (54).

**Recommendations**

<table>
<thead>
<tr>
<th>Treat hyperparathyroidism in the recipient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use absorbable threads for the urinary anastomosis.</td>
</tr>
<tr>
<td>Treat urinary obstructions and infections.</td>
</tr>
<tr>
<td>Check calciuria.</td>
</tr>
</tbody>
</table>

4.3.4 **Transplant Renal Artery Stenosis**

Transplant Renal Artery Stenosis (TRAS) has an incidence of 10% (range, 1-23%). TRAS risk factors are donor
and recipient age, expanded criteria donor, delayed graft function, ischemic heart disease and induction
immunosuppression (55). It is suspected when existing arterial hypertension becomes refractory to medical
treatment and/or there is an increase in serum creatinine without hydronephrosis (56,57). It is diagnosed by
Doppler sonography showing high velocity > 2m/s.

Treatment options include medical treatment and renal function follow-up, with interventional
treatment indicated if the stenosis is > 70% (58). Transluminal dilatations, with or without stenting, give poorer
results (70%) than surgery, but their simplicity makes them the first-line treatment for aligned and distal
stenosis (34,59).

Open surgery is reserved for plication or anastomotic stenosis, failure of percutaneous dilatation, and
involves resection with direct implantation. Repair with the saphenous vein must be avoided.

**Recommendations**

| Use aortic patch from the donor. |
| Examine the artery intima, fix it or re-cut the artery when necessary. |
| Keep a long left renal vein, and lengthen the right one with the vena cava. |
| Avoid too tight anastomoses. |

4.3.5 **Arteriovenous fistulae and pseudo aneurysms after renal biopsy**

Arteriovenous fistulae are seen in 10% (range, 7-17%) of cases and are suggested by repeated haematuria
(60,61). Diagnosis is by Doppler ultrasound and is confirmed by MRI or by angiography. Angiography is also
the first step in treatment. Fistulae may regress spontaneously (20), but when persistent haematuria or when
diameter > 15 mm, selective embolisation should be used. Pseudo aneurysms are often due to mycotic
infection (62) and can be fatal.

**Recommendation**

<table>
<thead>
<tr>
<th>Avoid very deep biopsy reaching the renal hilum.</th>
<th>GR</th>
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<td>C</td>
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</table>

4.3.6 **Lymphocele**

Lymphocele comprises 1-20% of complications. It occurs secondary to insufficient lymphostasis of the iliac
vessels and/or of the transplant kidney. Obesity and the use of some immunosuppressant agents such as
m-TOR inhibitors are associated with a higher risk of lymphocele (63-65). Generally, it is asymptomatic, but
there may be pain caused by ureter compression or infection. No treatment is necessary for mild lymphocele or
if there is no compression of the iliac vessels or the transplant ureter. Otherwise, laparoscopic marsupialisation
is the treatment of choice. Open surgery is indicated when laparoscopy (66) is not available or dangerous (67).

### Recommendation

<table>
<thead>
<tr>
<th>Description</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict lymphostasis should be maintained by clips or ligatures of the lymphatic vessels of the transplant and during dissection of the iliac vessels.</td>
<td>C</td>
</tr>
</tbody>
</table>

#### 4.4 References


4.5  Kidney transplantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- The technique used to implant transplant ureters in augmentations or conduits is the same as the method used with a patient’s own ureter, e.g. following cystectomy for bladder cancer (Bricker, Wallace) patients.
- In patient with ileal conduits, kidney transplant may be placed upside down to avoid ureter loops.
- In bladder augmentations or continent pouches, ureters are implanted by tunnel technique (Goodwin-Hohenfellner), or extravesically (favoured in most patients), e.g. using Lich Gregoir or Leadbetter methods (1-3).
- In ureterocystoplasty, it is feasible to perform uretero-ureterostomy with one of the patient’s own ureters (1,4).
- In patients with continent ileocoecal pouches with umbilical stoma or ileocystoplasties/ileal neobladders, transplant kidneys must be placed on the contralateral left side with the transplant ureters, crossing the abdomen subsigmoidally (2,3,5) (LE: 3-4).
5. MATCHING OF DONORS AND RECEPIENTS

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ABO blood group and the HLA-A, -B, and -DR phenotypes should be determined for all candidates awaiting kidney transplantation.</td>
<td>B</td>
</tr>
<tr>
<td>To avoid hyper-acute rejection, a lymphocyte cross-match test must be performed before each kidney and combined kidney/pancreas transplantation.</td>
<td>B</td>
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</tbody>
</table>

#### 5.1 Histocompatibility matching

Histocompatibility (HLA) matching is still very important in kidney transplantation because transplant outcome correlates with the number of HLA mismatches (1, 2). HLA incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This leads to cellular and humoral graft rejection.

Histocompatibility antigens show remarkable polymorphism. Matching should concentrate on HLA antigens, which impact on rejection rates. The HLA-A, HLA-B, and HLA-DR phenotypes should be determined in all potential recipients and donors. Kidneys from deceased donors should preferentially be allocated to potential recipients with the lowest number of HLA mismatches. This is also true for living-donor transplantation, although HLA-compatibility is less important in living- than in deceased-donor kidney transplantation (3). In living-donor transplantation, other risk factors for graft rejection, e.g. cold ischaemia time, brain death, and donor’s age, can be minimised.

#### 5.1.1 Practical aspects of histocompatibility-testing

Laboratories that provide HLA-testing and cross-matching for a transplant centre must have a valid accreditation to ensure accuracy and reliability. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics. Other practical considerations include (4):

- Obtain cells for HLA-typing from the recipient's peripheral blood using an appropriate anticoagulant, e.g. ammonium heparin, ethylene diamine tetra-acetic acid (EDTA) or acid-citrate-dextrose (ACD). Most HLA laboratories use 20 mL heparinised peripheral blood for serological HLA typing and 10 mL EDTA peripheral blood for molecular typing.
- Type donors using lymphocytes from lymph nodes, spleen, or peripheral blood.
- Use a comprehensive set of reagents capable of detecting all commonly occurring HLA antigens in the relevant ethnic group.
- For HLA-A and HLA-B specificities, serological or molecular typing is accepted. For HLA-DR, only molecular typing is accepted. For reporting HLA antigens, the latest WHO nomenclature should be used (5).
- Use family typing or DNA typing to detect possible homozygosity if the phenotype of a potential recipient shows fewer than six HLA-A, -B, -DR antigens.

### References

5.2 Cross-matching
To avoid hyper-acute rejection (HAR), a cross-match test must be performed before each kidney and combined kidney/pancreas transplantation. Patients at risk are those who have HLA-specific allo-antibodies or have had an allo-immunising event, such as pregnancy, blood transfusion, or a previous transplantation.

The cross-match test detects preformed allo-antibodies in the recipient's serum directed against lymphocytes of the potential donor. Routinely, a complement-dependent lymphocytotoxicity (CDC) assay is used. Cross-matches must be carried out using unseparated lymphocytes or T-enriched lymphocytes of the potential donor. B-cell cross-matches must be performed if required by the relevant transplantation programmes. T-lymphocytes express only HLA class I antigens. As B-lymphocytes express, besides HLA class I antigens also HLA class II antigens on their surface, a B-cell cross-match is considered to be more sensitive than a cross-match with T-lymphocytes. Spleen contains more B-lymphocytes than peripheral blood. A cross-match with unseparated lymphocytes from spleen is therefore more sensitive than a cross-match with unseparated lymphocytes from peripheral blood. A positive T-cell cross-match is generally a contraindication to transplantation. A positive B-cell cross-match result can occur for different reasons, including anti-HLA class I/II antibodies or allo-antibodies, immune complexes, therapy with anti-B-cell agents (rituximab, alemtuzumab), and non-HLA allo-antibodies (not shown yet). For a positive B-cell cross-match, individual decisions should be made based on the recipient’s antibody status and immunological history. Sera obtained 14 days after a potentially sensitising event should be included in a final cross-match.

Be aware of false-positive cross-match results, especially in autoimmune diseases, which often exhibit clinically irrelevant IgM auto-antibodies. Inactivation of IgM antibodies by serum treatment with dithiothreitol (DTT) can minimise false-cross-match results. However, be aware that IgM-anti-HLA allo-antibodies are also DTT-sensitive. Anti-HLA allo-antibodies of the IgM isotype are rare and a positive cross-match result due to IgM-anti-HLA is currently considered as potentially relevant.

Flow cytometry cross-match may be used in presensitised recipients at high risk of antibody-mediated graft rejection. However, the great sensitivity of flow cytomteric cross-match may exclude unnecessarily a high number of patients from transplantation (1,6). An enzyme-linked immunosorbent assay (enzyme-linked immunosorbent assay, ELISA) cross-match test, which uses solid-phase technology to detect donor-specific anti-HLA antibodies, is being evaluated.

5.3 Pre-existing histocompatibility-specific antibodies
Sera from potential organ recipients should be screened for HLA-specific antibodies every 3 months or as stipulated by the national and/or international organ exchange organisations. Screening for HLA-specific antibodies should be carried out at 2 and 4 weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation.

The results of HLA-antibody testing in a recipient’s serum are expressed as the percentage of panel reactive antibodies (%PRA) and as the HLA specificity against which these antibodies react. To detect antibodies to HLA class II antigens, a technique must be used that distinguishes them from antibodies to HLA class I antigens. In the standard CDC assay, the panel of lymphocytes used cover most of the common HLA-alleles in the donor population and should optimally contain at least 50 different HLA-typed cells.

As the assay is not sufficiently sensitive, clinically relevant anti-HLA class I and class II antibodies may go undetected in the traditional microlymphocytotoxicity assay (7). Non-complement fixing antibodies are not detected at all. More specific and sensitive solid-phase techniques have been developed, such as flow cytometry and ELISA, which use solubilised or recombinant HLA molecules instead of lymphocytes. Preformed non-HLA allo-antibodies may also influence graft outcome (8). Solid-phase assays are strictly HLA-specific and cannot detect non-HLA antibodies. It is not clear whether clinically relevant non-HLA antibodies are expressed on B-lymphocytes and can therefore be recognised by lymphocytotoxicity testing. No antibody screening methods can reliably detect all clinically relevant allo-antibodies, and a combination or alternate use of lymphocytotoxic and solid-phase antibody screening methods is therefore recommended (5).

Presensitised patients with high PRA have two major disadvantages:
• Due to an often positive cross-match, they generally wait longer for an organ than non-sensitised patients;
• Overlooked antibodies or higher alloreactivity in the cross-match may adversely affect the graft outcome.

5.3.1 Eurotransplant Acceptable Mismatch (AM) programme
Special efforts, such as the acceptable mismatch (AM) programme of Eurotransplant, have achieved successful transplantation in highly sensitised patients (PRA ≥ 85%) (9). A careful analysis of HLA antibody specificities is carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. Patients accepted for the AM programme of
Eurotransplant are given high priority during organ allocation if the donor cross-match test is negative.

5.4 **ABO compatibility**
Compatibility for ABO blood group antigens is of critical importance in kidney transplantation. Since blood group antigens can behave as strong transplant antigens (i.e. expression on renal vascular endothelium), incompatibility in the ABO antigen system between donor and recipient can cause early HAR and must be avoided. However, with the introduction of antibody elimination methods and anti-B cell agents, increasing numbers of centres are performing successful ABO-incompatible transplants, even without splenectomy (10).

Despite an elevated risk of post-transplant haemolytic disease due to resting donor B-cells in the graft, the kidneys of potential donors with blood group O can theoretically be transplanted in A, B, or AB recipients. To avoid an increasing imbalance between demand and supply in deceased-donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys. In living-donor transplantation, ABO compatibility is as acceptable as ABO identity.

5.5 **References**
2. UNOS United Network for Organ Sharing. [http://www.unos.org](http://www.unos.org) [access date January 2012]

6. **IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION**

6.1 **Introduction**
The principle underlying successful immunosuppression is ‘the balance of survival’. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient’s health. Increased understanding of immune rejection has led to the development of safe modern immunosuppressives (1), which suppress sensitised lymphocyte activity against a transplant. Immunosuppression is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.
In later post-operative stages, ‘graft adaptation’ occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) (2,3) (LE: 1b).

Non-specific side-effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections (1-3). All immunosuppressants also have dose-dependant specific side-effects. Current immunosuppressive protocols aim to reduce drug-specific side-effects using a synergistic regimen (4). A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs, so reducing side-effects, while still maintaining efficacy due to the synergistic effects of the immunosuppressants (LE: 1b).

Current standard initial immunosuppression provides excellent efficacy with good tolerability (5,6). It is given to most patients and consists of:

- CNIs (cyclosporine or tacrolimus)
- Mycophenolate (MMF or enteric-coated mycophenolate sodium, EC-MPS)
- Steroids (prednisolone or methylprednisolone)
- With or without induction therapy.

This multidrug regimen reflects today the standard of care for the majority of transplant recipients worldwide (5,6) (LE: 1b).

This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed (7). In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side-effects, lack of efficacy or protocol-driven requirements (3,4,6).

6.2 Primary immunosuppressive prophylaxis

6.2.1 Calcineurin inhibitors (CNIs)

Both cyclosporine and tacrolimus have significant side-effects that are hazardous to the graft and patient (1-3) (8,9). Most importantly, both are nephrotoxic (10,11) (LE: 1a), and long-term use is a major cause of chronic allograft dysfunction, eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs (12).

6.2.1.1 Cyclosporine A

Cyclosporine A micro-emulsion (CsA-ME; Neoral) has a better pharmacokinetic profile and appears to be more acceptable to patients compared to the previous formulation (Sandimmune) (1,6,13,14). More importantly, the area under the absorption curve is higher with CsA-ME than with Sandimmune, enabling a reduction in the dosage of cyclosporine without affecting efficacy (8). CsA-ME treatment is also associated with a reduced rejection rate 1 year post transplant (8) (LE: 1b).

Although CsA-ME has proven efficacy and safety, it is a ‘critical-dose’ drug, so that any deviations from exposure can lead to severe toxicity or failure of efficacy (13,14). The demonstration of bioequivalence in healthy volunteers according to standard criteria is not sufficient evidence to support treatment of all renal allograft recipients with generic formulations of cyclosporine. Until more data are available, the patient and physician prescribing generic cyclosporine formulations must be aware of potential differences in exposure, maximal drug concentration, variability and food effects (15,16). Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one cyclosporine formulation to another (13,14) (LE: 2a).

Pharmaceutical companies and researchers are asked to provide sufficient data on key pharmacokinetic parameters in target populations, including de-novo transplanted patients. Drug agencies should institute more stringent criteria for ‘critical dose’ drugs requesting approval (LE: 4).

Cyclosporine causes hypercholesterolaemia, hypertension, gum hypertrophy, constipation, hirsutism, and acne (1-3,8,10) (LE: 1a). Therapeutic drug monitoring is mandatory (17,18) (LE: 3) because of its narrow therapeutic window and the potential for drug-to-drug interaction. The drug level at 2 hours after intake (C2) may correlate better with exposure with retrospective studies suggesting a better correlation for C2 levels with outcome parameters (17,18) (LE: 3). However, no prospective comparative studies have been undertaken, and C2 levels alone may not adequately reflect cyclosporine exposure in the early post-transplant period (17,18) (LE: 2b). Furthermore, the determination of C2 levels may cause logistical problems. Most importantly, similar overall outcomes were achieved with conventional monitoring strategies. In summary, both cyclosporine-monitoring strategies are useful for assessing cyclosporine exposure. The additional measurement of a trough level in C2-monitored patients or of a C2 level in trough-level monitored patients may provide a more accurate assessment of drug exposure (18) (LE: 4).
6.2.1.2 Tacrolimus

Tacrolimus is a more powerful immunosuppressive than cyclosporine, as indicated by its more potent prophylaxis of transplant rejection. However, its use is associated with diabetes, neurological side-effects (tremor, headache), hair loss, gastrointestinal side-effects (e.g. diarrhoea, nausea, vomiting), and hypomagnesaemia (1-3,8,10) (LE: 1a). In combination with a mycophenolate, it may also more often cause over-immunosuppression, namely polyoma nephritis (19) (LE: 1b).

A new modified-release formulation (Advagraf), which allows once-daily dosing of tacrolimus (20,21), has been approved in Europe, though not yet in the USA. Advagraf fulfills standard bioequivalence criteria, although it results in slightly lower exposure, lower peak levels and lower trough levels, which therefore require a higher dosage to maintain exposure (20-23) (LE: 1b). Too low a level of exposure may be critical, especially early after transplantation.

Both tacrolimus formulations provide effective rejection prophylaxis and overall similar outcomes compared to cyclosporine (22) (LE: 1b). Because of its narrow therapeutic window and the potential for drug-to-drug interaction, tacrolimus should be monitored using trough levels, which provide a reasonable estimate for exposure (20,21) (LE: 3).

6.2.1.3 Summary

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival (8) (LE: 1a). Some analyses have shown that tacrolimus provided better rejection prophylaxis and was associated with slightly better graft survival, when censored for death in some analyses. Renal function was favourable for tacrolimus-treated patients, but did not reach statistical significance in most analyses. Several more recent trials have confirmed that rejection prophylaxis is better with tacrolimus (22,24,25), but failed to show any benefit with respect to patient and graft survival. Thus, in summary, both Calcineurin-inhibitors (CNIs) can be used for the effective prevention of acute rejection (LE: 1a).

In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes, polyoma nephropathy) conversion to the other CNI can be a successful strategy to reduce side effects (26,27) (LE: 1b). Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient (LE: 4).

Despite their side-effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than 20 years because they have resulted in an exemplary improvement in kidney graft survival. This has led to success in pancreas, heart, liver, and lung transplantation (1) (LE: 1a). Future protocols aim to minimise or even eliminate CNIs. However, until such strategies provide superior outcomes, CNIs remain the standard of care in the initial post-operative period (2,3) (LE: 1b). For severe CNI-related side-effects, CNI withdrawal, replacement, or profound reduction may be needed (10) (LE: 2b). Special attention should be paid to maintenance patients, which may need less CNIs than previously thought (26,28) (LE: 1b).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>Rejection prophylaxis with Calcineurin-inhibitors represents current best practice pending publication of long-term results using newer agents.</td>
<td>A</td>
</tr>
<tr>
<td>The choice of Calcineurin-inhibitors depends on the immunological risk, recipient characteristics, concomitant immunosuppression, and socio-economic factors.</td>
<td>A</td>
</tr>
<tr>
<td>Blood-level monitoring of both cyclosporine and tacrolimus is mandatory to prevent under-immunosuppression (enhanced risk of rejection) and excessively high blood levels (resulting in a high risk of chronic side-effects, particularly nephrotoxicity).</td>
<td>A</td>
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6.2.2 Mycophenolates

The mycophenolates, MMF and EC-MPS, are based on mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase. This is the rate-limiting step for the synthesis of guanosine monophosphate in the de novo purine pathway. As the function and proliferation of lymphocytes is more dependent on de novo purine nucleotide synthesis compared to other cell types, inosine monophosphate dehydrogenase (IMPDH) inhibitors may provide a more specific lymphocyte-targeted immunosuppression (1). Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause gastrointestinal side-effects particularly diarrhoea (29,30). Both MPA formulations are equally effective with an almost identical safety profile (29) (LE: 1b), though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking (31,32) (LE: 2a).

The co-administration of mycophenolate with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections (33) (LE: 1b). A retrospective study Mycophenolate mofetil decreased the relative rate for chronic allograft rejection by 27% versus azathioprine, an effect independent of the reduction
of acute cellular rejection in patients receiving MMF (33) (LE: 3). Recent retrospective studies have suggested that MPA dose reductions are associated with inferior outcomes (31) (LE: 3).

Other side-effects include the potential for over-immunosuppression, especially a higher incidence of CMV infections and severe CMV disease, and a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus (1-3) (LE: 1b). Standard doses in combination with cyclosporine are MMF 1 g bid or EC-MPS 720 mg bid (LE: 1b), although higher initial doses have been suggested, recently (34,35) (LE: 2b). MPA is not formally approved for use with tacrolimus, though this is the most frequently used drug combination in many countries worldwide (5). Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination (34,35). Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine (34,35) (LE: 2a). Most transplant centres use the same starting dose compared to cyclosporine-treated patients (35) (LE: 2b), however dose reductions are frequent, especially because of gastrointestinal side-effects (35). After 6-12 months, most patients are treated with a daily dose of MMF, 1000-1500 mg, or EC-MPS, 720-1080 mg (22,24,25). Due to the high incidence of side effects, some centres perform a protocol-driven MPA dose reduction in tacrolimus treated patients (34,35) (LE: 3).

Regular monitoring for polyoma is recommended in patients given MPA combined with tacrolimus (36,37) (LE: 3). Due to a higher incidence of CMV disease with MPA, either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted (37-40) (LE: 1a). CMV prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants, because prophylaxis recently has been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients (40), and leads to better long-term graft survival in kidney allograft recipients (38) (LE: 1a).

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients (34,35,41-44) (LE: 1b).

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients (45,46) (LE: 1a) or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function (2,3,28,47) (LE: 1b). Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first 3 years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies (47-49) (LE: 1b). In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond 5 years’ post-transplant and resulted in improved renal function (50,51) (LE: 1b). It is under investigation whether or not early CNI withdrawal under combination therapy of MPA, steroids and m-TOR inhibitors is safe and efficacious.

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Mycophenolates are the current standard of care. The standard dose of MMF combined with cyclosporine is 1 g bid or EC-MPS 720 mg bid.</td>
<td>A</td>
</tr>
<tr>
<td>Combination therapy of mycophenolates with tacrolimus is not formally approved. Optimal mycophenolate dosing is not yet clear, as tacrolimus-treated patients develop higher MPA exposure compared to cyclosporine-treated patients. The standard starting dose of MMF combined with tacrolimus is MMF 1 g bid or EC-MPS 720 mg bid. This dosage, which is applied in most centres, is often reduced resulting in 30-50% lower doses at 1 year.</td>
<td>A</td>
</tr>
<tr>
<td>Mycophenolate drug monitoring cannot be recommended for all patients due to limited evidence supporting its benefit.</td>
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EC-MPS = enteric-coated mycophenolate sodium; MMF = mycophenolate mofetil

### 6.2.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprine, MPA reduced rejection rates significantly in prospective randomised trials (1,5,6,28,29) (LE: 1b). Although a recent, large, prospective study found that azathioprine may give acceptable results in a low-risk population (52) (LE: 1b), azathioprine is usually reserved for patients who cannot tolerate MPA (5,6). When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters (53) (LE: 1a).
Azathioprine may be used in a low-risk population as initial immunosuppression, especially for those intolerant to MPA formulations. **A**

There is no firm evidence for the efficacy of azathioprine in combination therapy with CNIs and steroids. **A**

**MPA** = mycophenolic acid

### Steroids

Steroids have a large number of side-effects (1-3,45,54), especially with long-term use. Most practitioners still consider prednisolone to be a fundamental adjunct to primary immunosuppression (5), even though successful prednisolone withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials (45,46,55,56) (LE: 1a). These trials suggest the risk of steroid withdrawal depends on the use of concomitant immunosuppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment period. (1-3,45,54,57) (LE: 3).

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Initial steroid therapy remains the standard in perioperative and early posttransplant period.</td>
<td>A</td>
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<tr>
<td>There is increasing evidence that steroids may be safely stopped in most patients after 3-12 months on combination therapy with Calcineurin-inhibitors and mycophenolic acid.</td>
<td>A</td>
</tr>
<tr>
<td>Steroid-free long-term therapy is inherently associated with a reduction of steroid-induced side effects.</td>
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### Inhibitors of the mammalian target of rapamycin (m-TOR)

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin (m-TOR) and suppress lymphocyte proliferation and differentiation. They inhibit both calcium-dependent and calcium-independent pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts, and tumour cells (1-3,57-60). m-TOR inhibitors are as effective as MPA when combined with CNIs in preventing rejection (57-60) (LE: 1b).

#### Side-effects

m-TOR inhibitors exhibit dose-dependent bone marrow toxicity. Other potential side-effects include hyperlipidaemia, oedema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility (57-60) (LE: 1b). When combined with CNIs, pneumocystis prophylaxis is mandated, e.g. low-dose cotrimoxazole (57-60) (LE: 3). Most importantly, combination therapy with CNIs aggravate CNI-induced nephrotoxicity, although m-TOR inhibitors themselves are non-nephrotoxic (57-60) (LE: 1b). Several studies suggest less favourable outcomes for this combination, especially if CNIs are maintained at standard dosages (57-61) (LE: 3). Calcineurin-inhibitors dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy (57-60) (LE: 1b).

#### Comparison of pharmacokinetics and licensed use

To date, no prospective comparative studies have been carried out on sirolimus and everolimus. Both m-TOR inhibitors have an almost identical side-effect profile and mainly differ in their pharmacokinetic properties (57-60). Sirolimus has a half-life of about 60 h, is given once a day and is licensed for prophylaxis of kidney recipients only. Everolimus has a half-life of about 24 h, is licensed for kidney and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine (57-60) (LE: 1b) and can be given simultaneously with cyclosporine, while sirolimus should be given 4 h after cyclosporine (57-60). Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine (57-60) (LE: 1b). Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions (57-60) (LE: 3).

#### Conversion from CNIs to m-TOR inhibitors

Despite an encouraging earlier metaanalysis (60), recent studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side-effect profile, particularly wound healing problems and lymphoceles (2,3,24,57-60) (LE: 1a). Other research suggests that m-TOR inhibitors can safely replace CNI at later stages, e.g. 3 months after transplantation, with improvements...
in renal function (2,3,57-60,62) (LE: 1a). However, especially early after transplantation, there is a slightly increased risk of rejection, which may be offset by the benefit of the non-nephrotoxic immunosuppression. Despite higher rejection rates, one study showed better long-term survival, better renal function and fewer malignancies under dual therapy with sirolimus and steroids compared to the more nephrotoxic therapy with cyclosporine, steroids and sirolimus. (2,3,57-60,62) (LE: 1b).

Proteinuria and poor renal function are associated with inferior outcomes. Conversion from CNI is not advisable in patients with proteinuria > 800 mg/day (57-60,63-65) (LE: 1b). A cautious and individual approach should be followed in patients with GFR < 30 mL/min (57-60,63-65) (LE: 3).

Due to an antiproliferative effect and a lower incidence of malignancy in sirolimus-treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy (57-60,66) (LE: 3). However, no controlled trials have reported better outcomes after conversion. To date, only a few data on long-term follow-up of m-TOR-treated patients have been reported. Emerging side-effects including proteinuria (66,67) and infertility (68) warrant an individual and cautious approach (LE: 3).

### Recommendations GR

**Acute rejection can be effectively prevented by m-TOR inhibitors, such as sirolimus and everolimus, in combination with CNIs. This combination regimen is associated with enhanced nephrotoxicity and inferior outcomes. CNI dosage must be significantly reduced to prevent aggravated nephrotoxicity.**

**A**

**Initial CNI-free combination therapy of m-TOR inhibitors with MPA and steroids is not sufficient to effectively prevent acute rejection compared to a standard regimen.**

**A**

**Use of m-TOR inhibitors is associated with impaired wound healing. Prophylactic surgical measures must be implemented if patients receive m-TOR inhibitors during the peri-operative period.**

**A**

**m-TOR inhibitors can safely replace CNIs beyond the early post-transplant period. They are a valid alternative to CNIs when there are severe CNI related side-effects, e.g. nephrotoxicity.**

**A**

**Blood levels of both sirolimus and everolimus must be measured at regular intervals.**

**A**

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**CNI = Calcineurin-inhibitors; MPA = mycophenolic acid**

6.2.6 **T-cell depleting induction therapy**

Prophylactic immunosuppression in many countries, particularly the USA, featured the emergence of ‘induction’ treatments, using biological T-cell depleting agents. These include anti-thymocyte globulin (ATG), OKT3 and more recently an anti-CD52 antibody (Campath1-H) after renal transplantation (1,5). Some centres use these agents to provide effective rejection prophylaxis while initiating CNIs after recovery of the graft from ischaemic injury, although evidence supporting this hypothesis is lacking (69,70) (LE: 1b). Graft rejection rates are initially lower with induction treatment (69-71); however, some studies suggest an increased rejection rate after cessation of lymphocyte depletion (70,72). There is no evidence of better long-term graft survival in patients receiving induction therapy versus those who have not (70,73-75) (LE: 3). In contrast, it is well documented that induction therapies with T-cell depleting agents carry an increased risk of post-operative opportunistic infections and cancer, especially post-transplant lymphoproliferative disease (70,73-75) (LE: 3).

**Potential life-threatening side-effects of T-cell depleting biological induction therapy include a higher incidence of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease.**

**B**

**Use of T-cell depleting antibodies has not been associated with improved outcomes in the overall population.**

**B**

**T-cell depleting antibodies should not be routinely used in a low-risk first-transplant recipient.**

**B**

**If such induction therapy is used, the increased risks of infection and cancer must be explained to the patient before starting therapy.**

**B**

6.2.7 **Interleukin-2 receptor antibodies**

Two high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibodies (daclizumab and basiliximab) are approved for rejection prophylaxis following organ transplantation (1,70,76-78). These agents are given in a short course during the post-transplantation period, are safe, and have been shown in randomised controlled trials to reduce the prevalence of acute cellular rejection by approximately 40% (70,78) (LE: 1a). Both antibodies appear to be equally efficacious, though no formal comparative study was performed.

A meta-analysis has confirmed the efficacy, although no positive effect on patient or graft survival
could be demonstrated (78) (LE: 1a) although large retrospective cohort studies and a recent large prospective study suggest such a benefit (24,70,73,75). The effect of these antibodies in combination with tacrolimus and/or mycophenolate was not investigated in the meta-analysis. Several recently published large controlled trials support the efficacy and safety of quadruple therapy with these agents (6,22,24,25,49,55,56,70) (LE: 1b). Interleukin-2 receptor antibodies may allow early steroid withdrawal (55,56) (LE: 1b), although higher rejection rates were described. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs, while maintaining excellent efficacy and renal function. (2,3,6,24,47) (LE: 1b).

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Use of IL-2R antibodies for preventing rejection is efficacious and safe, and effectively reduces the rate of acute rejection, enabling CNI- and steroid sparing regimens.</td>
<td>A</td>
</tr>
<tr>
<td>Formal evidence for improved patient and graft outcome is lacking, although recent large clinical trials suggest such a benefit.</td>
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CNI = Calcineurin-inhibitors

### References


7. IMMUNOLOGICAL COMPLICATIONS

7.1 Introduction
Immunological rejection is a common cause of early and late transplant dysfunction (1,2). There is great variation in the timing and severity of rejection episodes and how they respond to treatment (Table 19). There are several main types of immunological reaction (Table 20).

Table 19: Determining factors in rejection episodes and response to treatment (1-5)

| Degree of sensitisation to HLA, measured by the panel-reactive antibody (PRA) and specific anti-HLA antibodies |
| Degree of HLA-mismatch, particularly in sensitised recipients (1) |

Table 20: Types of immunological reaction

<table>
<thead>
<tr>
<th>Type of reaction</th>
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<tbody>
<tr>
<td>Acute rejection</td>
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<tr>
<td>Chronic rejection</td>
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<tr>
<td>Antibody-mediated rejection</td>
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<td>Cell-mediated rejection</td>
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<td>Complement-mediated rejection</td>
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Table 20: Main types of rejection (1-7)

<table>
<thead>
<tr>
<th>Hyper-acute rejection (HAR)</th>
<th>Antibody-mediated rejection is caused by pre-formed anti-HLA or anti-AB (blood group) antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Now rare due to donor-recipient ABO matching and routine pre-transplant cross-matching between donor</td>
</tr>
<tr>
<td></td>
<td>cells and recipient serum</td>
</tr>
<tr>
<td>Acute cellular rejection (ACR)</td>
<td>Much more common than HAR, occurring in 10-40% of transplants</td>
</tr>
<tr>
<td></td>
<td>Usually occurs from 5 days’ post transplant</td>
</tr>
<tr>
<td></td>
<td>Most likely within the first 3 months, though may occur after this time</td>
</tr>
<tr>
<td></td>
<td>Usually responds well to steroid bolus treatment</td>
</tr>
<tr>
<td>Acute humoral rejection (AHR)</td>
<td>Much less frequent than ACR, occurring in 5-20% of transplants</td>
</tr>
<tr>
<td></td>
<td>Most likely within the first 3 months’ post transplant</td>
</tr>
<tr>
<td></td>
<td>Presence of certain histological features and/or positive C4d immunostaining and/or anti-HLA antibodies</td>
</tr>
<tr>
<td></td>
<td>Worse prognosis than ACR because more difficult to treat</td>
</tr>
<tr>
<td>Chronic allograft rejection (CAR)</td>
<td>Rare, slowly progressive, immunological process</td>
</tr>
<tr>
<td></td>
<td>Certain non-specific histological features and/or anti-HLA antibodies</td>
</tr>
<tr>
<td></td>
<td>Requires clear strong evidence for a solely chronic immunological process</td>
</tr>
</tbody>
</table>

The gold standard for the diagnosis of ACR, AHR and CAR is transplant biopsy (1,2) (see below), which may demonstrate a mixed histological picture in many cases. The Banff criteria (6,7) are uniform criteria applied to biopsy, which are updated regularly and are the basis for deciding prognosis and treatment (8) (LE: 3).

The term ‘IF/TA’ replaces the previously used terms ‘chronic allograft nephropathy’. This term was used to refer to chronic destruction of the graft associated with fibrosis and arteriosclerosis in renal biopsy and of uncertain aetiology. IF/TA is the common histological manifestation of some damage to the graft, where it is not possible to make a specific diagnosis of the underlying cause (6-9). IF/TA is probably the commonest histological feature in failed grafts and is present to some degree in the vast majority of grafts up to 10 years’ post transplant (9).

‘Chronic allograft dysfunction’ is the term used to refer to the chronic deterioration of graft function without histological evidence (LE: 4).

7.2 Hyper-acute rejection

Hyper-acute rejection (HAR) is the most dramatic and destructive immunological attack on the graft (1-5). It results from circulating, complement-fixing IgG antibody, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium. It occurs in most ABO-incompatible grafts due to the presence of pre-existing IgM iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies (1-5) (LE: 3).

With the development of the cross-match test, HAR has become an extremely uncommon complication. The complement-dependent cytotoxicity test (CDC) is now universally employed in all transplant centres. Recently, newer techniques have been developed, allowing a more sensitive detection of specific anti-HLA antibodies (4,5) (see Chapter 5). However, validation of these techniques is ongoing. If such diagnostic tests demonstrate the possibility of specific anti-HLA antibodies in the presence of a negative CDC cross-match, an individual decision has to be made whether to transplant or not (LE: 4).

Hyper-acute rejection is a rare complication usually seen at the time of surgery. Within minutes or hours of vascularisation, the kidney becomes mottled and then dark and flabby. Histology reveals generalised infarction of the graft (4). Delayed HAR may occur within a week of the transplant, and may be recognised by
acute anuria, fever, and a swollen graft. Hyper-acute rejection is treated by graft nephrectomy.

7.2.1 Prevention
Hyper-acute rejection can be prevented by the avoidance of an ABO-incompatible renal transplant and by performing a regular CDC cross-match before transplantation (LE: 3). All patients registered for renal transplantation should have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions (4,5,10) (LE: 3). Highly sensitised patients (>50% PRA) should be considered for prioritisation in a points-based matching algorithm (10) (LE: 3).

In a national kidney-sharing programme, identification of the specificity of anti-HLA antibodies in highly sensitised patients and cross-matching allows the detection of acceptable and unacceptable antigens present in the donor (10). This information can be highlighted with the patient’s details on the transplant registry database, so preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity (10) (LE: 3).

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>All recipients and donors must be tested for blood group antigens and blood group incompatibility must be avoided, except intentional living-donor ABO-incompatible transplantation.</td>
<td>B</td>
</tr>
<tr>
<td>All centres practising renal transplantation should have access to elective serological profiling of all potential, and actual, waiting-list recipients to define the percentage and specificity of PRA and their isotypes, IgG or IgM.</td>
<td>B</td>
</tr>
<tr>
<td>The laboratory service should provide a 24-h donor-recipient cross-matching service to be able to quickly inform a surgeon of the CDC cross-match result before a deceased donor renal transplant (within 5 h).</td>
<td>B</td>
</tr>
</tbody>
</table>

PRA = panel-reactive antibody; CDC = complement-dependent cytotoxicity (testing).

7.3 Acute allograft rejection
Acute allograft rejection can be classified into either T-cell mediated (acute cellular rejection, ACR) or antibody-mediated (acute humoral rejection, AHR) according to the most recent Banff criteria (1-7). Tubulo-interstitial infiltrate of T-cells, macrophages, and to a lesser extent, neutrophils invading the tubular epithelium is a hallmark of T-cell mediated ACR.

Humoral rejection commonly accompanies ACR and causes the same clinical signs. As in ACR, the diagnosis of AHR becomes apparent on renal allograft biopsy. It can be categorised into capillary or arterial antibody-mediated rejection. During post-operative humoral rejection, antibodies are formed against donor antigen on the endothelium. In 20-25% of cases, these antibodies may be detected in the serum during rejection (4, 5). Acute humoral rejection is under-diagnosed (11,12). On biopsy, the appearance may be of oedema and haemorrhage with focal necrosis. The C4d fraction of complement in renal biopsy is required for diagnosis according to the current Banff criteria (6,7,11,12). Not surprisingly, the prognosis is poorer than when ACR occurs alone (4,5,11,12) (LE: 3).

Because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis or CNI nephrotoxicity), a biopsy is necessary to correctly diagnose and treat the patient (1-6) (LE: 3). If possible, all rejections must be verified by renal biopsy and graded according to the most recent Banff criteria, except when contraindications for a renal biopsy are present (6-8) (LE: 3). Renal transplant biopsy should be conducted preferably under ultrasound control, using an automated needle biopsy system (e.g. tru-cut, biopsy gun) (13) (LE: 3).

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Renal transplant practitioners must be continuously aware of the possibility of acute rejection, particularly during the first 6 months after renal transplant.</td>
<td>B</td>
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<tr>
<td>During hospitalisation, regular blood and urine samples should be taken for renal and haematological studies in addition to regular ultrasound examinations.</td>
<td>B</td>
</tr>
<tr>
<td>Rejection should be strongly suspected in any patient who suffers fever, graft tenderness, or reduced urine output. In case of suspected acute rejection, other potential causes of graft dysfunction need to be ruled out immediately.</td>
<td>B</td>
</tr>
<tr>
<td>All patients with suspected acute rejection episodes should undergo renal biopsy, which should be graded according to the most recent Banff criteria. Only if contraindications to renal biopsy are present, can “blind” steroid bolus therapy be initiated. Steroid treatment for rejection may start before biopsy is performed.</td>
<td>B</td>
</tr>
</tbody>
</table>
7.3.1 Treatment of T-cell mediated acute rejection
As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience than on clinical evidence (1-4,14). Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for 3 days (1-4) (LE: 3). Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another 3-day course of pulsed methylprednisolone therapy (1-4) (LE: 3). In addition, baseline immunosuppression should be re-evaluated to ensure adequate drug exposure (1-4) (LE: 3).

In severe rejection, a conversion from cyclosporine to tacrolimus should be considered (1-4) (LE: 3). T-cell depleting biological agents, such as anti lymphocyte globulin (ALG) or anti-CD3 monoclonal antibody (OKT3), may be considered in severe steroid-refractory cases (1-4,14) (LE: 1a). If biological agents are used, other immunological suppression should be reduced or stopped and daily T-cell monitoring should be done to minimise the dose of the biological agent (15,16) (LE: 4). Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately (LE: 4).

Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th>Treatment with steroid bolus therapy is recommended.</th>
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<tbody>
<tr>
<td>B</td>
<td>Treatment with steroid bolus therapy is recommended.</td>
</tr>
<tr>
<td>B</td>
<td>In addition, steroid-resistant rejection, consider intensified immunosuppression, including high-dose steroid treatment, conversion to tacrolimus, and T-cell depleting agents.</td>
</tr>
</tbody>
</table>

7.3.2 Treatment of acute humoral rejection
Acute humoral rejection (AHR) is treated in a similar way as T-cell mediated rejection (4,17) (LE: 3). Treatment relies on retrospective studies and empirical treatment guidelines. Treatment with a steroid bolus (at least 3 days of 500 mg/day) and conversion to tacrolimus therapy with trough levels > 10 ng/mL are common (4,17) (LE: 3). Although T-cell depleting agents appear to have limited value, there are several retrospective case series and a small prospective trial in children and adolescents describing the successful use of the anti-CD20 antibody, rituximab (4,17,18) (LE: 1b). However, no further prospective trials have been published and neither the dose, side-effects nor efficacy parameters have been evaluated in a larger cohort with adequate follow-up. Most centres also try to remove antibodies using plasmapheresis or immunoadsorption columns. Retrospective and prospective case series clearly suggest efficacy (4,17,19) (LE: 1b), although details of the procedures vary widely.

Some centres advocate intravenous immunoglobulin (IVIG)(20), which may modulate and/or suppress antibody production (4,17,20) (LE: 3). Dosages vary widely from 0.2-2.0 g/kg bodyweight. No comparative studies have been published. Several regimens have proven efficacious in AHR. However, the lack of firm evidence does not permit evidence-based recommendations for treatment, except for a beneficial effect of early antibody removal.

Recommendations

<table>
<thead>
<tr>
<th>GR</th>
<th>Treatment of acute hormonal injection should include early antibody elimination.</th>
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<tbody>
<tr>
<td>B</td>
<td>In addition, steroid bolus therapy, conversion to tacrolimus, T-cell depleting agents and intravenous immunoglobulin treatment are used frequently.</td>
</tr>
<tr>
<td>B</td>
<td>Anti-CD20 (rituximab) may be efficacious. However, firm evidence on efficacy and side-effects are lacking.</td>
</tr>
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</table>

7.4 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy
Many patients lose their grafts due to chronic allograft dysfunction (9). Histology will usually reveal a chronic process of interstitial fibrosis and tubular atrophy (IF/TA). An unknown, but rather small number of these patients will have ‘true’ immunological CAR (1,2). IF/TA takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum creatinine level over months
It is likely that IF/TA is more common in patients who have had early attacks of ACR, which is a good reason for preventing acute cellular rejection. The main differential diagnoses are chronic nephrotoxicity, which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney (9). Histological features on biopsy are fibrosis, cortical atrophy, concentric intimal fibroplasia of larger arteries with capillary dilatation, arteriolar hyalinosis, and thickened split basement membranes. (LE: 3).

### 7.4.1 Diagnosis and treatment

Diagnosis is by renal biopsy (5,6). In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen (22-24) (LE: 1a). Conversion to m-TOR inhibitors is safe. Favourable outcomes have been observed without significant proteinuria (< 800 mg/day) (24,25) (LE: 1a). Alternatively, successful conversion to a MPA-based regimen has been described, especially in patients beyond the first 3 years’ post transplant (22,23) (LE: 1b). If there is intolerance to m-TOR inhibitors or MPA, conversion to an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance (26) (LE: 1a). If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA (21,27) (LE: 1b). In patients with proteinuria, intervention with an ACE inhibitor, or angiotensin II receptor blocker (28) may slow down renal decompensation (LE: 3). Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis, and bone disease (29-34) (LE: 3). However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

### Recommendations

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>During the years of follow-up after renal transplantation, regularly monitor serum creatinine, creatinine clearance, blood pressure, and urinary protein excretion.</td>
<td>A</td>
</tr>
<tr>
<td>Changes in these parameters over time should trigger hospital admission for renal biopsy and further diagnostic work-up including a search for infectious causes and anti-HLA antibodies. An ultrasound of the graft should rule out obstruction and renal artery stenosis.</td>
<td></td>
</tr>
<tr>
<td>If a specific cause for deteriorating renal function can be identified, appropriate treatment should be instituted.</td>
<td>A</td>
</tr>
<tr>
<td>If unspecific IF/TA is confirmed, begin appropriate medical treatment (e.g. control of hypertension, proteinuria).</td>
<td>A</td>
</tr>
<tr>
<td>Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease) and cardiovascular risk factors (e.g. hyperlipidaemia, diabetes).</td>
<td></td>
</tr>
<tr>
<td>In patients with IF/TA under current CNI therapy and/or with histological signs suggestive for CNI toxicity (e.g. arteriolar hyalinosis, striped fibrosis) without significant proteinuria (&lt; 800 mg/day), conversion to an m-TOR inhibitor or substantial CNI reduction under MPA protection may be indicated. In chronic maintenance patients beyond 5 years, post-transplant CNI withdrawal under MPA and steroids is another safe option.</td>
<td>A</td>
</tr>
</tbody>
</table>

CNI = Calcineurin-inhibitor; IF/TA = interstitial fibrosis and tubular atrophy; MPA = mycophenatic

### 7.5 References


8. **MALIGNANCY**

There are three situations in which malignancy occurs in kidney transplant recipients:
- transmitted malignancy by the donor
- known or latent prior malignancy in the recipients
- ‘de-novo’ malignancies developed in the recipient after transplantation.

8.1 **Transmission of a donor neoplasia to the recipient**

The risk of a donor disease transmission is estimated at 0.2% (1) with increased use of older donors and marginal kidneys. Donors can be divided into three groups according to the risk of transmission of cancer:
- donors without cancer
- donors with a per-operative diagnosis of cancer
- donors with a history of cancer.

However, even in the first situation, there remains a very small risk that donors may carry an intraclinical tumour, particularly of the prostate (2).

Pre-operative suspicion of cancer was reported in 337 (4.4%) out of 7608 donors (3). Among them, there were 131 donors suitable for donation, who donated a total of 241 organs without any donor-related tumour transmission to the recipients. In 1069 donors with a history of cancer and no tumour transmission, the
most common cancers were non-melanoma skin cancer (31%), central nervous system (CNS) tumours (25%), and uterine and cervical cancers (13%) (4). Melanoma and choriocarcinoma are the most aggressive donor-transmitted malignancies (5).

Individuals with active cancer or a history of metastatic cancer or who have had cancers with a high risk of recurrence (e.g. medulloblastoma and glioblastoma multiforme) should not be donors (6). Occasionally, brain metastasis may masquerade as a primary brain tumour or cerebral haemorrhage and must be excluded as it is a contraindication for donation.

However, a prior history of neoplasia is no longer an absolute contraindication for organ donation. Non-melanoma low-grade skin cancer and selected CNS tumours that have not undergone surgical manipulation may also be acceptable. The following tumours are not contraindications to donation:

- basal cell carcinoma
- non-metastatic spinocellular carcinoma of the skin
- cervical carcinoma in situ
- carcinoma in situ of the vocal cords.

There is no consensus on donors with transitional cell carcinoma of the bladder at the TaG1 Tumour Node Metastasis (TNM) stage. Screening for prostate cancer is different from country to country and is suggested only when there are reasons for such a test.

Donors affected by certain low-grade (grades 1 and 2) brain tumours (Table 21) are suitable for kidney donation. Individuals affected by brain tumours of any grade who have undergone ventriculo-peritoneal shunting must be excluded because of the high risk of systemic dissemination of tumour cells through the shunt (LE: 3).

Table 21: Low-grade brain tumours that do not exclude organ donation

<table>
<thead>
<tr>
<th>Low-grade astrocytoma</th>
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<tbody>
<tr>
<td>Pituitary adenomas</td>
</tr>
<tr>
<td>Epidermoid cysts</td>
</tr>
<tr>
<td>Colloid cysts of the third ventricle</td>
</tr>
<tr>
<td>Pilocytic astrocytoma, ependymoma</td>
</tr>
<tr>
<td>Low-grade oligodendroglioma (Schmidt A and B)</td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
</tr>
<tr>
<td>Ganglionic cell tumour (ganglioma, gangliocytoma)</td>
</tr>
<tr>
<td>Benign meningioma</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
</tr>
<tr>
<td>Haemangioblastoma (not associated with Von Hippel Lindau syndrome)</td>
</tr>
<tr>
<td>Acoustic Schwannoma</td>
</tr>
<tr>
<td>Pineocytoma</td>
</tr>
<tr>
<td>Well-differentiated teratoma</td>
</tr>
</tbody>
</table>

When a kidney has been transplanted from a donor with a post-transplant diagnosis of cancer, graft nephrectomy and suspension of immunosuppression are not always necessary. The risks and benefits should be discussed with the recipient.

Due to a low risk of recurrence, kidneys with small renal cell carcinoma (RCC) can be considered for local excision and transplant after the recipient has given informed consent. The risk of RCC transmission to the contralateral kidney and/or to other organs is even lower; again, the patient’s informed consent is necessary (LE: 4).

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Donors with active cancer or history of metastatic cancer and cancers with a high risk of recurrence should not be considered as possible donors.</td>
<td>C</td>
</tr>
<tr>
<td>A prior history of neoplasia is no longer an absolute contraindication for organ donation.</td>
<td>C</td>
</tr>
</tbody>
</table>
8.2 Prior malignancy in the recipient
Any active tumour in the recipient is an absolute contraindication for kidney transplantation because of the risk of dissemination and fatal outcome. However, a previous history of cancer does not automatically exclude transplantation. It can be difficult to decide who should be considered as suitable for transplantation and particularly ‘when’. So far, clinical decision has been mainly based on the Cincinnati Registry, which essentially considers the type of tumour and the delay between its treatment and kidney transplantation. However, a better approach would be based on type of tumour, TNM stages, and the risk of recurrence after treatment.

For most tumours, the waiting time for transplantation is 2 years on the Registry. However, a 2-year waiting period would eliminate only 13% of colorectal recurrences, 19% of breast cancer recurrences, and 40% of prostatic cancer recurrences (7,8). In contrast, a 5-year waiting period would eliminate most recurrences, but this is not practical in the elderly (9) and unnecessary for most tumours. There is therefore not enough evidence to support a fixed waiting period before transplantation.

Recipients who have tumours with a low recurrence rate can be considered for immediate transplantation after successful treatment of the tumour (e.g. incidental RCC, non-melanoma skin cancer, and in-situ uterine/cervical cancer). In the remaining cases, because of the risk of dormant metastases, the waiting period should be individualised according to the type and TNM stage and grade of the tumour, age and recipient’s general condition. Patients on the waiting list and after transplantation must be evaluated regularly to detect recurrence (LE: 4).

Modification of immunosuppression may be considered in these patients following a recent report that the use of m-TOR inhibitors is associated with a reduced incidence of malignancy (10), as is similarly a reduction in immunosuppressive therapy.

Recommendations

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Any active tumour in the recipient is an absolute contraindication for kidney</td>
<td>C</td>
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<tr>
<td>transplantation because of the risk of dissemination and fatal outcome.</td>
<td></td>
</tr>
<tr>
<td>The waiting period before transplant in recipients with a history of malignancy</td>
<td>C</td>
</tr>
<tr>
<td>depends on the type, TNM stage and grade of the tumour, and recipient’s age and</td>
<td></td>
</tr>
<tr>
<td>general health.</td>
<td></td>
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<tr>
<td>Recipients with tumours that have a low recurrence rate can be considered for</td>
<td>C</td>
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<tr>
<td>immediate transplantation after successful treatment.</td>
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</tr>
<tr>
<td>Close follow-up is mandatory particularly after transplantation.</td>
<td>C</td>
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</tbody>
</table>

TNM = Tumour Node Metastasis

Patients with ESRD on the waiting list for kidney transplantation will be ageing, and thus carry a higher, potential risk of latent neoplasia being activated following kidney transplantation. Candidates for kidney transplantation, particularly > 50 years old, should be screened for the presence of a pre-existing cancer (Table 22).

Table 22: Screening of potential recipients for malignancy

| Exhaustive history and physical examination, including a dermatological examination |
| Gynaecological examination: vaginal cytology and colposcopy, regardless of age |
| Mammography in women over 40 years old or with a family history of breast cancer |
| Prostate examination: prostate-specific antigen (PSA) levels and digital rectal examination (DRE) in men aged over 50 years |
| Faecal occult blood testing or colonoscopy according to current guidelines |
| Chest x-ray |
| Abdominal ultrasound to exclude renal cell carcinoma or other abdominal tumour |

8.3 ‘De-novo’ tumours in the recipient
The risk of cancer after kidney transplantation is several times higher than in the general population (11,12). Post-transplantation cancer is one of the most common long-term causes of death; with up to 35% of heart transplant recipients dying of cancer (13). Most malignancy affects the skin (40%) or the lymphatic system (11%). Several factors contribute to the high prevalence of cancers in transplant recipients (Table 23). Annual screening is mandatory to detect a new cancer or co-morbidity.
Table 23: Factors increasing risk of de-novo tumour in recipient

<table>
<thead>
<tr>
<th>Factors</th>
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<tbody>
<tr>
<td>Sun exposure: skin cancer</td>
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<tr>
<td>Analgesic abuse: urothelial cancer</td>
</tr>
<tr>
<td>Acquired multicystic renal disease: renal cancer</td>
</tr>
<tr>
<td>Immunosuppressants, e.g. CNIs and lymphocyte-depleting antibodies</td>
</tr>
<tr>
<td>Viral infections, e.g. EBV, herpes 8 virus, human papillomavirus, HBV, HCV, HEV</td>
</tr>
</tbody>
</table>

8.3.1 Skin cancer and Kaposi’s sarcoma
The risk of skin cancer increases with age (> 50 years) (14), cyclosporine (10), and duration of immunosuppression. Its incidence rises with time to 5% at 5 years, 16% at 10 years, and 52% at 20 years’ post transplant (15). Skin cancer represents 40-60% of post-transplantation tumours, with up to 50% of all skin cancers being squamous cell. The male-to-female ratio is 4.8 to 1.3 (16). It is closely linked to sun and ultraviolet exposure, the presence of HLA-B27 antigen and the degree of immunosuppression. Skin cancer often recurs, particularly in heart and kidney recipients (17). An annual dermatological examination and use of total sun block are recommended (18,19) (LE: 2a).

The prevalence of Kaposi’s sarcoma ranges from 0.5% to 4%, depending on the country (20). It is associated with HHV-8 positive serology. Screening for HHV8 in high-risk patients (Mediterranean countries) and prophylactic measures may be considered (21) (LE: 3). The use of m-TOR inhibitors may be preferable over CNIs, which seem to promote the appearance of Kaposi’s sarcoma (19) (LE: 3).

Recommendations

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<th>Recommendations</th>
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<tbody>
<tr>
<td>Oral and written information on the risk of skin cancer and protective measures should be given.</td>
<td>C</td>
</tr>
<tr>
<td>Dermatological examination before, and at least annually after, transplantation is mandatory.</td>
<td>C</td>
</tr>
<tr>
<td>The use of m-TOR inhibitors instead of Calcineurin-inhibitors is advised in patients with Kaposi’s sarcoma or a history of Kaposi’s sarcoma.</td>
<td>C</td>
</tr>
</tbody>
</table>

8.3.2 Lymphatic disease
Post-transplantation lymphoproliferative disease (PTLD) is a life-threatening complication because of extra-nodal dissemination and a poor outcome (12,22). The incidence (1-5%) has increased since the introduction of cyclosporine (23) and the induction regimen by ALG and OKT3 with a SIR (standardized incidence ratio) between 9 and 29 (24). The disease usually occurs within the first year after transplantation and is characterised by non-Hodgkin’s lymphomas and EBV-infected B-lymphocytes. Treatment involves reduction or even suspension of immunosuppressive therapy, with a remission rate of 50-68%. Anti-CD20 antibody therapy, with or without chemotherapy, and antiviral drugs (acyclovir, ganciclovir) may be helpful (25,26) (LE: 3).

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Use of induction therapy with T-cell depleting agents should be restricted whenever possible.</td>
<td>C</td>
</tr>
<tr>
<td>Clinical examination every 3 months during the first post-transplant year is advised for young recipients and for patients who have received T-cell depleting agents.</td>
<td>C</td>
</tr>
</tbody>
</table>

8.3.3 Gynaecological cancers
Cervical cancer is 3 to 16 times more common in transplanted females compared to the general population. In 70% of cases, it will be in-situ carcinoma or cervical intraepithelial neoplasia (CIN).

Cervical cancer appears to be arising from infection of the cervix with sexually transmitted oncogenic strains of human papillomavirus (HPV). Increased risk of cervical cancer in transplant recipients is due to re-activation of latent HPV in the immunosuppressed recipient. The prevalence of HPV in the cervix of transplanted females is almost 45%, though this figure is currently decreasing, as is also CIN prevalence (27). Data on successful HPV immunization are not available, but young female transplant recipients may benefit from HPV immunisation.

Annual colposcopy and cytology are required. Mammography and gynaecological ultrasound should be periodically performed, although formal evidence for this preventive strategy is lacking (28) (LE: 4).

8.3.4 Prostate cancer
The prevalence of clinical prostatic adenocarcinoma in the male transplanted population is 0.3% to 1.8%. Prevalence increases with the age of the recipient and can reach 5.8% if PSA screening is performed in all males. All recipients over 50 years old should have an annual PSA test and DRE. Prostate serum antigen levels
are not modified by kidney transplantation and most prostate cancers detected in transplanted patients are clinically localised (84%) at diagnosis (29) (LE: 4).

8.3.5 **Bowel cancer**
The association of colon cancer with kidney transplantation is much more controversial than for other cancers, even though an increased risk factor of 2.6 has been reported at 10 years' post transplant. However, it is difficult to advise on the most appropriate method of follow-up and its frequency. An annual faecal blood test is acceptable and cost-effective, but not performed routinely worldwide. Colonoscopy every 5 years is also acceptable in the absence of other factors implying a high risk of colon cancer, despite the absence of data on screening in this population. A risk factor is the re-activation of CMV and EBV infections (28) (LE: 4).

8.3.6 **Urothelial tumours**
The incidence of urothelial tumours is three times higher than in the general population (29). Tumours are usually transitional cell neoplasia, though the incidences of bladder adenocarcinoma and nephrogenic adenoma have both increased. Urinary cytology is routinely performed in patients with microhaematuria, analgesic nephropathy, or a prior history of urothelial cancer, despite its poor sensitivity of 30%. Recipients with gross haematuria should undergo a detailed study of the whole urinary system, bladder, ureters, and kidneys.

8.3.7 **Renal tumours**
Renal cell carcinoma usually occurs in the patient’s own kidneys, but can also present in the graft. The prevalence ranges between 0.5% and 3.9%, which is 10 to 100 times greater than in the general population (29). The main risk factor is the presence of acquired chronic kidney disease (ACKD). Other risk factors include previous history of RCC, Von Hippel Landau disease, and (perhaps) polycystic kidneys. The main histological patterns are RCC and tubulopapillary carcinoma (30).

Annual ultrasound of the patient’s native kidneys and the graft is recommended (28,29) (LE: 4). Any renal solid tumour should be treated with retroperitoneoscopic or laparoscopic nephrectomy (LE: 4).

8.3.8 **Chest x-ray**
An annual chest x-ray is recommended in order to detect lung cancer and cardiothoracic abnormalities (28) (LE: 4).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The risk of cancer is several times greater in transplanted patients than in the general population and is the main concern of the medical team in the long-term follow-up of all organ recipients.</td>
<td>B/C</td>
</tr>
<tr>
<td>Screening should be carried out annually for cancers of the skin, lymphatic system and native kidneys. For all other organs, screening should be the same as in the general population.</td>
<td>B/C</td>
</tr>
</tbody>
</table>

8.4 **References**


9. ANNUAL SCREENING

The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population (1,2). Cancer is a cause of significant morbidity and mortality in the transplanted population (1). Cardiovascular disease is the most frequent cause of death in renal allograft recipients (2,3) (LE: 3).

9.1 Recommendations for annual screening

The following recommendations can be made for annual screening of a transplant recipient. They include:

• Lifelong regular post-transplant follow-up by an experienced and trained transplant specialist is strongly recommended at least every 6-12 months.
• More frequent follow-up visits (e.g. every 4-8 weeks) for renal function and immunosuppression and side-effects by a physician.
• Annual screening should include a dermatological examination, tumour screening (including a nodal examination, faecal occult screening, chest x-ray, gynaecological and urological examination), and an abdominal ultrasound, including ultrasound of the native and transplanted kidney).
• Special attention during post-transplant care should also focus on proteinuria, recurrence of original disease.
• Posttransplant care should aim to detect cardiac disease and cardiovascular risk factors. Cardiac exam and cardiac history should be taken, and if appropriate further diagnostic tests should be prompted to exclude the progression of cardiac disease.
• Blood pressure, blood glucose and blood lipids should be determined at appropriate intervals, and adequate measures to control these risk factors should be instituted.
• The physician should also focus on the adequate prophylaxis, detection and treatment of concomitant diseases (e.g. bone disease, anaemia) and infections.

9.2 References


### 10. GRAFT AND PATIENT SURVIVAL

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft survival following unselected kidney transplantation should be at least 85% after 1 year and 70% after 5 years (1,2) (Figure 1).</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Patient survival following unselected kidney transplantation should be at least 90% after 1 year and 85% after 5 years (1,2) (Figure 2).</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

**Figure 1: Improvement of graft survival following kidney transplantation during the last two decades**

Reproduced from CTS Collaborative Transplant Study by kind permission of Prof. Dr. G. Opelz, Heidelberg, Germany.
This general outcome following kidney transplantation depends on several criteria that are discussed below:

10.1 Deceased and living donors

10.1.1 Graft survival

Graft survival after living-donor kidney transplantation is generally better than after deceased-donor kidney transplantation (Figure 3). A better selection of donors, absence of brain death and a shorter cold ischaemia time are the most likely explanations.

Figure 3: Graft survival following deceased- and living-donor kidney transplantation

The 1-year graft survival of living-donor kidney is in mean 97% for HLA-identical siblings and 95% for 1-haplotype-identical related donors compared to 88% for deceased-donor kidneys (Figure 4). The 3-year graft
survival of living-donor kidney is in mean 95% for HLA-identical siblings and 90% for 1-haplotype-identical related donors compared to 83% for deceased-donor kidneys (Figure 4).

Figure 4: Graft survival following deceased- and living-donor kidney transplantation.

![Relationship First Kidney Transplants 1997-2005](image)

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Excellent graft outcomes have been reported in unrelated living-donor transplantation, even if the donor-recipient pairs were poorly HLA-matched (3). CTS data show that poorly matched kidneys from unrelated living donors demonstrate a much better outcome than poorly matched kidneys from deceased donors. However, this difference almost disappears in donors aged between 15 and 45 years old (Figure 5). This suggests that a good outcome in unrelated living-donor transplantation may mainly be due to optimal selection of donors and absence of brain death.

Figure 5: Graft survival in poorly HLA-matched deceased-donor and unrelated living-donor kidney transplantation

![Unrelated Living vs Cadaver Donors 1997-2005](image)

Reproduced from CTS Collaborative Transplant Study by kind permission of Prof. Dr. G. Opelz, Heidelberg, Germany.
Husband-to-wife and wife-to-husband transplantations performed between 1991 and 2005 show virtually identical results with a 3-year graft survival of 87% (Figure 6). If a wife recipient has been pregnant, the outcome may be worse (3).

**Figure 6: Graft survival in living unrelated kidney transplantation**

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10.1.2 **Patient survival**

Nowadays, patient survival following living-donor kidney transplantation is about 98% after 1 year and 90% after 5 years. This is better than patient survival following deceased donor kidney transplantation with a 1-year survival rate of 95% and a 5-year survival rate of about 80% (1,2).

10.2 **Age of donor and recipient**

10.2.1 **Donor's age**

The donor’s age has a highly significant influence on the outcome of kidney transplantation in deceased-donor transplantation. With increasing age of donor (except in paediatric transplantation), there is a worsening of initial function, long-term function and survival rate. The 3-year graft-survival rate of a deceased-donor transplant is up to 20% higher for donors aged 18-30 years than for donors older than 70 years (Figure 7) (1,2,4).
Other than in deceased-donor transplantation, donor’s age appears to influence graft outcome only marginally in living-donor transplantation (4). The most likely interpretation of this difference is that living donors are selected for organ donation based on their general status of health whereas such selection is not made in the case of deceased donor transplantation. Furthermore, it is likely that the process of brain death, which is associated with the release of cytokines, chemokines, etc., further contributes to the lower success of grafts from elderly deceased donors.

10.2.2 Recipient’s age
The recipient’s age has an important impact on transplant outcome (5). Five-year graft survival in recipients aged 18-34 years is 72% versus 59% in recipients more than 65 years old (2). Nevertheless, the transplantation of kidneys from old donors to old recipients is feasible with acceptable success rates (6). The importance of HLA-matching is not clear in this ‘old for old’ group.

10.3 Histocompatibility-matching
Despite impressive improvements in graft success rates in recent years (Figure 1), the ‘relative’ impact of HLA compatibility on graft outcome has not changed. Between 1995 and 2004, the relative risk for graft loss was 0.77 for 0-1 HLA-A+B+DR mismatches and 1.17 for 5-6 HLA-A+B+DR mismatches. These relative risk values were almost identical with the 0.76 and 1.16 values calculated for 0-1 and 5-6 mismatches, respectively, for transplantations between 1985 and 1994 (7,8).

According to UNOS, in patients transplanted between 1997 and 2005, recipients of 0 HLA-A+B+DR mismatched deceased-donor kidneys showed an 11% lower 5-year graft survival than recipients of 6 mismatched kidney transplants which is similar to the CTS data (Figure 8). Also similar to the findings in the CTS database, UNOS data confirm that graft outcome gradually worsens with every additional mismatch (2). HLA matching is still important even with ‘modern’ immunosuppressive agents such as tacrolimus, MMF, rapamycin, or IL-2 receptor antibodies (Figure 9). It is still debatable whether HLA-DR compatibility influences graft outcome more than compatibility for HLA-A+B.
Figure 8: Impact of HLA compatibility on deceased-donor kidney graft survival

Reproduced from CTS Collaborative Transplant Study by kind permission of Prof. Dr. G. Opelz, Heidelberg, Germany.

Figure 9: Impact of HLA compatibility on kidney graft survival under ‘modern-day’ immunosuppression

Reproduced from CTS Collaborative Transplant Study by kind permission of Prof. Dr. G. Opelz, Heidelberg, Germany.

CYA = cyclosporine A; MPA = mycophenolate mofetil; RAPA = rapamycin.
10.4 Immunosuppression

Data from the CTS study clearly demonstrates the advantage of cyclosporine A-based immunosuppression. Graft-survival rates are about 15% superior to survival rates following immunosuppression without cyclosporine A (Figure 10). However, different combinations of ‘modern’ immunosuppressive drugs do not appear to result in major differences in graft outcome (Figure 11).

Figure 10: Influence of cyclosporine A-based immunosuppression on kidney graft survival in first transplant recipients

![Graph showing graft survival rates](image1.png)

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CYA = cyclosporine A; FK: FK506; MMF: mycophenolate mofetil; AZA = azathioprine; STE = steroids.

Figure 11: Influence of different immunosuppressive agent combinations on graft survival following kidney transplantation

![Graph showing graft survival rates](image2.png)

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CYA = cyclosporine A; FK: FK506; AZA = azathioprine; MMF: mycophenolate mofetil.
10.5 Number of transplantations
The 4-year graft survival rate decreases by about 5% from the first to second and second to third transplantation. The 4-year graft survival rate for the first deceased-donor transplantation is 80% versus 75% for the second, 70% for the third, and 63% for the fourth or more transplants (Figure 12). For living donors, the worsening of graft function between first and second transplantation is less marked (about 2%) (1).

Figure 12: Number of transplantations and kidney graft survival

![Graph showing graft survival rates for different numbers of transplantations.](image)

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10.6 Cold ischaemia time
The success of unrelated living-donor kidney transplantation suggests that short cold ischaemia time plays an important role in kidney transplantation. However, according to CTS data, graft survival is influenced only marginally by ischaemia times up to 24 h (Figure 13) and that HLA matching has a significant effect on outcome, even with a short ischaemic preservation time (Figure 14). Compared to other preservation solutions, UW-solution was associated with significantly better outcome in the CTS study with ischaemia > 24 h (7).
Figure 13: Impact of cold ischaemia time on graft survival in deceased-donor kidney transplantation

![Cold Ischaemia Time](image)

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Figure 14: HLA-match dependent impact of cold ischaemia time on graft survival in deceased-donor kidney transplantations performed between 1990 and 2005

![Cold Ischemia - HLA-A+B+DR Mismatches](image)

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10.7 Time on dialysis

According to CTS data, graft outcome is best if the patient never received dialysis and diminishes with every additional year of dialysis treatment (Figure 15). These findings are in agreement with data from reports that underline the importance of pre-emptive transplantation (9).
Figure 15: Impact of time on dialysis on graft survival in deceased-donor kidney transplantation

![Graph showing impact of time on dialysis on graft survival in deceased-donor kidney transplantation.](image)

Reproduced from CTS Collaborative Transplant Study by kind permission of Prof. Dr. G. Opelz, Heidelberg, Germany.

### 10.8 References

11. ABBREVIATIONS USED IN THE TEXT

This list may not include the most commonly known abbreviations

- ABO: blood group system consisting of groups A, AB, B and O
- ACD: acid-citrate-dextrose
- ACKD: acquired cystic kidney disease
- ACR: acute cellular rejection
- ADPKD: autosomal dominant polycystic kidney disease
- AHR: acute humoral rejection
- ALG: anti-lymphocyte globulin
- AM: acceptable mismatch
- Anti-GBM: anti-glomerular basement
- ATG: anti-thymocyte globulin
- AVF: arterio-venous fistula
- AZA: azathioprine
- BMI: body mass index
- CAR: chronic allograft rejection
- CDC: complement-dependent cytotoxicity test
- CMV: cytomegalovirus
- CNIs: Calcineurin-inhibitors
- CsA-ME: cyclosporine A micro-emulsion
- CT: computed tomography
- CYA: cyclosporine A
- DTT: dithiothreitol (test)
- DRE: digital rectal examination
- EAU: European Association of Urology
- EBV: Epstein-Barr virus
- EC: EuroCollins (solution)
- EC-MPS: enteric-coated mycophenolate sodium
- EDTA: ethylenediaminetetra-acetic acid
- EDHEP: European Donor Hospital Education Program
- ELISA: enzyme-linked immunosorbent assay
- ESRD: end stage renal disease
- ESWL: extracorporeal shockwave lithotripsy
- ET: Eurotransplant
- FSGS: focal and segmental glomerulosclerosis
- GFR: glomerular filtration rate
- GR: grade of recommendation
- HAR: hyper-acute rejection
- HbA1C: glycosylated haemoglobin
- HBcAb: hepatitis B core antibody
- HBsAg: hepatitis B surface antigen
- HBV: hepatitis B virus
- hCG: human chorionic gonadotrophin
- HCV: hepatitis C virus
- HIV: human immunodeficiency virus
- HLA: human leukocyte antigen, histocompatibility antigen
- HTK: histidine-tryptophan-ketoglutarates
- IF: interstitial fibrosis
- IL-2: interleukin-2
- IMPDH: inosine monophosphate dehydrogenase (inhibitors)
- IVIG: intravenous immunoglobulin
- LCDD: light-chain deposit disease
- LE: level of evidence
- LLDN: laparoscopic live donor nephrectomy
- MMF: mycophenolate mofetil
- MPA: mycophenolic acid
- MRI: magnetic resonance imaging
- NHBD: non-heartbeating donor
Conflict of interest
All members of the Renal Transplantation Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Lasers and Technologies

T.R. Herrmann, E.N. Liatsikos, U. Nagele, O. Traxer, A.S. Merseburger (chair)

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### 11. ABBREVIATIONS USED IN THE TEXT
1. INTRODUCTION

The European Association of Urology (EAU) Guidelines Office have set up a Guidelines Working Panel to analyse the scientific evidence published in the world literature on lasers in urological practice. The working panel consists of experts who, through these guidelines, present the findings of their analysis, together with recommendations for the application of laser techniques in urology. The guidelines also include information on the characteristics of lasers, which the panel believes will be very helpful to clinicians.

The aim of this document is to provide information on technical considerations and supplement the information in other EAU organ-specific guidelines documents, rather than be in competition.

These guidelines on the use of lasers and novel technologies in urology provide information to clinical practitioners on physical background, physiological and technical aspects, as well as present the first clinical results from these new and evolving technologies. Emphasis is given on interaction between technical tools and human tissue, surgical aspects and abilities, advantages and disadvantages of new tools, including operator convenience. In this document the panel focused on lasers, with the intention to expand further in the years to come.

The application of lasers in treating urological disorders is a swiftly developing area, with laser technology currently used for a variety of urological procedures. In some therapeutic areas, lasers have become the primary method of treatment and standard of care.

As with many other surgical or interventional procedures, there is a lack of high-quality publications. But particularly in the field of lasers, where technological advances are occurring so rapidly, many technologies will never be in use long enough for long-term study. This is obviously a challenge for anyone attempting to establish an evidence-based discussion of this topic, and the panel are very aware that these guidelines will require re-evaluating and updating within a short time frame. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences and individual circumstances of patients into account.

1.1  Safety
Safety is very important when using lasers. All intra-operative personnel should wear proper eye protection to avoid corneal or retinal damage. This is particularly important with neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers, which penetrate deeply and can burn the retina faster than the blink reflex can protect it. Although holmium:YAG (Ho:YAG) lasers do not penetrate as deeply, they can cause corneal defects if aimed at the unprotected eye. For all lasers, adequate draping should be used to cover external areas, with wet towels draped over cutaneous lesions. Ideally, reflective surfaces (e.g. metal instruments) should be kept away from the field of treatment; however, if this is not possible, the field of treatment should be draped with wet drapes. Furthermore, it is very dangerous to use a laser if oxygen is in use anywhere near the operative field, as this may result in a laser fire and significant burns (1).

1.2  Methodology
The primary objective of this structured presentation of the current evidence base in this area is to assist clinicians in making informed choices regarding the use of lasers in their practice. A secondary objective was to apply EAU Guidelines methodology to this area where there is limited evidence available.

1.2.1  Data identification
Structured literature searches using an expert consultant were designed for each section of this document. Searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform. The controlled terminology of the respective databases was used and both Mesh and Emtree were analysed for relevant entry terms.

The search strategies covered the last 25 years for Medline and for Embase (1974). A total number of 436 papers were identified, of which one was a Cochrane review (laser prostatectomy for benign prostatic obstruction (BPO) (2). A separate literature search for cost-effectiveness was carried out and yielded seven unique publications.
Publication history
A scientific paper is now available based on this document (4). This resulted in minor changes to this published version of the Guidelines on Laser Technologies.

Quality assessment of the evidence
The expert panel extracted relevant data from individual publications, the key findings of which are presented in tables throughout the document. Papers were assigned a level of evidence and recommendations have been graded following the listings in Tables 1 and 2.

Table 1: Level of evidence (LE)

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected Authorities.</td>
</tr>
</tbody>
</table>

Modified from Sackett et al. (3).

Table 2: Grade of recommendation (GR)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

Modified from Sackett et al. (3).

References
   http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD001987/frame.html
2. LASER-BASED TREATMENTS FOR BLADDER OUTLET OBSTRUCTION (BOO) AND BENIGN PROSTATIC ENLARGEMENT (BPE)

2.1 Introduction
Benign prostate obstruction (BPO) and enlargement (BPE) can be treated with a range of laser treatments using different laser systems and applications. The different systems produce different qualitative and quantitative effects in tissue, such as coagulation, vaporisation or resection and enucleation via incision (Table 3). Laser treatment is considered to be an alternative treatment to transurethral resection of the prostate (TURP). It must therefore achieve the same improvement in symptoms and quality of life (QoL) as TURP. It must also improve all urodynamic parameters, such as maximal urinary flow rate ($Q_{\text{max}}$), post-void residual urine volume (PVR) and maximal detrusor pressure ($P_{\text{detmax}}$) with less morbidity and shorter hospitalisation than with TURP.

This section focuses on contemporary laser treatments for the management of BPE or BPO.

2.2 Physical principles of laser action
LASER is an acronym that stands for Light Amplification by Stimulated Emission of Radiation. Laser radiation is simply the directed light of a narrow bandwidth. This is synonymous to a single colour and applies to all regions of the invisible and visible electromagnetic spectrum (1).

2.2.1 Reflection
When the laser beam encounters tissue, a percentage of the beam is reflected by the boundary layer and may therefore heat and damage surrounding tissue. Reflection mainly depends on the optical properties of the tissue and the irrigant surrounding it. Because reflection is not very much affected by wavelength, it can be ignored when evaluating a laser wavelength for surgical purposes.

2.2.2 Scattering
The heterogeneous composition of tissue causes an intruding laser beam to scatter. Scattering diverts part of the laser beam away from its intended direction and therefore its intended purpose. The amount of scattering depends on the size of the particles and the wavelength of the laser. Shorter wavelengths are scattered to a much higher degree than longer wavelengths, i.e. blue laser radiation is scattered more than green, green more than red, and red more than infrared.

2.2.3 Absorption
Absorption is the most important process of light interaction, though it is not the only process. Intensity of the laser beam decreases exponentially as the absorbing medium increases in density. Absorbed laser radiation is converted into heat, causing a local rise in temperature. Depending on the amount of heat produced, tissue will coagulate or even vaporise. Heat is more likely to be generated next to the tissue surface than further below because of the exponential decrease in beam intensity as it passes into the tissue and the immediate action of the absorption process.

However, absorption can only occur in the presence of a chromophore. Chromophores are chemical groups capable of absorbing light at a particular frequency and thereby imparting colour to a molecule. Examples of body chromophores are melanin, blood and water. Figure 1 shows the wavelength dependence and absorption length of a laser beam. The absorption length defines the optical pathway, along which 63% of incident laser energy is absorbed.

2.2.4 Extinction length
The extinction length defines the depth of tissue up to which 90% of the incident laser beam is absorbed and converted into heat. An extinction length is equal to 2.3 absorption lengths. Haemoglobin and water are widely used as chromophores for surgical lasers (Figure 1).

For a short time after absorption of a circular laser beam, the generated heat is confined in a cylindrical-shaped volume, which has the height of the laser beam’s extinction length and the approximate diameter of the laser fibre. The density of the absorbed energy determines the effect of the laser on tissue.

It is important to match the achieved effect along the extinction length with the intended surgical effect. At the same power wattage, a laser wavelength with a long extinction length may create a deep necrosis, whereas a laser wavelength with a much shorter extinction length will produce an increase in temperature above boiling
point and immediate vaporisation of tissue.

Table 3: Lasers: crystals, abbreviations, wavelength, techniques and acronyms

<table>
<thead>
<tr>
<th>Active crystal</th>
<th>Abbreviation</th>
<th>Wavelength (nm)</th>
<th>Technique</th>
<th>Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmium</td>
<td>Ho:YAG</td>
<td>2140</td>
<td>Holmium laser ablation</td>
<td>HoLAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Holmium laser resection of prostate</td>
<td>HoLRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Holmium laser enucleation of prostate</td>
<td>HoLEP</td>
</tr>
<tr>
<td>Neodym</td>
<td>Nd:YAG</td>
<td>1064</td>
<td>Visual laser ablation of prostate</td>
<td>VLAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contact laser ablation of prostate</td>
<td>CLAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interstitial laser coagulation of prostate</td>
<td>ILC</td>
</tr>
<tr>
<td>Kalium titanyl phosphate</td>
<td>KTP:Nd:YAG (SHG)</td>
<td>532</td>
<td>Photoselective vaporisation of prostate</td>
<td>PVP</td>
</tr>
<tr>
<td>Lithium borate</td>
<td>LBO:Nd:YAG (SHG)</td>
<td>532</td>
<td>Photoselective vaporisation</td>
<td>PVP</td>
</tr>
<tr>
<td>Thulium</td>
<td>Tm:YAG</td>
<td>2013</td>
<td>Thulium laser vaporisation of prostate</td>
<td>ThuVAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thulium laser vaporesection of prostate</td>
<td>ThuVARP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thulium laser vapoenucleation of prostate</td>
<td>ThuVEP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thulium laser enucleation of prostate</td>
<td>ThuLEP</td>
</tr>
<tr>
<td>Diode lasers</td>
<td>-</td>
<td>830</td>
<td>Interstitial laser coagulation of prostate</td>
<td>ILC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>940</td>
<td>Vaporisation</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>980</td>
<td>Vaporisation</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1318</td>
<td>Vaporisation</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1470</td>
<td>Vaporisation</td>
<td>-</td>
</tr>
</tbody>
</table>

2.3 Historical use of lasers

2.3.1 Nd:YAG laser

The Nd:YAG laser has a wavelength of 1064 nm. It has a long extinction length and penetrates tissue by approximately 4-18 mm, making it suitable for haemostasis and tissue coagulation. At that time it appeared to be ideal for the treatment of benign prostatic hypertrophy (BPH) (2). Since 1985, many Nd:YAG laser-driven transurethral treatments have been described for both BPE and BPO (3).

2.3.2 Nd:YAG laser-based techniques

Several Nd:YAG approaches have been extensively studied, including: visual laser ablation of the prostate (VLAP) (4); contact laser ablation of the prostate (CLAP) (5); interstitial laser coagulation (ILC) (6), and Nd:YAG laser hybrid techniques (7).

However, all these techniques have been superseded by the advent of newer laser-based techniques (8). As these techniques are no longer contemporary, they will not be discussed further in these guidelines. However, they are discussed in the EAU guidelines on the conservative treatment of non-neurogenic male lower urinary tract symptoms (LUTS) (9).

2.4 References


3. CONTEMPORARY LASER SYSTEMS

3.1 Introduction

Following the first generation of laser-based treatments for BOO and BPE, four (groups of) laser systems are currently used:

- KTP (kalium titanyl phosphate, KTP:Nd:YAG [SHG]) and LBO (lithium borat, LBO:Nd:YAG [SHG]) lasers;
- Diode lasers (various);
- Holmium (Ho):YAG (yttrium-aluminium-garnet) lasers;
- Thulium (Tm):YAG (yttrium-aluminium-garnet) lasers.

All the above-mentioned contemporary (and historical) laser therapies for the treatment of BOO and BPE use physiological sodium 0.9% solution for irrigation. This eliminates the risk of hypotonic hypervolaemic transurethral resection of the prostate (TURP) syndrome, which occurred in 1.4% of patients in large TURP reported series (1). A second advantage (that applies to all endoscopic minimal invasive therapies for the prostate) is the avoidance of secondary wound healing skin disorders, which occurred in 5.5% of the patients in a major series of open prostatectomy (OP) (2).

3.2 KTP (kalium titanyl phosphate, KTP:Nd:YAG [SHG]) and LBO (lithium borat, LBO:Nd:YAG [SHG]) lasers

The KTP and LBO lasers are both derived from the Nd:YAG laser. The addition of a KTP or LBO crystal to the laser resonator converts the Nd:YAG wavelength from 1064 nm to 532 nm. This is a green wavelength, which is strongly absorbed by oxyhaemoglobin. The resultant laser has a short extinction length and penetrates vascular tissue by only a few micrometres. In red, well-circulated tissue, the density of absorbed power is high and immediately raises the tissue temperature above the boiling point (Figure 1). This causes tissue to vapourise, leaving behind a coagulated seam where the increased tissue temperature has resulted in haemostasis (3). In this seam, haemoglobin is bleached but not vaporised. The applied laser energy must travel through the coagulated seam, where the laser beam experiences mainly scattering. The lack of absorption in coagulated tissue impairs its removal, while the scattering of the green wavelength reduces the laser beam’s intensity, impairing its vapourising effect on the next tissue layer (4).
Figure 1: Wavelength of different laser types, depth of penetration in media and absorption coefficient


3.2.1 Physical properties
All new lasers are extensively studied in preclinical trials in comparison with the most common vaporising laser, i.e. an 80 W KTP or 120 W LBO laser. The specific heat capacities of renal (3.89 kJ/kg/°K) and prostatic tissues (3.80 kJ/kg/°K) are almost equivalent, so making the isolated, blood-perfused, porcine kidney a very useful model for the study of laser procedures (5).

Animal models have been very useful in evaluating laser characteristics, including tissue ablation rate, efficacy of ablation in correlation to the power setting (output power efficiency), haemostatic properties, and the extent of morphological tissue necrosis. Table 4 provides a comparison of different lasers and their individual characteristics derived from a series of ex-vivo comparison studies in a porcine, perfused kidney model. The data has been given as a statistical mean or interval, according to the original publication.

3.2.1.1 Ablation capacity
The tissue ablation rate achieved with KTP and LBO lasers increases with increasing output power. In comparison to the Tm:YAG laser (70 W) KTP laser, the tissue ablation rate reached 3.99 g/10 min (80 W KTP) and 6.56 g/10 min (70 W Tm:YAG) (p < 0.05). When compared to TURP, both laser devices produced significantly lower rates of tissue removal (8.28 g/10 min) (6). However, the LBO laser, with its tissue ablation rate of 7.01 g/10 min laser ablation at 120 W offered a significantly higher ablation capacity compared with KTP laser at 80 W (p < 0.005) (7).

3.2.1.2 Bleeding rate
The KTP laser shows excellent haemostatic potential, with a bleeding rate for the 80 W KTP laser of 0.21 g/min compared with 0.16 g/min for the continuous wave (cw) 70 W Tm:YAG laser. In contrast, TURP is associated with a much higher bleeding rate of 20.14 g/min (p < 0.05) (6). The bleeding rate for the 120 W LBO laser was also higher at 0.65 g/min when compared to 80 W KTP with 0.21g/min, respectively (p < 0.05) (7).

3.2.1.3 Coagulation zone
In the porcine perfused kidney tissue ablation model, the KTP laser (p = 0.05) showed a 2.5-fold deeper coagulation zone (666.9 μm) than the cw Tm:YAG (264.7 μm) laser and TURP (287.1 μm). Tissue ablation resulted in a dense coagulation zone at the tissue surface (6). The corresponding depths of the coagulation zones at 120 W LBO laser and 80 W KTP laser were 835 μm and 667 μm (p < 0.05), respectively (7).
Table 4: Ex-vivo study on ablative capacity, haemostatic properties and coagulation zone due to tissue penetration in porcine perfused kidney model

<table>
<thead>
<tr>
<th>Study</th>
<th>Bach et al. 2010 (8)</th>
<th>Heinrich et al. 2010 (7)</th>
<th>Wendt-Nordahl et al. 2008 (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Type</td>
<td>Tm:YAG</td>
<td>KTP</td>
<td>Tm:YAG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LBO</td>
<td>KTP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HF (TURP)</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>2013</td>
<td>2013</td>
<td>2013</td>
</tr>
<tr>
<td>Power setting (W)</td>
<td>70</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Tissue ablation rate (g/10 min)</td>
<td>9.80</td>
<td>16.41</td>
<td>3.99 ± 0.69</td>
</tr>
<tr>
<td>Bleeding rate (g/min)</td>
<td>0.11</td>
<td>0.15</td>
<td>0.21 ± 0.07</td>
</tr>
<tr>
<td>Coagulation zone (mm)</td>
<td>0.36</td>
<td>0.40</td>
<td>0.667</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.835</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2647</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.669</td>
</tr>
</tbody>
</table>
| KTP = kalium titanyl phosphate; LBO = lithium borate; Tm:YAG = Thulium: yttrium aluminium garnet.

3.2.2 Surgical technique of KTP/LBO lasers

Both KTP and LBO lasers operate at a wavelength at which absorption in water is minimal. In the absence of a haemoglobin molecule, the extinction length increases dramatically and the beam penetrates deeply into irrigant and/or tissue. This technique is described as the photoselective vaporisation of prostate (PVP) (9). In addition, side-firing fibres are used in PVP to ensure that the surgeon has better, direct, visual control of the point at which the laser beam strikes the tissue.

Laser energy is directed towards prostatic tissue using a 70° 600 μm side-firing probe. Under direct vision, vaporisation is performed with a fibre-sweeping technique, starting at the bladder neck and continuing with the lateral lobes and the apex. The prostate gland is vaporised from inside the gland to its outer layers. This also occurs with TURP, but in contrast to TURP, no tissue remains for histopathological evaluation (10).

Since 2006, a LBO laser with a power of 120 W and collimated beam has been available (7,11).

As with all lasers, surgeon must wear safety goggles. These goggles must include a coloured filter in the KTP/LBO laser setting.

3.2.3 Urodynamic results and symptom reduction

In 1998, Malek et al. (12) showed that the 60 W KTP laser was both feasible and safe. Since then, most laser therapy trials prior to 2010 have used the 80 W KTP laser. There has been only limited data on the higher-powered 120-W LBO laser. Almost 10 years after the clinical introduction of 532-nm lasers, two randomised controlled trials (RCT) were published comparing 80 W KTP with TURP with follow-up periods up to 12 months (13,14). One of the trials compared 80 W KTP with OP (15), while the other trial compared 120 W LBO laser with TURP (16) (Table 5).

One RCT showed equivalent results to TURP (12) at 1-year follow-up, while another, non-randomised, two-centre study reported equivocal results (17). In contrast, a second RCT clearly showed that TURP resulted in greater urodynamic improvement (Qmax) than the KTP PVP laser (14). Another study comparing KTP PVP with OP showed equivalence in Qmax improvement, PVR and symptom score reduction at 18-month follow-up (15). Prostate-specific antigen (PSA), as a surrogate marker of tissue removal, decreased by 68.2% with OP and 61.2% with KTP PVP (15). However, other studies have reported much lower rates for PSA reduction using KTP PVP, including 45% reduction (18), 41.7% (19) and 37% (20).

Kalium titanyl phosphate PVP showed a higher retreatment rate in larger prostates > 80 ml within a 12 month follow-up (21). The study comparing LBO PVP treatment with TURP showed equivalence in Qmax improvement, PVR and symptom score reduction at 36-month follow-up (16). PVP demonstrated reduced detrusor pressure at maximum flow (Pdetqmax) (22) at 1-year follow-up. In addition, prospective, non-randomised trials have demonstrated the safety and efficiency of LBO PVP laser in patients receiving ongoing oral anticoagulation (23), in patients with retention (24), or with prostates > 80 mL (21).

In studies comparing TURP with KTP PVP, OT time was significantly shorter in prostates larger than 80 ml by 30 to 50 min (17). This difference comes down to 9 min with the LBO PVP (120 Watt) (16).
Table 5: KTP and LBO lasers: improvement in urodynamic parameters, symptom score and PSA reduction

<table>
<thead>
<tr>
<th>Reference</th>
<th>Laser source (power)</th>
<th>Follow-up (mo)</th>
<th>Patients (n)</th>
<th>Mean prostate size (mL)</th>
<th>PSA reduction (%)</th>
<th>Change in symptoms (%)</th>
<th>Change in Q\textsubscript{max} (mL/s) (%)</th>
<th>PVR change (%)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouchier-Haydes et al. 2006 (13)</td>
<td>KTP PVP</td>
<td>12</td>
<td>38</td>
<td>42.4</td>
<td>n.a.</td>
<td>49.83</td>
<td>+12.1 (167)</td>
<td>81.63</td>
<td>1b</td>
</tr>
<tr>
<td>TURP</td>
<td>38</td>
<td>33.2</td>
<td>n.a.</td>
<td>50.23</td>
<td>+9.2 (149)</td>
<td>68.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horasanli et al. 2008 (14)</td>
<td>KTP PVP</td>
<td>6</td>
<td>39</td>
<td>86.1</td>
<td>31.8</td>
<td>30.68</td>
<td>+5.8 (157)</td>
<td>87.05</td>
<td>1b</td>
</tr>
<tr>
<td>TURP</td>
<td>37</td>
<td>88</td>
<td>44.6</td>
<td>68.31</td>
<td>+13.8 (225)</td>
<td>73.98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tasci et al. 2008 (17)</td>
<td>KTP PVP</td>
<td>24</td>
<td>40</td>
<td>108.4</td>
<td>56.8</td>
<td>82.66</td>
<td>+13.5 (307.7)</td>
<td>83.69</td>
<td>2a</td>
</tr>
<tr>
<td>TURP</td>
<td>41</td>
<td>104.2</td>
<td>78.7</td>
<td>83.33</td>
<td>+12.8 (306.4)</td>
<td>84.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skolarikos et al. 2008 (15)</td>
<td>KTP PVP</td>
<td>18</td>
<td>65</td>
<td>93</td>
<td>61.2</td>
<td>50</td>
<td>+7.4 (186)</td>
<td>84.53</td>
<td>1b</td>
</tr>
<tr>
<td>OP</td>
<td>60</td>
<td>96</td>
<td>68.2</td>
<td>59.52</td>
<td>+7.0 (187.5)</td>
<td>86.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Ansari et al. 2010 (16)</td>
<td>LBO</td>
<td>36</td>
<td>60</td>
<td>61.8</td>
<td>38.4</td>
<td>60.29</td>
<td>+9.6 (239)</td>
<td>78.9</td>
<td>1b</td>
</tr>
<tr>
<td>TURP</td>
<td>60</td>
<td>60.3</td>
<td>62.5</td>
<td>65.9</td>
<td>+13.6 (312.5)</td>
<td>80.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KTP = potassium titanyl-phosphate laser; LBO = lithium triborate; OP = open prostatectomy; PVP = photoselective vaporisation of the prostate; TURP = transurethral resection of the prostate.

3.2.4 Risk and complications, durability of results

3.2.4.1 Intra-operative complications

Several studies have proven the intra-operative safety of PVP with KTP and LBO lasers, including prospective studies (25–27) and RCTs in comparison to TURP (13,14,28,29) or OP (15). Furthermore, safety was demonstrated in subgroup analyses of patients with large prostates (30,31), receiving anticoagulant therapy (31,24), or in retention (31,24).

An RCT comparing 80 W KTP PVP with TURP demonstrated significantly less blood loss in KTP PVP (0.45 g/dL) versus TURP (1.46 g/dL, p < 0.005), resulting in a blood transfusion rate in TURP (13). Another RCT of 80 W KTP PVP compared with TURP supported these findings with a blood transfusion rate of 8.1% for TURP (14). In an RCT comparing LBO PVP to OP, the transfusion rate was 0% following KTP PVP, but 13.3% for OP (15). A total of 7.69% of patients in the KTP PVP group required intra-operative conversion to TURP for the control of bleeding, most probably due to capsule perforation (15). A study comparing LBO PVP laser therapy with TURP reported a blood transfusion rate of 20%, a capsule perforation rate of 16.7%, and a TURP syndrome of 5% for the TURP treatment arm, but none of these complications were reported for LBO PVP (16).

These findings are supported by a number of studies (not including RCTs). A major multicentre study of 500 patients comparing PVP to TURP reported an intra-operative bleeding rate in 3.6%, capsule perforation in 0.2% and conversion to TURP due to bleeding, prostate size or fibre defect in 5.2% of patients. No blood transfusions were necessary. The highest rate of intra-operative bleeding occurred in a subgroup of patients with prostates > 80 mL (5.7% of subgroup) (25). One non-RCT study of LBO PVP reported an intra-operative bleeding rate of 2.6%, capsule perforation of 1% and blood transfusion rate of 0.4% (27). In another non-RCT study of LBO PVP, various subgroups of patients were compared, including patients not in retention with patients in retention, patients taking anticoagulant therapy versus patients not taking anticoagulants, and prostate size < 80 mL versus > 80 mL. Intra-operative bleeding which required conversion to TURP occurred in 1.5-3.8% (> 80 mL). Capsule perforation occurred in 0.8-1.5% of patients taking anticoagulants (31). These findings have been supported by studies from other authors in the same patient subgroups (23,24,30,32).

3.2.4.2 Early post-operative complications

An RCT that compared KTP PVP to TURP in patients with prostates > 70 mL found a significantly higher rate of urinary retention after KTP PVP (15.3 vs 2.7%, p < 0.05). Reinterventions were necessary in 17.6% of patients following KTP PVP versus 0% for TURP (14). Another RCT reported 0% and 16.7% clot retention in KTP PVP and TURP, respectively, while transient urinary retention with recatheterisation occurred in 5% of both groups.
Urinary tract infection (UTI) occurred in 3.3% and 5% of KTP PVP and TURP, respectively, while re-admissions were necessary in 1.6% and 5%, respectively (13).

An RCT comparing KTP PVP with OP for prostatic adenomas > 80 mL showed no statistical significant difference in the incidence of post-operative complications. Prolonged dysuria was noted in 7.6% of KTP PVP and 11.6% of OP patients, while UTIs were reported in 21.5% of KTP PVP versus 27% of OP patients (15). In an RCT comparing LBO PVP with TURP, clot retention occurred in 10% of TURP-treated patients compared with none in the LBO PVP group. In the same study, dysuria within 30 days following surgery was reported in 31.7% of TURP and 93.3% of LBO PVP. In contrast, a non-RCT study on LBO PVP reported dysuria in 7.5-14.6% in all patient subgroups (31).

The above findings are supported by the data of a major study of 500 patients (25). Following PVP using the KTP laser, haematuria was reported in 9.8%, blood transfusion in 0.4%, revision in 0.6%, acute renal failure in 0.6%, urosepsis in 0.4%, dysuria in 14.8%, transient urge incontinence in 2.4%, and UTI in 6.8% (25). Haematuria was significantly more common in patients taking anticoagulation treatment (17.2 vs 5.4%, p = 0.001) (23) or with prostates > 80 mL (17.2 vs 9.8%, p < 0.05) (25). Patients with prostates < 40 mL had a significantly higher rate of dysuria than the overall study population (24.3 vs 14.8%, p < 0.01) (25).

3.2.4.3 Late complications and durability of results
The longest follow-up of an RCT in evaluating the longevity and long-term morbidity of KTP PVP and LBO PVP is the study of Al-Ansari comparing LBO PVP to TURP with a follow-up of 36 months (16). Longer follow-up of 60 months is presented by a non-randomised study of Hai. Retreatment with PVP due to recurrent adenoma occurred in 7.7% of 246 patients, three (1.2%) underwent incision of the bladder neck resulting in an overall retreatment rate of 8.9% (33).

In an RCT with a 6-month follow-up, 8.1% in the TURP group and 5.1% in the KTP PVP group underwent internal urethrotomy in response to a urethral stricture. Reintervention was required in 17.9% of patients treated with KTP PVP because coagulated tissue was significantly obstructing the bladder outlet. Retrograde ejaculation rates were similar in both groups (56.7% TURP and 49.9% KTP PVP) (14). Another RCT with a 12-month follow-up reported submeatal/urethral strictures or bladder-neck stenosis in 13.3% of TURP patients and 8.3% of KTP PVP patients (13). In an RCT of KTP PVP versus OP, and an 18-month follow-up, the reoperation rates due to urethral structure were 3.1% versus 1.6%, bladder neck contracture (0% vs 3.3%), or need for apical resection (1.5%), with a total of 4.6% of KTP PVP and 5% OP, respectively (15). Comparing LBO PVP with TURP reported a significantly lower retreatment rate of 1.8% for LBO PVP versus 11% for TURP. Bladder neck contractures were incised in 3.6% and 7.4%, respectively.

These findings are supported by a large case series RCT for KTP PVP, with a global retreatment rate of 14.8% due to recurrent or persisting adenoma tissue (6.8%), bladder neck strictures (3.6%), or urethral strictures (4.4%) (32). The limitation of this study lies in the number of patients available at 5-year follow-up (27/500) (25). Anticoagulation and urinary retention at the time of surgery have no significant influence on the rate of long-term complications (23,24).

It is possible that KTP PVP has reduced efficacy in patients with larger prostates. According to a prospective, multicentre study, PVP efficacy was lower in patients with KTP PVP because coagulated tissue was significantly obstructing the bladder outlet. Retrograde ejaculation rates were similar in both groups (56.7% TURP and 49.9% KTP PVP) (14). Another RCT with a 12-month follow-up reported submeatal/urethral strictures or bladder-neck stenosis in 13.3% of TURP patients and 8.3% of KTP PVP patients (13). In an RCT of KTP PVP versus OP, and an 18-month follow-up, the reoperation rates due to urethral structure were 3.1% versus 1.6%, bladder neck contracture (0% vs 3.3%), or need for apical resection (1.5%), with a total of 4.6% of KTP PVP and 5% OP, respectively (15). Comparing LBO PVP with TURP reported a significantly lower retreatment rate of 1.8% for LBO PVP versus 11% for TURP. Bladder neck contractures were incised in 3.6% and 7.4%, respectively.

There is evidence from RCTs that persistent urinary stress incontinence is rare. Incontinence varies from 1.4% for KTP PVP (34) to 0.7% for LBO PVP (27).

There is limited data on sexual function following PVP. After a 24-month follow-up, overall sexual function in men undergoing KTP PVP was found to be maintained. In those IIEF-5 (International Index of Erectile Function-5) > 19, the pre-operative median value was significantly decreased from 22 to 16.7 (p < 0.05) (36). In an RCT of LBO PVP compared with TURP, none of the 82 patients in follow-up for 36 months presented with erectile dysfunction, and there was a comparable rate of retrograde ejaculation (PVP 49.9% vs TURP 56.7%, p = 0.21) (14). Another study, comparing KTP PVP and OP, reported no change in erectile function post-operatively (15). In a case series of LBO PVP, erectile function remained stable or improved in patients with mild or mild-to-moderate erectile dysfunction (37-39).
### 3.2.5 Conclusions and recommendations for the use of KTP and LBO lasers

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with small to moderate-sized prostates, TURP remains the standard of care.</td>
<td>1a</td>
</tr>
<tr>
<td>KTP PVP and LBO PVP are safe and effective in the treatment of BOO and BPE in patients with a small or medium prostate gland.</td>
<td>1b</td>
</tr>
<tr>
<td>Over a follow-up of 3-5 years, re-treatment rates appear comparable to those with TURP.</td>
<td>1b (at 3 yr) 4 (at 5 yr)</td>
</tr>
<tr>
<td>KTP PVP and LBO PVP are safe and effective for patients receiving anticoagulation medication or patients in retention.</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>KTP/LBO PVP is an alternative treatment for patients with BOO and BPE for small and medium glands.</td>
<td>A</td>
</tr>
<tr>
<td>KTP/LBO PVP can be offered as an alternative to TURP for patients with refractory urinary retention.</td>
<td>B</td>
</tr>
<tr>
<td>KTP/LBO PVP can be offered to patients using anticoagulant medication.</td>
<td>B</td>
</tr>
<tr>
<td>KTP/LBO PVP is a safe method for volume reduction in large size prostate glands.</td>
<td>A</td>
</tr>
</tbody>
</table>

BOO = bladder outlet obstruction; BPE = benign prostatic enlargement; KTP = potassium titanyl-phosphate laser; LBO = lithium triborate; PVP = photoselective vaporisation of the prostate; TURP = transurethral resection of the prostate.

### 3.2.6 References


3.3  Diode lasers
3.3.1  General aspects

The term diode laser refers to the method of laser beam generation.

Laser light can be generated by a resonator or a diode. The main advantages of diode lasers compared with Nd:YAG lasers are a smaller box size and a much higher wall-plug efficiency (i.e., how much of the mains supply is converted into laser power). These differences arise out of the technical principles behind the generation of laser radiation and energy. Depending on the type of laser generator, the efficiency of diode lasers is more than one order of magnitude better. Furthermore, the thermal power loss of diode lasers is much less and therefore they can be operated from a standard wall mounted power outlet.

Diode lasers in the wavelength range of 808–980 nm experience a similar absorption in water and generate a similar tissue effect to the Nd:YAG laser (1,2). Other diode lasers have wavelengths of 1318 and 1470 nm (3). The 830 nm (Indigo) diode laser has been extensively used in interstitial laser coagulation (ILC) (4).

Various types of diode lasers operating at wavelengths of 940, 980 or 1470 nm are available for the application in diode-laser prostatectomy. Currently, there are only a few studies investigating the clinical applications of diode lasers and the maximum follow-up is 1 year.
3.3.2 Physical properties

3.3.2.1 Ablation capacity

In the porcine perfused kidney model, the 1318 nm diode laser achieved the highest ablation rate (12.43 g/10 min, 100 W) when compared to the 1470 nm diode laser (5.27 g/10 min, 80 W), the 980 nm diode laser (8.99 g/10 min, 200 W), or the 120 W LBO laser (7.01 g/10 min, 120 W). The same result was achieved when the output power efficiency (g/W/10 min) was calculated (3). The 980 nm and 1.470 nm diode lasers showed no statistical difference when compared with the LBO laser (3). The 940 nm diode laser also showed a large ablation capacity when tested in canine prostate (15.17 g/10 min) (5). In a further study, the 980 nm diode laser showed increased tissue ablation rates in the continuous-wave (cw) mode, with increasing output power levels reaching 7 g/10 min at 120 W while the KTP laser displayed a significantly lower ablation capacity. Compared with TURP, both laser devices resulted in significantly lower tissue removal (6) (Table 6).

3.3.2.2 Bleeding rate

In a perfused ex-vivo porcine kidney, the haemostatic properties, calculated by bleeding rate, of the 980 nm (0.35 g/min), the 1318 nm (0.27 g/min) and the 1470 nm (0.24 g/min) diode lasers were significantly better than for the LBO laser (0.65 g/min) (3). For the 940 nm diode laser, 60 W resulted in a bleeding rate of 0.21 g/min (5).

3.3.2.3 Coagulation zone

The 980 nm (4.62 mm), 1318 nm (4.18 mm) and the 1470 nm (1.30 mm) diode laser showed significantly deeper necrotic zones compared to the LBO laser (0.84 mm) (3). The 980 nm diode laser was shown to achieve a mean coagulation zone of 8.43 mm, 9.15 mm and 9.58 mm in a porcine, perfused kidney model at 60, 90, and 120 W output powers, respectively. Compared with 80 W KTP, the coagulation capacity in the porcine kidney model for diode lasers was 7.7 to 8.7 times deeper (p < 0.0001). A shift towards the pulsed emitting mode did not change these results (p < 0.001) (6). These results are within the range of the Nd:YAG laser (2).

In a further in-vivo study, the 1470 nm diode laser achieved a coagulation zone of 2.30 mm at 100 W (7). The diode laser had an up to 2.7 times deeper coagulation capacity than KTP (p < 0.005). The 940 nm diode laser was studied in a porcine perfused kidney model. The coagulation depth measured 0.86 (10 W) up to 9.54 mm (60 W). In the same study, the coagulation depth in a canine prostate model was limited to 4 mm (200 W continuous wave mode) (7).

Table 6: Physical properties of diode laser in an ex-vivo porcine perfused kidney

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Type</td>
<td>Diode</td>
<td>LBO</td>
<td>Diode</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>1318</td>
<td>1470</td>
<td>980</td>
</tr>
<tr>
<td>Power setting (W)</td>
<td>100</td>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td>Fibre confirmation</td>
<td>bare fibre</td>
<td>side fire</td>
<td>side fire</td>
</tr>
<tr>
<td>Animal model</td>
<td>ppk</td>
<td>ppk</td>
<td>ppk</td>
</tr>
<tr>
<td>Tissue ablation rate (g/10 min)</td>
<td>12.34*</td>
<td>5.27§</td>
<td>8.99§</td>
</tr>
<tr>
<td>Output power efficacy (g/W/10 min)</td>
<td>0.124</td>
<td>0.066§</td>
<td>0.045§</td>
</tr>
<tr>
<td>Bleeding rate (g/min)</td>
<td>0.35§</td>
<td>0.24*</td>
<td>0.27§</td>
</tr>
<tr>
<td>Tissue necrosis (mm)</td>
<td>4.62*</td>
<td>1.3§</td>
<td>4.18§</td>
</tr>
</tbody>
</table>

§ Statistically not significant compared with LBO laser
* p < 0.001 compared to LBO laser;
§ p = 0.0066 compared to LBO laser;
§ mean [3.8-4.2];
& mean [0.038-0.042];
† statistically significant compared to KTP laser, p < 0.001.

bp = beagle prostate; cp = canine prostate; n.a. = not applicable.
3.3.3 **Diode laser techniques**

Diode lasers work at a wavelength at which absorption in water is low. As with KTO and LBO lasers, procedures executed with diode lasers use side-firing techniques to ensure better direct visual control of the surgeon on the point of impact of the laser beam on the tissue (1). Reported techniques are vaporising techniques (8-12). Because laser penetration levels are deeper and the coagulation zone is wider (3,7,13), some authors have suggested power should be reduced when treating the apex with the underlying sphincter region (10,11).

3.3.4 **Clinical results**

3.3.4.1 **Urodynamic parameters, symptom score reduction, PSA reduction**

Clinical data is limited to short-term follow-up (maximum follow-up 1 year) and comprises case-control studies or cohort studies (randomised cohort trials) (9-12,14). Two trials compared diode laser treatment with LBO laser systems as a standard treatment arm (9,14). The most substantial data is for the 980 nm diode laser (9-11,14).

At the end of the follow-up period, there was a significant improvement in urodynamic parameters (peak urinary flow [Q\text{max}], PVR) (Table 7). There was a reduction in PSA levels, as a surrogate parameter marker for a reduction in prostatic tissue, in the range of 30% (11) and 58% (10). However, an RCT, as well as a non-RCT, did not show significant differences in improved urodynamic parameters and symptom score reduction (Table 7).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Laser source (power, W)</th>
<th>Follow-up</th>
<th>Patients (n)</th>
<th>Mean prostate size (mL)</th>
<th>PSA reduction (%)</th>
<th>Change in symptoms (%)</th>
<th>Change in Q\text{max} (mL/s) (%)</th>
<th>PVR change (%)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seitz et al.</td>
<td>1470 (50 W)</td>
<td>12</td>
<td>10</td>
<td>47.8</td>
<td>-42</td>
<td>-69.32</td>
<td>13.5 (251.68)</td>
<td>-88.93</td>
<td>3b</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>980 (200/150W)</td>
<td>6</td>
<td>55</td>
<td>66.3</td>
<td>-58.82</td>
<td>-75.62</td>
<td>13.7 (349.01)</td>
<td>-87.74</td>
<td>3b</td>
</tr>
<tr>
<td>Erol et al.</td>
<td>980 (132/80 W)</td>
<td>6</td>
<td>47</td>
<td>51.4</td>
<td>-30.31</td>
<td>-54.99</td>
<td>9.4 (205.97)</td>
<td>-58.11</td>
<td>3b</td>
</tr>
<tr>
<td>Ruszat et al.</td>
<td>980 (n.a.)</td>
<td>6</td>
<td>55</td>
<td>64.7</td>
<td>-58.13</td>
<td>-75.93</td>
<td>5.1 (147.66)</td>
<td>-85.55</td>
<td>3b</td>
</tr>
<tr>
<td>LBO PVP</td>
<td></td>
<td></td>
<td>65</td>
<td>67.4</td>
<td>-45</td>
<td>-57.89</td>
<td>11.3 (191)</td>
<td>-80.64</td>
<td></td>
</tr>
<tr>
<td>Chiang et al.</td>
<td>980 (200 W)</td>
<td>12</td>
<td>55</td>
<td>66.3</td>
<td>-42.19</td>
<td>-84.26</td>
<td>14 (425.58)</td>
<td>-86.37</td>
<td>1b</td>
</tr>
<tr>
<td>LBO PVP</td>
<td></td>
<td></td>
<td>84</td>
<td>60.3</td>
<td>-58.82</td>
<td>-83.08</td>
<td>11.2 (303.64)</td>
<td>-85.40</td>
<td></td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; Q\text{max} = peak (maximal) urinary flow rate; PVR = postvoid residual urine volume; LE = level of evidence; LBO PVP = LBO photoselective vaporisation.

3.3.5 **Risk and complications, durability of results**

3.3.5.1 **Intra-operative complications**

Published available studies of 980 nm (9-11,14-17) and 1470 nm (12) diode lasers are all case series or case control series or comparative studies. The studies have indicated a high level of intra-operative safety. In the RCT, which compares the safety and efficacy of the 980 nm diode laser versus the 120 W LBO laser, the rate of intra-operative bleeding was significantly lower in the diode laser group (0% vs 13%). Anticoagulant medication was being taken by 23.6% of patients receiving diode laser treatment and 25.0% of patients in the LBO PVP group (9).

These findings are supported by a non-RCT, which found almost the same results (0% vs 11.9%). In this study (14) 52% of patients in the laser diode treatment arm and 43% in the LBP PVP treatment arm were on anticoagulant medication (14). This study is supported by preclinical studies on the novel laser energy sources, showing almost equal haemostatic potential and coagulation features to the Nd:YAG laser (6). Furthermore, one comparative non-RCT reported no capsule perforation with the 980 nm diode laser. The necessity for
conversion to TURP was reported in 4% (980 nm diode) and 8% (LBO PVP) of patients (9).

3.3.5.2 Early post-operative complications
Although there is only a limited amount of data, several conclusions can still be made. The incidence of early post-operative complications reported is low. No post-operative blood transfusions occurred.

In a comparison of the 980 nm diode laser to LBO PVP, a non-RCT showed the following complications: post-operative haematuria in 20% versus 19%, transient incontinence in 14.5% versus 2.4% (p < 0.05), transient urgency in 34.5% versus 16.7% (p < 0.05), scrotal oedema 3.6% versus 0%, anal pain 3.6% versus 0%, and epididymitis 1.2% versus 9.1% (14).

A comparative study reported dysuria in 24% (980 nm diode laser) versus 18% (LBO PVP), urinary incontinence 7% versus 0% and a blood transfusion rate of 0% versus 2% (14). The recatheterisation rate was between 4.3% (11) and 20% (9).

3.3.5.3 Late complications
Diode laser vaporisation of the prostate seems to carry a high rate of late complications. In a case series, 32.1% of patients needed reoperation within a follow-up of 12 months after 980 nm diode treatment due to obstructive necrotic tissue or bladder neck stricture (15).

This finding is supported by an RCT comparing the 980 nm diode laser with LBO: 9.1% versus 3.6%, respectively, of patients required reoperation with TURP due to bladder neck obstruction; 5.5% versus 2.4% developed urethral strictures; and 1.8% versus 0% developed urethral stone formation (14).

Another study, which compared diode laser to LBO PVP found higher rates of bladder neck stricture (14.5% vs 1.6%, p < 0.01), higher retreatment rates (18.2% vs 1.6%, p < 0.01) and persistence of stress urinary incontinence (9.1% vs 0%; p < 0.05) (9).

However, other reports have shown only transient combined urge and stress incontinence in 4.3% of patients for 2 weeks (11). This discrepancy has been a controversial issue conducted via scientific communication within the urological community (16). A further case series has reported sloughed-off tissue in 14.5% in cystoscopic intervention and a reoperation rate with TURP in 7.3% of patients. Urinary stress incontinence remained in 1.8% of patients during a 6-month follow-up period (10). Furthermore, in 20% of patients, a repeat of TURP was necessary within a 1-year follow-up after treatment with a 1.470 nm diode laser (12).

3.3.5.4 Practical considerations
In view of the available data on the use of the diode laser, it should not be a standard treatment option for BPE. The literature show a retreatment rate of up to 35%. Transitory and permanent incontinence seem to be higher than for alternative treatments. This treatment may offer a high inter-operative control of bleeding for patients on anticoagulative drugs.

3.3.5.5 Recommendation for prostate treatment with diode lasers

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients presenting with BOO and BPE and who have bleeding disorders or are receiving anticoagulants, diode laser treatment is an alternative.</td>
<td>1b</td>
<td>C</td>
</tr>
</tbody>
</table>

BOO = bladder outlet obstruction; BPE = benign prostatic enlargement

3.4 Holmium (Ho:YAG) laser

3.4.1 General aspects
The crystalline matrix for the holmium laser is yttrium-aluminium-garnet (YAG). In order to prevent excessive heating inside the crystal, chromium, thulium and holmium are mixed with the YAG melt from the crystal. Excitation energy is virtually handed to the holmium via a cascade from chromium over thulium. However, heat accumulation within the laser crystals restricts the holmium laser under flash lamp excitation at room temperature to pulsed operation at moderate repetition rates. Holmium laser radiation has a short extinction length in tissue due to strong absorption of the water molecule around 2140 nm (Figure 1). At this wavelength, the depth of penetration is approximately 400 μm. The density of absorbed power in irrigant and/or in tissue is high and results in an immediate increase of temperature above the boiling point.

In a typical endourological setting, the onset of vaporisation is in the irrigant next to the fibre tip, where a steam bubble is generated with each laser pulse. The diameter of the bubble depends on the energy of the laser pulse
and is a few millimetres wide. The duration of this steam bubble is similar to duration of the laser pulse, which is about 500 μs (18). This duration is too short for human perception and therefore invisible.

In holmium laser enucleation of the prostate (HoLEP), the steam bubbles separate tissue layers by tearing the tissue apart (19). In soft tissue surgery, tissue vaporisation is dominated by the way in which the steam bubble tears tissue and laser radiation is absorbed in tissue. This explains the white fibrous appearance of the surgical sites during holmium laser surgery on soft tissue under irrigation. The tissue effect is rapid and haemostasis of the holmium laser is excellent.

Common pulse energy settings for holmium lasers are in the range of 2 J. Depending on the flash lamp driver technology installed, the laser pulse duration may be between 150 μs and 1 ms. About 100 μs is required for heat to diffuse out of a short cylinder established by the fibre diameter and the extinction length (thermal relaxation time). The heat generated during the absorption process accumulates during the duration of the laser pulse at the point of impact, until heat conduction levels out the temperature profile.

In laser lithotripsy, some laser radiation is absorbed inside the stone generating an immediate build-up of steam pressure, which causes fragmentation. A laser pulse duration that is shorter or of the order of the thermal relaxation time confines the absorbed energy within the above-mentioned cylinder. The shorter the laser pulse duration at a given pulse energy, the higher the pulse peak power will be and the more effective is stone fragmentation (20).

3.4.2 Physical properties
General physical properties have been covered in section 3.4.1. Ho:YAG lasers have not been investigated to that extend like KTP, LBO, Tm:YAG and various diode lasers. Therefore, very limited data on these aspects are available so far.

3.4.3 Holmium laser techniques
All holmium laser techniques are based on vaporisation. The energy is delivered to the prostate through an end-firing laser fibre with a diameter of about 500-600 μm. Holmium laser techniques evolved from holmium laser ablation of the prostate (HoLAP) (21) to holmium laser resecting techniques (HoLRP) (22) and, finally with the introduction of the tissue morcellator, to the holmium laser enucleation technique (HoLEP) (23). A later modification combined HoLEP with electrocautery resection of the enucleated lobe, while still attached at the bladder neck (24). As for physical characteristics, the vaporising effect of holmium laser-emitted energy is limited (15%) compared to other lasers.

3.4.4 Holmium laser vaporisation (ablation) of the prostate (HoLAP)
Today, HoLAP procedure is carried out using a side-firing fibre in close contact with the surface in a sweeping fashion like PVP. The energy absorbed by the water molecule means that this technique would be safe, even if performed with bare fibre. In this manner, prostatic tissue is ablated and a cavity created similar to TURP. The strong absorption of holmium laser energy by water (Figure 1) results in a sufficiently high energy density to vapourise prostatic tissue, so creating tissue ablation without deep coagulation.

There are little data on HoLAP treatment of the prostate. A single RCT has compared 60 W and 80 W HoLAP versus TURP in 36 patients (25). Qmax improvement was equivocal at 3, 6, and 12 months after the operation, while prostate volume was reduced by 39% (HoLAP) and 47% (TURP), respectively. However, no RCT exists for the new high-power, 100 W HoLAP versus TURP or OP. One RCT comparing 100 W HoLAP with KTP reported results from a short- and intermediate-term follow-up (Table 8). Anticoagulant medication was being taken by 12.2% of patients treated with HoLAP and 15.3% treated with TURP. No difference was found except for operation time, which was 1.5-fold greater than that for TURP (26,27).

3.4.5 Holmium laser resection of the prostate
In contrast to HoLAP vaporisation, the HoLRP procedure uses vapourisation only to cut small pieces out of the prostate. This results in multiple small prostate chips falling into the bladder before being removed with a syringe at the end of the operation, similar to TURP.

Because the technological emphasis has been on HoLEP, the clinical application of HoLRP and HoLAP declined. Thus, most of the clinical data available in holmium-based literature discuss HoLEP.

The HoLRP technique is limited to small prostates. Resection time of larger prostates would take almost double the time of HoLEP, making HoLRP less suitable for treatment of BPE/BOO. One RCT compared TURP
with HoLRP in 120 patients with BOO. The patients had prostates < 100 mL in volume. The study published results at three time-points in the follow-up period (28-30). Resection time was almost doubled for HoLRP when compared to TURP (42.1 versus 25.8 minutes, p < 0.005). The mean catheter time was significantly shorter (20.0 versus 37.2 hours, p < 0.005). Symptomatic and urodynamic improvement were equivalent in the two groups. However, at 12 and 18 months after the operation, HoLRP showed superior results to TURP (25.2 versus 20.4 mL/s, respectively, at 12 months, and 25.1 versus 19.2 mL/s at 18 months). The superiority of HoLRP vanished at 24 months, until the end of the study at 48 months after the operation. The Qmax of patients treated by HoLRP or TURP was 22.2 versus 18.5 mL/s, respectively. This data is inconclusive because it is not possible to determine whether HoLRP is better or worse than standard treatment. However, the results favoured HoLRP with regard to quality of life, hospitalisation time and catheterisation time. Patients with large median lobes and patients in urinary retention can be safely treated (31,32).

3.4.6 Holmium laser enucleation of the prostate

Holmium laser enucleation of the prostate (HoLEP) is based on the same physical principle as HoLRP. However, during the HoLEP procedure, the surgical capsule of the prostate is exposed by incision and vaporisation of the periurethral prostatic tissue. After identifying the plane at the surgical capsule, the prostatic adenoma is separated from the capsule by disruption of the adenoma from the capsule, similarly to OP. Disruption is achieved by the pulsating steam bubble caused in front of the fibre by the pulsed laser energy emitting mode of Ho:YAG lasers. The introduction of HoLEP resulted in a significant improvement in the technique. The entire lobes are enucleated, moved into the bladder and morcellated (23), or fragmented with the TUR-sling at the bladder neck (mushroom technique) (24).

Several RCTs have compared HoLEP with TURP and OP, with the main findings given in Table 8.

A meta-analysis observed a tendency towards HoLEP for an improved symptom score during the entire follow-up period of up to 30 months, with larger mean changes in post-operative measurements. However, the differences in the individual studies were not statistically significant (weighted mean difference −0.82, 95% CI: −1.76-0.12; p=0.09). In the same meta-analysis, the same result was found for Qmax at 12-month follow-up. Compared with TURP, significantly higher Qmax rates were reported for HoLEP (weighted mean difference 1.48 mL/s, 95% CI: 0.58-2.40; p=0.002) (33).

In another meta-analysis, HoLEP was superior (pooled estimates) to TURP with regard to catheterisation time (17.7-31.0 h vs 43.4-57.8 h, respectively; p< 0.001), hospital stay (27.6-59.0 vs 48.3-85.5 days; p=0.001). In contrast, TURP was superior (pooled estimates of the difference) to HoLEP with regards to the duration of operation (33.1-73.8 vs 62.1-94.6 h respectively; p=0.001) (34).

Beside the evaluated RCTs, other non-RCT studies demonstrated that HoLEP has a low morbidity and is also effective in patients with urinary retention (35,36). One RCT compared changes in the urodynamic parameters of HoLEP versus TURP using computer urodynamic investigation (37). Pressure-flow studies before surgery and 6 months after the operation indicated that Pdetqmax after HoLEP (76.2 vs 20.8 cm H2O) decreased significantly more compared to TURP (70 vs 40.7 cm H2O; p < 0.001). Furthermore, the Schaefer BOO grade before and 6 months after the operation decreased significantly more after HoLEP (3.5 vs 0.2) compared to TURP (3.7 to 1.2; p < 0.001).

In recent years, a considerable number of studies regarding intermediate and long-term outcome of HoLEP alone in comparison to TURP or OP have been published. Gilling et al. (38) reported long-term data with a mean follow-up of 6.1 years showing that HoLEP results are durable and most patients remain satisfied. In prostates > 100 mL, HoLEP proved to be as effective as OP, regarding improvement in micturition with equally low re-operation rates at 5-year follow-up (39).
Table 8: Results of HoLAP, HoLRP and HoLEP with regard to improvement in urodynamic parameters, symptom score and PSA reduction

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Laser source/ Technique</th>
<th>Follow-up (mo)</th>
<th>Patients (n)</th>
<th>Mean prostate size (mL)</th>
<th>PSA reduction (%)</th>
<th>Change in symptoms (%)</th>
<th>Change in $Q_{\text{max}}$ (mL/s) (%)</th>
<th>PVR change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mottet et al. 1999 (25)</td>
<td>HoLAP</td>
<td>12</td>
<td>23</td>
<td>39</td>
<td>n.a.</td>
<td>-70</td>
<td>11.1 (226)</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>13</td>
<td>34</td>
<td>n.a.</td>
<td>-80</td>
<td>9.6 (229)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Elmansy et al. 2010 (26)</td>
<td>HoLAP</td>
<td>36</td>
<td>46</td>
<td>33.1</td>
<td>-0.40</td>
<td>-71</td>
<td>11 (264)</td>
<td>-0.81</td>
</tr>
<tr>
<td></td>
<td>KTP</td>
<td>42</td>
<td>37.3</td>
<td>-0.28</td>
<td>-64</td>
<td>12.10 (289)</td>
<td>-0.80</td>
<td></td>
</tr>
<tr>
<td>Westenberg et al. 2004 (30)</td>
<td>HoLRP</td>
<td>48</td>
<td>61</td>
<td>44.3</td>
<td>n.a.</td>
<td>-76</td>
<td>13.6 (253)</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>59</td>
<td>44.6</td>
<td>n.a.</td>
<td>-75</td>
<td>9.4 (203)</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Kuntz et al. 2004 (40)</td>
<td>HoLEP</td>
<td>18</td>
<td>60</td>
<td>114.6</td>
<td>n.a.</td>
<td>-90</td>
<td>23.60 (721)</td>
<td>-97</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>60</td>
<td>113</td>
<td>n.a.</td>
<td>-90</td>
<td>24.40 (778)</td>
<td>-98</td>
<td></td>
</tr>
<tr>
<td>Kuntz et al. 2004 (41)</td>
<td>HoLEP</td>
<td>12</td>
<td>100</td>
<td>53.5</td>
<td>n.a.</td>
<td>-92</td>
<td>23 (569)</td>
<td>-98</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>100</td>
<td>49.9</td>
<td>n.a.</td>
<td>-82</td>
<td>21.80 (469)</td>
<td>-88</td>
<td></td>
</tr>
<tr>
<td>Briganti et al. 2006 (42)</td>
<td>HoLEP</td>
<td>24</td>
<td>60</td>
<td>73.30</td>
<td>n.a.</td>
<td>-83</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>60</td>
<td>58.20</td>
<td>n.a.</td>
<td>-83</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Gupta et al. 2006 (43)</td>
<td>HoLEP</td>
<td>12</td>
<td>18</td>
<td>57.9</td>
<td>n.a.</td>
<td>-78</td>
<td>19.20 (527)</td>
<td>-83</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>16</td>
<td>59.8</td>
<td>n.a.</td>
<td>-76</td>
<td>19.95 (487)</td>
<td>-77</td>
<td></td>
</tr>
<tr>
<td>Naspro et al. 2006 (44)</td>
<td>HoLEP</td>
<td>24</td>
<td>41</td>
<td>113.27</td>
<td>n.a.</td>
<td>-61</td>
<td>11.36 (245)</td>
<td>n.a.</td>
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<tr>
<td></td>
<td>TURP</td>
<td>39</td>
<td>124.21</td>
<td>n.a.</td>
<td>-63</td>
<td>11.79 (242)</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Wilson et al. 2006 (45)</td>
<td>HoLEP</td>
<td>24</td>
<td>31</td>
<td>77.8</td>
<td>n.a.</td>
<td>-77</td>
<td>12.6 (250)</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>30</td>
<td>77.0</td>
<td>n.a.</td>
<td>-78</td>
<td>11.0 (233)</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Montorsi et al. 2008 (46)</td>
<td>HoLEP</td>
<td>12</td>
<td>52</td>
<td>70.3</td>
<td>n.a.</td>
<td>-81</td>
<td>16.9 (306)</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>48</td>
<td>56.2</td>
<td>n.a.</td>
<td>-82</td>
<td>17.20 (326)</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Gilling et al. 2008 (38)</td>
<td>HoLEP</td>
<td>72</td>
<td>71</td>
<td>58.5</td>
<td>n.a.</td>
<td>-67</td>
<td>10.9 (235)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Kuntz et al. 2008 (39)</td>
<td>HoLEP</td>
<td>60</td>
<td>60</td>
<td>114.6</td>
<td>n.a.</td>
<td>-86</td>
<td>20.5 (639)</td>
<td>-96</td>
</tr>
<tr>
<td></td>
<td>OP</td>
<td>60</td>
<td>113</td>
<td>n.a.</td>
<td>-86</td>
<td>20.8 (678)</td>
<td>-98</td>
<td></td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; $Q_{\text{max}}$ = peak (maximal) urinary flow rate; PVR = postvoid residual urine volume; LE = level of evidence; HoLAP = holmium laser vaporisation (ablation) of the prostate; TURP = transurethral resection of prostate; n.a. = not applicable; HoLRP = holmium laser resection of the prostate; HoLEP = holmium laser enucleation of the prostate; OP = open prostatectomy.
3.4.7 **Risk and complications, durability of results**

The published literature describing Ho:YAG treatment of the prostate is dominated by discussion of HoLEP with few publications for HoLAP and very few for HoLRP. The introduction of KTP resulted in less interest in Ho:YAG as a solely vaporising laser. However, the recent availability of 100 W Ho:YAG laser devices has led to a renewed interest in HoLAP because of the popularity of vaporising using a side-fire technique (26,27).

3.4.8 **Intra-operative complications**

3.4.8.1 HoLAP

An RCT comparing HoLAP with KTP PVP reported no intra-operative bleeding in the HoLAP-treated group, while three KTP PVP-patients required intra-operative conversion to TURP electrocauterisation (27). Another RCT comparing HoLAP versus TURP did not report any intra-operative complications (25).

3.4.8.2 HoLRP

The RCTs available for HoLRP (28-30) tend to focus on the outcome for improved symptom score and urodynamic parameters. Intra-operative complications for HoLRP are not specifically displayed. In comparison, the TURP treatment arm in these studies showed a blood transfusion rate of 6.7%. Furthermore, the available case series do not focus on intra-operative complications (31,32,47).

3.4.8.3 HoLEP

The safety and low intra-operative morbidity of HoLEP has been proven in seven RCTs (40-46). Several reviews (48) and two meta-analyses (33,34) have investigated the safety and peri-operative morbidity of HoLEP. One meta-analysis found a lower rate of blood transfusion after holmium laser enucleation (relative risk 0.27, 95% CI: 0.07-0.95; p=0.04) compared with TURP (33); a finding supported by a second meta-analysis (34). In addition, a second meta-analysis showed that HoLEP reduced catheterisation time and duration of hospital stay, although TURP resulted in a shorter total operation time (34).

In a review of studies published from 2003 until 2006, 1,847 patients were identified who had been treated with HoLEP. The blood transfusion rate was 1% and peri-operative mortality was 0.05%. A further review showed a capsular perforation rate ranging from 0.3% (49) to 10% (50). The perforations were mainly classified as small capsular lacerations and the patients’ course was not affected. Superficial mucosal laceration with the morcellation device was reported ranging from 0.5% (50) to 18.2% (46). The rate of superficial ureteric orifice injury that did not require insertion of a ureteral stent or nephrostomy ranged from 1.0% (51) to 2.1% (52). The incidence of incomplete morcellation ranged from 1.9% (52) to 3.7% (54) in all cases. Cardiac adverse events were reported in up to 1.2% of patients (52).

The experience of the surgeon was the most important factor affecting the overall occurrence of complications (55,56) and intra-operative complications. In trained hands, prostate size had no statistically significant influence on complications (57). The likelihood of capsular perforations increased with smaller prostates, while injury of the ureteric orifice occurred more often during resection of large and endovesically growing median lobes (52,55).

Two meta-analyses have demonstrated that in comparison to TURP and OP, patients undergoing HoLEP have a shorter catheterisation time and hospital stay, reduced blood loss and a smaller likelihood of blood transfusions, but comparable functional outcomes (33,34).

3.4.9 **Early post-operative complications**

3.4.9.1 HoLAP

An RCT comparing HoLAP with TURP reported that 20% of patients had mild urgency or burning after catheter removal. These problems did not resolve until the first month (25). Another study, comparing HoLAP with KTP PVP, did not specifically address peri-operative complications. However, seven patients (12.2%) in the HoLAP group and six (11.5%) in the KTP PVP group required recatheterisation (26,27). Dysuria and irritative symptoms following surgery resolved before the first post-operative visit at 1 month (25).

3.4.9.2 HoLRP

An RCT comparing HoLRP to TURP has reported the rate for UTIs as 4.9% versus 8.4%, respectively. There are no other broad assessments of peri-operative complications (30).

3.4.9.3 HoLEP

Peri-operative complications within the first months after HoLEP have been assessed by several RCTs, case
series, comparative studies and meta-analyses (34,41,48). In an RCT comparing HoLEP and OP for patients with prostates > 70 g, transitory urge incontinence was equally observed in 34.1% (HoLEP) and 38.6% (OP) of patients at 3 months’ follow-up, whereas dysuria was significantly more frequent in the HoLEP group (68.2 vs 41.0%, p < 0.001) (44). In contrast, the reported rate of transitory urge incontinence showed no significant difference in a multicentre RCT comparing HoLEP and TURP. Dysuria occurred significantly more often in patients after HoLEP (58.9 vs 29.5%, p = 0.0002) (46). Haemorrhage requiring coagulation is reported in 0-6% (58) and clot retention in 0% (59) to 3.6% (60).

3.4.10 Late complications

3.4.10.1 HoLAP
An RCT comparing HoLAP with TURP found one patient with stress urinary incontinence and one patient had opted out of the study at 6 months’ follow-up. Two patients in the TURP group were treated for bladder neck contracture at 2 and 6 months by cold-knife incision. No significant difference was found in the potency and antegrade ejaculation rate between the two groups. The potency rate after 1 year was 90% for the laser group and 100% for the TURP group. The antegrade ejaculation rate was 50% in both groups (25). The retreatment rate at 7 years’ follow-up was 15% (61).

An RCT comparing HoLAP versus KTP PVP found comparable complication rates at follow-up after 36 months. The overall retreatment rate was 15.8% for HoLAP and 19.3% for PVP. Urethral stricture rate was 3.5% and 5.8%, respectively. Bladder neck contracture occurred in 5.3% versus 7.7%, respectively. The re-operation was reported to be 7% for HoLAP-treated patients versus 5.8% for KTP PVP (26,27).

One patient (1.8%) with HoLAP versus two patients (3.8%) with PVP had urgency and urge incontinence that did not resolve with anticholinergic therapy at the last follow-up. There was no significant difference in post-operative complications between the two groups. The overall retreatment rate was 15.8% for HoLAP versus 19.3% for PVP.

Retrograde ejaculation of sexually active patients was reported in 36.3% of the HoLAP group compared with 43.3% of the KTP PVP group. Between the two groups, no significant difference between pre-operative and post-operative sexual function in terms of orgasmic function, sexual desire, or intercourse or overall satisfaction was reported (26).

3.4.10.2 HoLRP
One RCT reported no difference between HoLRP and TURP in terms of urodynamic parameters, potency, continence, symptoms scores and major morbidity at 48 months. Complication rates were comparable. Persisting de novo urine leakage was reported to be 3.3% in the HoLRP group versus 1.7% in the TURP group. The overall retreatment rate was 8.2% for HoLRP versus 11.8% for TURP. 1.7% in the TURP arm needed artificial sphincter implantation. Urethral stricture rate was 9.8% versus 10.1%, respectively. Bladder neck incision for bladder neck contracture occurred in 4.9% versus 5.1%, respectively (30). Pre-operatively 50% of HoLRP versus 70% of TURP were potent, at the 4-year follow-up (53% of HoLRP versus of 60% TURP patient had sufficient erection for intercourse. A decrease in erectile quality was reported in 8% of the HoLRP and 17% of the TURP groups. However, 10% of the HoLRP group and 7% of the TURP group reported an improvement of erections (30).

3.4.10.3 HoLEP
In a meta-analysis, no statistically significant differences were noted between HoLEP and TURP for urethral stricture (2.6 versus 4.4%; p = 0.944), stress incontinence (1.5 versus 1.5%; p = 0.980), blood transfusion (0 versus 2.2%; p = 0.14) and reintervention (4.3 versus 8.8%; p = 0.059). No obvious publication bias was noted (p = 0.170, Egger’s test) (34).

A further meta-analysis evaluated the risk of erectile dysfunction after HoLEP compared to standard treatment. Erectile dysfunction rates showed were similar to TURP (33). In the same meta-analysis the rate of strictures during follow-up after holmium laser enucleation was similar to those after transurethral resection (33).

Numerous trials involving the long-term outcome of HoLEP have been published and have confirmed the long-term and significant improvement in voiding parameters and the low complication rate. In a 6-year follow-up analysis of 38 patients treated with HoLEP, urge incontinence was reported in three of 38 (7.9%) patients, mixed incontinence in 10.5% and stress incontinence in 2.6%. Re-operation was necessary in 1.4% after 5 years and one patient 1.4% underwent urethrotomy at 6 months (38,61).
Comparable long-term results were reported from other studies with a re-operation rate of 4.2% due to residual adenoma, urethral strictures (1.7%), meatal stenosis (0.8%) and bladder neck contracture (0.8%), resulting in a 5-year surgical retreatment rate of 8%. The earlier group of patients showed a higher retreatment rate (8 vs 1.4%) (62). Another study observed a re-operation rate of 2.7% during a 36-month follow-up. In the group of patients with prostates < 50 mL, the incidences of urethral stenosis and bladder neck contracture were significantly higher (63).

Re-operation rates in a RCT comparing HoLEP with TURP were comparable at 3-year follow-up with a rate of 7.2 and 6.6%, respectively (64). These data are confirmed by other prospective trials comparing HoLEP to TURP (43). In an RCT comparing HoLEP versus OP, the re-operation rate at 5-year follow-up was 5% for HoLEP and 6.7% for OP-treated patients (39).

Studies focussing on sexual function after HoLEP are rare. Due to retrograde ejaculation HoLEP and TURP significantly lowered the IIEF orgasmic function domain in one RCT. Similar results were observed in the comparison of HoLEP and OP, with no significant reduction of erectile function compared with baseline (39). Patients after HoLEP and TURP reported retrograde ejaculation in 75% and 62%, respectively (45,61).

3.4.11 Practical considerations
Although the literature has mainly focused on HoLEP, both HoLAP and HoLRP are suitable as alternatives for vaporising (HoLAP) or resecting (HoLRP) approaches in the treatment of BOO and BPE. One issue for both techniques that needs to be considered is the longer ablation or resection time. HoLEP is the most studied novel minimal therapy approach and is a real alternative to TURP for medium- and large-sized prostates for OP. However, the excellent early results obtained with HoLEP, as the prototype for transurethral laser enucleation, have not been matched by the wider use of this technique.

3.4.12 Recommendations for holmium (Ho:YAG) laser treatment

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoLAP can be offered to patients with BOO or BPE with small-</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>to medium-sized prostates.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HoLRP can be offered to patients with BOO or BPE with small-</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>to medium-sized glands.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HoLEP can be offered to any patient with BOO and BPE.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>HoLEP can be offered to patients in chronic urinary retention.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>HoLEP can be offered to patients on anticoagulant or antiplatelet medication.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

BOO = bladder outlet obstruction; BPE = benign prostatic enlargement

3.4.13 References


3.5 Thulium:yttrium-aluminium-garnet (Tm:YAG) laser

Laser energy is emitted at a wavelength of about 2000 nm in a continuous-wave fashion (1-4). In contrast to the flash-lamp excitation of the holmium laser, thulium ions are directly excited by high-power laser diodes. Although a thulium laser has the same absorption characteristics as a holmium laser in water and tissue, it has superior properties in soft tissue surgery because of the continuous-wave output. Due to the slightly shorter wavelength, the depth of penetration is decreased to 250 μm. The wavelength is close to the absorption peak of water and, together with the short penetration depth, this results in a high-energy density leading to rapid vaporisation of water and tissue. Instead of the tearing action on tissue caused by the pulsed emission of Ho:YAG, the continuous-wave output of Tm:YAG allows smooth incision and vaporisation of tissue with excellent haemostasis. The ubiquity of the water molecule as the target chromophore provides constant conditions for the laser tissue chromophore and therefore tissue interaction. Water retains its absorption properties when heated by the laser beam up to the boiling point, which marks the onset of tissue vaporisation.

The tissue left behind after each laser pass is covered by a coagulated seam of tissue, which provides haemostasis. It still contains sufficient water for efficient absorption of the following laser pass. Thus the laser tissue effect remains unchanged and effective throughout the entire surgical procedure. In contrast to the pulsed emission mode of Ho:YAG, the continuous emission does not allow lithotripsy.

3.5.1 Physical properties

To date, one clinical paper has reported data on vaporisation efficacy using the Tm:YAG 2013 nm (2 μm) continuous-wave (cw) laser. There is one publication each for the 70 W and 120 W Tm:YAG 2-μm cw laser devices in an identical, experimental, organ perfused, porcine kidney model.

3.5.1.1 Ablation capacity

The tissue ablation rate increases with increasing output power. In comparison to the KTP laser, the tissue ablation rate reached (mean) 6.56 g/10 min (70 W Tm:YAG) and 3.99 g/10 min (80 W KTP) (p > 0.05). When compared to TURP, both laser devices produced significantly lower rates of tissue removal (8.28 g/10min) (5).

The ablative potential of Thu:YAG lasers was confirmed in a further study. At 70 W, 3.03 g/10 min were ablated using the 550 μm bare fibre. At 120 W, the amount of ablated tissue increased to 16.41 g/10 min using the 550 μm bare fibre. These rates were reduced when using a larger fibre core diameter (800 μm), as energy density is a function of core diameter (6).

3.5.1.2 Bleeding rate

The thulium laser has good haemostatic potential. In the same model, the bleeding rate for the cw 70 W thulium laser reached 0.16 ± 0.07 g/min, compared to 0.21 ± 0.07 g/min for the 80 W KTP laser. In contrast, TURP showed a significantly increased bleeding rate of 20.14 g/min (p < 0.05) (5). The results were unaffected by increasing the energy output and core diameter (6).

3.5.1.3 Coagulation zone

In the kidney perfused tissue ablation model, continuous-wave thulium showed the shallowest coagulation depth. Histological examination revealed that tissue ablation resulted in a dense coagulation zone at the tissue surface. The corresponding depth of the coagulation zone was 284.7 ± 41.3 μm for the continuous-wave thulium laser, which is almost as deep as that achieved with TURP (287.1 ± 27.5 μm), but less than the 2.5-fold deeper coagulation zone (0.6669 mm) of the KTP laser (p < 0.05) (Table 4) (5). With increased power output and increased fibre diameter, the extent of coagulation and the necrotic tissue zone remained stable (6).
Tissue ablation increased with increasing power and was superior to that achieved with the 80 W KTP laser. Furthermore, the bleeding rate was for the cw 70 W thulium laser reached 0.16 ± 0.07 g/min, compared to 0.21 ± 0.07 g/min for the 80 W KTP laser, though considerably lower than with monopolar TURP (5). In contrast to the 120 W LBO laser (7), the bleeding rate remained stable for the 120 W Tm:YAG laser with an increase in ablation rate. In addition, the study demonstrated shallow penetration and an energy-independent zone of tissue necrosis of 0.4 mm (6).

3.5.2 Thulium laser techniques
Four different technical approaches have been described so far:
1) Tm:YAG vapourisation of the prostate (ThuVAP);
2) Tm:YAG vaporesection (ThuVARP);
3) Tm:YAG vapoenucleation (ThuVEP);
4) Tm:YAG laser enucleation of the prostate (ThuLEP) (8).

As the data from prospective RCTs are very sparse, these techniques cannot be assessed to levels of evidence. But, a number of studies, including two RCTs and one non-RCT have been published so far. The evidence of these studies will be discussed below.

3.5.2.1 Thulium laser vapourisation of the prostate
ThuVaR is a solely vapourising technique. Because the beam is fully absorbed in water, there is no necessity for side-fire application, as with KTP or LBO. A multicentre, non-randomised, case series study has reported clinical data of pure vapourisation of the prostate in 99 patients with small prostates (< 35 mL). As the results are presented alongside the results for patients with larger prostates (> 35 mL), the clinical data cannot be separated. The improvement of urodynamic parameters in the whole group of patients (n = 200) shows clinically efficient vapourisation or vaporesection in 12 months of follow-up (Table 9). These findings reflect the results of two preclinical trials in an organ-perfused model investigating the physical properties of Tm:YAG.

In comparison with a KTP laser, the 70 W Tm:YAG laser showed a larger ablation capacity, reduced bleeding rate and shallower coagulation zone (5). The 70 W Tm:YAG and the novel 120 W KTP showed a similar bleeding rate and coagulation properties (6), in contrast to 120 W LBO, which showed a higher bleeding rate and slight increase in coagulation zone (7). Higher energy resulted in a marked increase of ablation capacity in both Tm:YAG and LBO lasers (Table 4).

Twelve patients on anticoagulant drugs have been treated safely with ThuVAP/ThuVARP (9). The operation time was between 25 and 140 minutes, with catheterisation for 16 hours and no transfusion required (10). No urethral stricture or bladder neck sclerosis was reported. However, seven patients received insufficient vapourisation and required retreatment, while four patients had urinary retention after catheter removal. Six per cent of ThuVAP patients demonstrated irritative voiding symptoms post-operatively, which resolved in 1-3 months.

3.5.2.2 Thulium laser resection of the prostate (ThuVARP)
ThuVARP is a technique that resects the prostate in TUR-like tissue chips. Although Tm:YAG is similar to the Ho:YAG with regard to its shallow tissue and water penetration and haemostasis, vapourisation capacity is significantly increased by the continuous-wave emitting mode. Therefore, tissue ablation is not only achieved by resection, but also by simultaneous vapourisation.

The largest number of thulium-associated publications have been published on ThuVARP. One RCT, one non-randomised controlled study and three prospective studies have been published since 2007. In total, 730 patients have been included in these trials, which have all been reported in peer-reviewed journals.

One RCT (11) and one non-RCT (12) compared ThuVARP with monopolar TURP. The two procedures showed similar clinical outcomes and an improvement in urodynamic parameters with reduced morbidity. The Tm:YAG-treated patient group showed reduced bleeding with lower transfusion rates and shorter catheter and hospitalisation times compared to the TURP-treated patient group (11,12). All other studies (13-16) showed clinical and urodynamic results in the range of the above studies with durable improvement in voiding function (Table 9), up to an 18-month follow-up. Post-operative PSA levels as a surrogate parameter for volume reduction declined by 56% (16) and 69.4% (15).

3.5.2.3 Thulium laser vapoenucleation of the prostate (ThuVEP)
The evolution in Tm:YAG prostate surgery has virtually followed the same path as for Ho:YAG surgery. ThuVEP
was introduced in 2008 for patients with larger prostates (10). Published data in peer-reviewed journals is sparse (1-3,17,18).

The clinical efficacy of ThuVEP versus HoLEP was studied in one prospective RCT (17) and ThuVEP alone was studied in three prospective non-RCTs (1,2,18) Efficient tissue reduction and consistent improvement in clinical symptoms was observed within the follow-up period of up to 18 months (1,2,18). Blood loss was reduced in the Tm:YAG group, when compared to HoLEP, with equi-effective de-obstruction within a short follow-up interval of 3 months (17). In patients with refractory urinary retention (RUR), no differences with regards to improvement of urodynamic parameters and peri-operative complications were recorded, except for a higher rate of UTIs (15.5 vs 4.6) in patients with RUR (4). ThuVEP was safely applied to 96 high-risk patients, of whom 16 were on anticoagulant drugs. Within the whole study group, six patients developed UTI, three of whom required either post-operative transfusion or second-look surgery due to clot retention, or had insufficient voiding function (13). Post-operative PSA levels, as a surrogate parameter for volume reduction, declined by 56.1 (11) to 69.4% (10) for ThuVAP and 88% for ThuVEP (18).

3.5.2.4 Thulium laser enucleation of the prostate (ThuLEP)
ThuLEP is a transurethral technique with widely blunt dissection of the adenoma, such as OP. Permanent incisions are made at the apex and the bladder neck, the nutrifying vessels from the peripheral to the transition zone are punctiformly coagulated, leaving the capsule widely untouched. Except for a description of the technique, no clinical data has been reported so far (19).

### Table 9: Results of ThuVAP, ThuVARP, ThuVEP for improvement in urodynamic parameters

<table>
<thead>
<tr>
<th>Trial</th>
<th>Laser source/Technique</th>
<th>Follow-up</th>
<th>N</th>
<th>Mean prostate size (mL)</th>
<th>PSA reduction (%)</th>
<th>Change in symptoms (%)</th>
<th>Change in Qmax (mL/s) (%)</th>
<th>PVR change (%)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattioli et al. 2008 (2)</td>
<td>ThuVAP</td>
<td>12</td>
<td>99</td>
<td>45*</td>
<td>n.a.</td>
<td>-67*</td>
<td>14.8 (289)*</td>
<td>-88.9*</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>ThuVARP</td>
<td>101</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xia et al. 2008 (6)</td>
<td>ThuVAP</td>
<td>12</td>
<td>52</td>
<td>59.2</td>
<td>n.a.</td>
<td>-84</td>
<td>15.7 (296)</td>
<td>-94.4</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>48</td>
<td>55.1</td>
<td>n.a.</td>
<td>-81</td>
<td>15.8 (290)</td>
<td>-92.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fu et al. 2009 (7)</td>
<td>ThuVAP</td>
<td>12</td>
<td>58</td>
<td>49.8</td>
<td>n.a.</td>
<td>-85.4</td>
<td>14.9 (329)</td>
<td>-84.3</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>42</td>
<td>48.2</td>
<td>n.a.</td>
<td>-81.1</td>
<td>15.5 (312)</td>
<td>-84.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bach et al. 2007 (8) 2009 (9)</td>
<td>ThuVAP</td>
<td>18</td>
<td>54</td>
<td>30.3</td>
<td>n.a.</td>
<td>-67</td>
<td>12.8 (258)</td>
<td>-86</td>
<td>2b</td>
</tr>
<tr>
<td>Fu et al. 2008 [10]</td>
<td>ThuVAP</td>
<td>12</td>
<td>72</td>
<td>65.8</td>
<td>-69.4</td>
<td>-72.6</td>
<td>15.1 (364)</td>
<td>-65.7</td>
<td>2b</td>
</tr>
<tr>
<td>Shao et al. 2009 (13)</td>
<td>ThuVEP</td>
<td>6</td>
<td>52</td>
<td>40.3</td>
<td>-40.8</td>
<td>-70</td>
<td>14.9 (350)</td>
<td>-80</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td>HoLEP</td>
<td>46</td>
<td>37.3</td>
<td>-35.7</td>
<td>-60</td>
<td>15.5 (330)</td>
<td>-80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bach et al. 2010 (12,14)</td>
<td>ThuVEP</td>
<td>18</td>
<td>88</td>
<td>61.3</td>
<td>n.a.</td>
<td>-63</td>
<td>15.7 (664)</td>
<td>-72.4</td>
<td>2b</td>
</tr>
<tr>
<td>Bach et al. 2011 (18)</td>
<td>ThuVEP</td>
<td>12</td>
<td>90</td>
<td>108.59</td>
<td>-88</td>
<td>-79.7</td>
<td>18.7 (326)</td>
<td>-90.8</td>
<td></td>
</tr>
</tbody>
</table>

* for both groups.

PSA = prostate specific antigen; PVR = postvoid residual urine volume; LE = level of evidence; ThuVAP = thulium laser vapourisation of the prostate; ThuVARP = Tm:YAG vaporesection; ThuVEP = Tm:YAG vapenucleation; TURP = transurethral resection of the prostate.
3.5.3  **Risk and complications, durability of results**
Several case series studies and two RCTs (11,17) have proven the intra-operative safety of Tm:YAG surgery of the prostate, as well as in subgroups of patients with large prostates (1,10), on anticoagulation therapy (3,9), or in retention (2).

3.5.3.1  **Intra-operative complications**
The rate of intra-operative complications occurring during ThuVARP or ThuVEP is low. There is no report on the occurrence of TURP syndrome. Intra- or early post-operative bleeding was reported in 3.4% of patients undergoing enucleation of the prostate and the rate of blood transfusions varied from 0% (17) to 2.2% (2) for ThuVEP. Transfusions are not reported during or after vaporesection of the prostate, whereas in a level 1b, prospective, randomised trial, blood transfusion was necessary in 4% (11) and 9.5% (12), respectively with TURP, while TURP syndrome occurred in 2.1% of patients (11).

3.5.3.2  **Early post-operative complications**
In the early post-operative course after ThuVEP, symptomatic UTI occurred in 6.8% (10), in 2.2% a second-look procedure during hospitalisation was necessary. In 1.1% of patients recatheterisation was necessary (10). Comparing the complications of patients with pre-operative urinary retention and indwelling catheter prior to enucleation of the prostate with catheter-naïve patients, a significantly higher rate of post-operative haematuria (3.1% vs 1.4%) and UTI (15.4% vs 4.2%) was observed in patients with pre-operative urinary retention (2).

The 3.9% rate of UTIs after ThuVARP was significantly lower than the 8.3% UTI rate after TURP (11), while similar UTI rates (6.9% vs 7.1%) were reported by another study.

Transitory early urge incontinence occurred less often than after TURP (23.1 vs 31.3%) (11). No difference was seen in the occurrence of mild-to-moderate dysuria for ThuVARP in 8.6% versus 7.1% for TURP, respectively. Irritative symptoms occurred in 26.2% and 29.3%, respectively (12).

3.5.3.3  **Late complications and retreatment rate**
In the current literature, data with a follow-up of 18 months after ThuVARP and ThuVEP are available. Within the 18 months follow-up after ThuVARP, no re-operation or recatheterisations occurred (14). De novo erectile dysfunction was not reported. A total of 55% of patients reported retrograde ejaculation after ThuVARP compared to 65% after TURP (11). Another study did not show a significant difference for retrograde ejacuation (44.2% vs 44.7%) (12). No bladder neck stricture occurred. Occurrence of urethral stricture was significantly lower in TuVARP, when compared to TURP (1.9% vs 6.5%, respectively) (11,12).

Within a follow-up of 18 months after ThuVEP, 2.2% of patients needed retreatment using ThuVARP. One patient (1.1%) required transient recatheterisation, while one patient developed a urethral stricture, requiring urethrotomia interna (1%) (1).

Transient recatheterisation was necessary in 5.6% of patients with an indwelling catheter prior to enucleation. The re-operation rate showed no difference between patients with and without an indwelling catheter prior to enucleation (2.8 vs 3.1%) within a 12-month follow-up period (14).

Despite the encouraging results, a follow-up period of 18 months is a relatively short time upon which to make final conclusions.

3.5.4  **Conclusions and recommendations for use of Thulium:YAG lasers**

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThuVARP showed equivalent effectiveness when compared to TURP in one RCT and one non-randomised prospective controlled trial with small and medium volume glands. Tm:YAG treated patient showed shorter catheterisation time and shorter hospitalisation time. Adverse events were significantly lower than in TURP (intra-operative and post-operative bleeding).</td>
<td>1b</td>
</tr>
<tr>
<td>Currently, only one RCT with a short follow-up has compared ThuVEP to HoLEP. Nevertheless, three prospective cohort studies with a follow-up of 18 months demonstrated efficacy for THUVEP, as well as low perioperative complications and retreatment rates.</td>
<td>1b</td>
</tr>
<tr>
<td>Study data are awaited comparing ThuVEP and ThuLEP to HoLEP. HoLEP is the most extensively studied transurethral enucleation technique to date and long-term anatomical data are of particular interest.</td>
<td>4</td>
</tr>
</tbody>
</table>
ThuVARP is an alternative to TURP for small- and medium-sized prostates.

ThuVARP and ThuVEP are suitable for patients at risk of bleeding or taking anticoagulant medication.

ThuVEP can be offered as an alternative to TURP, to HoLEP and OP for large size prostates.

References

4. APPLICATION OF LASER DEVICES FOR THE TREATMENT OF BLADDER CANCER PATHOLOGIES

4.1 Introduction
The use of laser devices in urology was first reported by Staehler et al. in 1978 (1) who described the successful destruction of urinary bladder tumours with a Nd:YAG-laser.

There are only retrospective analyses concerning laser ablation of bladder cancer, mostly single-institution studies with small patient numbers. In 2001, there were the first reports of bladder tumours being resected en bloc using the holmium laser (2), while in 2008, there was the first report of a bladder malignancy being resected by thulium laser (3).

4.2 Clinical application and results
Although various lasers have been used to treat bladder tumours, there has been no prospective comparison of the different devices (4). Some studies have compared TUR of the bladder (TURB) with laser treatment in non-controlled, retrospective analyses (5-7). Most studies compared laser therapy to standard TURB procedures. No indwelling catheter was used. Some studies reported carrying out the procedure under local anaesthesia in an ambulant setting (8-11). Although there have been some reports of adjacent bowel injury when using lasers with a deep penetration, the bladder wall remained intact (12,13). Major studies are represented in Table 10.

The use of lasers to treat bladder tumours in non-muscle invasive disease has the major drawback of a lack of tissue for histopathological evaluation if only laser vaporisation is used.

Total complication rates were reported ranging from as low as 5.1% up to 43%. Data regarding the morbidity and complications of TURB describe the rate of UTIs as up to 24%, bleeding (2.8-8%), haemorrhage requiring transfusion (0.9-13%) and bladder perforation (1.3-5%) (14-18). The use of holmium laser for en bloc resections may help to evaluate pathological stage and grades in primary bladder tumours for evaluating the pathological stage and grade (8,10,19). At this time, there are not enough data to predict progression rates, but based on currently available data, recurrence rates after holmium laser application in bladder cancer appear similar, or lower, compared with TURB (11). The effect of lower scattering leading to a decrease in local and out-of-field recurrence rates is under debate (20). Overall recurrence rates, however, seem to be comparable to TURB.

According to current data, the optimal indication for laser excision of a bladder tumour is a relatively small tumour located at the trigonum, lateral bladder wall, or bladder neck. It has been suggested that the oncological outcome following laser treatment is comparable to TUR. However, at present, there are no larger studies able to provide reliable long-term equivalence.

In experienced hands, laser treatment of bladder pathologies, e.g. tumours, diverticles, and ureteroceles, provides an alternative to conventional TUR surgery in well-selected patients.
Table 10: Applications of laser devices for the treatment of bladder cancer pathologies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design</th>
<th>LE</th>
<th>Patients (n)</th>
<th>Surgical technique</th>
<th>Operation time (min)</th>
<th>Complications</th>
<th>Follow-up (mo)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho:YAG (holmium) laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Das et al. 1998 (5)</td>
<td>Prospective</td>
<td>3</td>
<td>23</td>
<td>Photoablation + biopsy</td>
<td>18.6</td>
<td>1 recatheterisation</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Saito 2001 (2)</td>
<td>Retrospective</td>
<td>3</td>
<td>35</td>
<td>En bloc + biopsy</td>
<td>n.a.</td>
<td>None</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Soler-Martinez et al. 2007 (19)</td>
<td>Prospective</td>
<td>3</td>
<td>35</td>
<td>Biopsy + photoablation</td>
<td>14 (5-17)</td>
<td>None</td>
<td>3, 6, 12</td>
<td>n.a.</td>
</tr>
<tr>
<td>Zhu et al. 2008 (10)</td>
<td>Prospective</td>
<td>2</td>
<td>101</td>
<td>En bloc</td>
<td>30.7 (±16.1)</td>
<td>1 perforated bladder</td>
<td>34 (18, 43)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Xishuang et al. 2009 (11)</td>
<td>Prospective</td>
<td>2</td>
<td>64</td>
<td>En bloc</td>
<td>16.5 (±3.8)</td>
<td>1 urethral stricture</td>
<td>24</td>
<td>n.a.</td>
</tr>
<tr>
<td>Zhong et al. 2010 (21)</td>
<td>Retrospective</td>
<td>3</td>
<td>25</td>
<td>En bloc</td>
<td>21.5 (±12.5)</td>
<td>None</td>
<td>12, 24</td>
<td>n.a.</td>
</tr>
<tr>
<td>Tm:YAG (thulium) laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gao et al. 2008 (3)</td>
<td>Prospective</td>
<td>3</td>
<td>32</td>
<td>En bloc</td>
<td>25 (15-35)</td>
<td>None</td>
<td>3, 6, 12</td>
<td>9, 22, 28</td>
</tr>
<tr>
<td>Zhong et al. 2010 (21)</td>
<td>Retrospective</td>
<td>3</td>
<td>34</td>
<td>En bloc</td>
<td>29.1 (±16.5)</td>
<td>None</td>
<td>12, 24</td>
<td>17.6, 29.9</td>
</tr>
<tr>
<td>Yang et al. 2009 (7)</td>
<td>Prospective</td>
<td>3</td>
<td>9</td>
<td>En bloc</td>
<td>7 (5-15)</td>
<td>1 perforated bladder</td>
<td>7.5 [6,9]*</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

LE = level of evidence; n.a. = not applicable.

4.3 Conclusions and recommendation for laser treatment of bladder cancer

**Conclusions**

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of lasers is feasible for resection, coagulation and enucleation of non-muscle invasive bladder tumours.</td>
<td>3</td>
</tr>
<tr>
<td>Transurethral resection of the bladder remains the gold standard.</td>
<td>1a</td>
</tr>
<tr>
<td>In laser coagulation of tumours, no tissue for pathological staging is obtained.</td>
<td></td>
</tr>
<tr>
<td>Long-term recurrence and progression rates are unknown for this novel technique.</td>
<td></td>
</tr>
<tr>
<td>Currently, no data are available to indicate superiority of one device over another in bladder pathology.</td>
<td></td>
</tr>
<tr>
<td>Complications are generally directly related to the laser’s wavelength (penetration depth) and surgical technique.</td>
<td></td>
</tr>
</tbody>
</table>

**Recommendation**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser treatment for bladder cancer should only be used in a clinical trial setting or for patients who, due to co-morbidities or other complications, are not fit for conventional treatment.</td>
<td>C</td>
</tr>
</tbody>
</table>
4.4 References


5. APPLICATIONS OF LASERS IN LAPAROSCOPY/ENDOSCOPY

5.1 Laser-assisted partial nephrectomy

5.1.1 Introduction

The need for hilar clamping in case of laparoscopic partial nephrectomy (PN) is currently necessary to create a bloodless field for renal excision. However, hilar clamping increases the complexity of the operation because of the time constraint and the significant risk for increased times of warm renal ischaemia and subsequent post-operative compromise of renal function. Laser technology presents a promising alternative to achieve tumour excision, pelvicaliceal water tightness and renal haemostasis in a time-sensitive manner, with or without hilar occlusion.

5.1.2 Clinical application and results

Several experimental studies have demonstrated the efficiency of laser-assisted partial nephrectomy in various experimental set-ups. However, up to date only eight small series concerning clinically tested laser-assisted PN have been published, of which only two series were performed laparoscopically (one conventional and one robotic) (Table 11) (1-8) (LE: 3). Consequently, the evidence is considered poor and further investigation is necessary in order to establish the method as a routine alternative for nephron-sparing surgery.

Early experience with laser technology in renal surgery can be traced back to 1982. Preliminary results with the use of carbon dioxide laser for renal ablation were promising, demonstrating a reduction in blood loss, shortening of operative time and preserving of functional integrity in remaining renal tissue (1,2). In 1986, the first series of PN without the need for hilar clamping was reported. Malloy et al. employed the Nd:YAG laser in the treatment of three elderly patients with renal cell carcinoma in a solitary kidney. The Nd:YAG laser was used together with standard open surgical techniques for tumour extraction. No occlusion of the renal artery was needed and the oncological outcome was considered perfect in all three cases (3) (LE: 3).

Initial experience with the use of contact Nd:YAG laser resection in PN was first described in 1993. In a series of six resections, surgeons occluded the renal artery to ensure good intra-operative haemostasis. Cutting properties of the laser were considered more accurate, while energy levels could be reduced causing less damage to the remaining parenchyma. Oncological outcome was considered perfect (4) (LE: 3). Additionally, the combination of both the KTP laser (for cutting) and the YAG laser (for coagulation of large vessels) allowed fast removal of kidney tissue, with minimal blood loss and minimal loss of renal parenchyma in as small a series of three paediatric cases of bilateral Wilms’ tumours (5).

The safety and feasibility of laser PN without the need for hilar occlusion was further supported in another small series of patients treated in an open fashion. A total of five patients with renal tumours up to 3.8 cm in size were subjected to open PN. A 2.0-μm continuous wave laser (RevoLix) by LISA laser, which is a diode-pumped solid-state laser emitting a wavelength of 2013 nm and penetrating tissue to a depth of about 0.5 mm was used. In all cases, no peri-operative haemorrhage was noted and no sutures or other means of haemostasis were needed. No post-operative massive bleeding or significant creatinine level alteration were noted. In accordance with the authors, efficient and safe vascular coagulation was possible up to a vessel diameter of 1.5 mm. The laser technique should only be used in peripheral renal tumours (6) (LE: 3).

Successful accomplishment of laparoscopic PN (LPN) without the need for hilar occlusion in three human cases using the Ho:YAG laser was first reported in 2002. The indications for LPN were a complicated renal cyst and a 2.5-cm renal-cell carcinoma in two adult patients and a non-functioning lower pole in a duplicated collecting system in an 8-year-old child. Energy settings used were 2 J/pulse at 60 pulses/sec and 0.8 J/pulse at 40 pulses/sec. Despite the fact that haemostasis was considered adequate, fibrin glue was applied in two
cases and oxidised cellulose in one case to reinforce the tissue against delayed bleeding. No complications were encountered and all patients left the hospital within 3 days.

The two major disadvantages of the technique were increased smoke accumulation during laser activation and significant splashing of blood onto the camera lens during resection, which occasionally impaired visibility (7) (LE: 3).

More recently, preliminary experience with laser robotic partial nephrectomy without hilar clamping was reported in two patients. KTP laser robotic partial nephrectomy was performed with a purpose-built, prototype, robotic, laser delivery instrument. A Greenlight HPS® laser unit was used at settings up to 50 W. In one patient, hilar clamping was necessitated during the procedure because of bleeding from a large central segmental vessel. The depth of thermal injury was estimated to be approximately 1 mm. No major complications were reported (8) (LE: 3).

Table 11: Clinical experience with laser-assisted partial nephrectomy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Laser beam</th>
<th>Hilar clamping</th>
<th>Comments or adverse effects</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barzilay et al. 1982 (1)</td>
<td>4</td>
<td>Partial nephrectomy (3), bivalving of kidney (1)</td>
<td>CO₂ laser beam</td>
<td>Yes</td>
<td>Open</td>
<td>3</td>
</tr>
<tr>
<td>Rosemberg 1985 (2)</td>
<td>3</td>
<td>Partial nephrectomy</td>
<td>CO₂ laser beam</td>
<td>Yes</td>
<td>Open</td>
<td>3</td>
</tr>
<tr>
<td>Malloy et al. 1986 (3)</td>
<td>3</td>
<td>Partial nephrectomy</td>
<td>Nd:YAG laser</td>
<td>No</td>
<td>Open</td>
<td>3</td>
</tr>
<tr>
<td>Korhonen et al. 1993 (4)</td>
<td>5</td>
<td>Partial nephrectomy</td>
<td>Nd:YAG laser</td>
<td>Yes</td>
<td>Open</td>
<td>3</td>
</tr>
<tr>
<td>Merguerian et al. 1994 (5)</td>
<td>3</td>
<td>Partial nephrectomy</td>
<td>Nd:YAG laser and KTP laser</td>
<td>Yes</td>
<td>Open</td>
<td>3</td>
</tr>
<tr>
<td>Gruschwitz et al. 2008 (6)</td>
<td>5</td>
<td>Partial nephrectomy</td>
<td>2.0-μm continuous wave laser</td>
<td>No</td>
<td>Open</td>
<td>3</td>
</tr>
<tr>
<td>Lotan et al. 2002 (7)</td>
<td>3</td>
<td>Partial nephrectomy</td>
<td>Ho:YAG laser</td>
<td>No</td>
<td>Laparoscopic/ smoke accumulation and splashing of blood on camera</td>
<td>3</td>
</tr>
<tr>
<td>Hodgson et al. 2008 (8)</td>
<td>2</td>
<td>Partial nephrectomy</td>
<td>KTP laser</td>
<td>No</td>
<td>Robotic / hilar clamping was necessitated in one occasion</td>
<td>3</td>
</tr>
</tbody>
</table>

Ho:YAG = Holmium: yttrium aluminium garnet; KTP = potassium titanyl-phosphate laser; Nd:YAG = neodymium-doped yttrium aluminium garnet.

5.1.3 Conclusions about laser-assisted partial nephrectomy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current data on nephron-sparing surgery using laser energy as an ablative method remain inconclusive.</td>
<td></td>
</tr>
<tr>
<td>Preliminary results indicate that laser-assisted laparoscopic PN without the need for hilar clamping is feasible.</td>
<td>3</td>
</tr>
<tr>
<td>No major complication has been reported in humans.</td>
<td>3</td>
</tr>
<tr>
<td>Laser-assisted PN is a promising alternative in renal surgery, which is worth further evaluation in clinical trials.</td>
<td></td>
</tr>
</tbody>
</table>
5.2 Laser-assisted laparoscopic nerve-sparing radical prostatectomy (LNSRP)

Experimental and preliminary clinical data have highlighted promising future applications of laser technology in laparoscopic nerve-sparing radical prostatectomy (LNSRP) (Table 12). After examining the suitability of the technique in an experimental set-up of radical prostatectomy in dogs, Gianduzzo et al. performed a 532 nm KTP laser robotic nerve-sparing radical prostatectomy in 10 patients using the AuraXP laser unit, delivering 12W through a 300-μm Endostat® fibre. The ability of KTP laser to be selectively absorbed by haemoglobin allows fine dissection, haemostasis and minimal tissue injury at the same time. However, in the current series, additional haemostasis using diathermy, suture or clips was required on several occasions for each case. Complications were one urine leak and one drain-site infection. Long-term potency outcomes were not demonstrated.

This is the first clinical evaluation of KTP laser as an ablative method in nerve-sparing radical prostatectomy (9) (LE: 3). In accordance with the author, the main disadvantage of the technique is the requirement for a filter for the KTP green light emission to prevent interference with the camera system, and the wearing of tinted safety glasses, both of which significantly detract from the laparoscopic view. Experimental data on dogs verify that the ability of KTP laser to preserve cavernous nerve function is comparable to the athermal techniques (sharp dissection and clip placement) (10). However, further clinical assessment is needed to determine the value of this technique.

Promising results in matters of LNSRP using Nd:YAG laser dissection have been reported as well. In a preliminary feasibility study enrolling five patients with clinically localised adenocarcinoma of the prostate neurovascular bundle (NVB) preservation was evaluated. The 1064 nm Nd:YAG laser was used and a continuous-wave mode applied in direct tissue contact at a 8-W power setting was suggested as the appropriate setup for most of the cases. Minimal blood loss, rapid dissection and minimal adjacent tissue injury estimated to be at 687μm (mean) were noted. As the NVBs were excised at the end of the operation for histological analysis erectile functional data could not be assessed, which is a limitation of the current study (9) (LE 3).

Table 12: Clinical experience with laser-assisted laparoscopic nerve-sparing radical prostatectomy

<table>
<thead>
<tr>
<th>References</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Laser beam</th>
<th>Comments or adverse effects</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gianduzzo et al. 2007 (9)</td>
<td>5</td>
<td>LNSRP</td>
<td>1064 nm Nd:YAG laser</td>
<td>Laparoscopic</td>
<td>3</td>
</tr>
</tbody>
</table>

LNSRP = Laser-assisted laparoscopic nerve-sparing radical prostatectomy; Nd:YAG = neodymium-doped yttrium aluminium garnet.

5.2.1 Conclusions about laser-assisted laparoscopic nerve-sparing radical prostatectomy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data are sparse and safe conclusions cannot be drawn yet.</td>
<td></td>
</tr>
<tr>
<td>Preliminary results indicate that laser-assisted LNSRP is feasible and could possibly enhance neurovascular bundle preservation.</td>
<td>3</td>
</tr>
<tr>
<td>Laser-assisted LNSRP remains experimental.</td>
<td></td>
</tr>
</tbody>
</table>

6. RENAL TUMOUR LASER INTERSTITIAL ABLATION

The current consensus for small renal tumours supports thermal coagulation as an alternative treatment option, but only in selected cases of patients with co-morbidities that make them unsuitable candidates for partial nephrectomy (11).

Clinical experience with renal tumour laser interstitial ablation is still limited (Table 13). Renal magnetic resonance imaging (MRI)-guided percutaneous laser thermal ablation (LTA) was first introduced by de Jode and used in a preliminary feasibility study, treating three patients with inoperable renal tumours using a Nd:YAG
laser delivered percutaneously to the renal tumour through a water-cooled interstitial fibre. MRI was used to both guide laser placement and monitor treatment in real time. Tissue necrosis within the targeted tissue was confirmed (12) (LE: 3).

Dick et al. evaluated the safety and feasibility of the technique in a series of nine patients with inoperable renal tumours. The operation took place under local sedation and opiate analgesia alone in 6 out of 9 patients, with the rest under general anaesthesia. A water-cooled 600 μm interstitial fibre was used to deliver 1064 μm Nd:YAG laser energy to the tumour. Laser energy was applied at 25 W for 10-30 minutes per treatment session. In all patients, the percentage enhancement of the tumour significantly decreased after LTA at the mean follow-up period of 16.9 months after the procedure. No subsequent infiltration of tumour into surrounding structures, e.g. peripheral fat and the renal vein, was noted. Reported complications were two cases of peripheral haematoma (resolving with conservative management) and one case of bradycardia (responded rapidly to atropine) (13) (LE: 3).

Table 13: Clinical experience with renal tumour laser interstitial ablation is still limited

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Disease</th>
<th>Laser beam</th>
<th>Comments</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Jode et al. 1999 (12)</td>
<td>3</td>
<td>Inoperable renal tumours</td>
<td>Nd:YAG laser</td>
<td>Percutaneously or MRI-guided</td>
<td>3</td>
</tr>
<tr>
<td>Dick et al. 2002 (13)</td>
<td>9</td>
<td>Inoperable renal tumours</td>
<td>Nd:YAG laser</td>
<td>Percutaneously or MRI-guided</td>
<td>3</td>
</tr>
</tbody>
</table>

6.1 Conclusions and recommendation for laser treatment of small renal masses

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data are poor and safe conclusions cannot be drawn yet regarding oncological outcome and safety.</td>
<td>4</td>
</tr>
<tr>
<td>Renal tumour interstitial laser ablation remains experimental.</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser-assisted laparoscopic PN, laser-assisted LNSRP and renal tumour laser interstitial coagulation are still experimental and should only be used in a clinical trial setting.</td>
<td>C</td>
</tr>
</tbody>
</table>

6.2 References

7. RETROGRADE LASER ENDOURETEROTOMY

7.1 Introduction
Endoureterotomy is often first-line treatment for benign ureteral strictures. Since its introduction in 1997, retrograde laser endoureterotomy has become a popular tool for this procedure (1). Publications concerning the approach are based on retrospective analysis, i.e. single-institution studies resulting in levels 3 and 4 evidence (1-12) (Table 14).

7.2 Clinical application and results
Success rates of laser endoureterotomy are not uniformly evident. Large variations in success rates variations between published literature most probably arise because benign ureteral strictures are comprised of several different entities, each possibly responding differently to laser endoureterotomy (6). Nevertheless, large retrospective studies are lacking to elucidate which strictures respond well and which do not (LE: 4). Non-ischaemic (e.g. iatrogenic) benign ureteral strictures after calculus management or abdominal surgery are reported to respond well to laser endoureterotomy, with a reported success rate between 68.4% and 91% (LE: 3). Stricture length is probably the most important predictor of outcome. Long ureteric strictures (> 2 cm) tend to be associated with poorer success rates (LE: 3). Stricture duration, ipsilateral renal function, stone impaction and stricture localisation (upper, middle or lower) have been also suggested to affect the outcome, though published results are controversial (LE: 3). Patients with ureteroenteric and malignant strictures do not respond well to laser endoureterotomy. Success rates in these cases are reported to be less than 60% (LE: 3).

The outcome of retrograde laser endoureterotomy compared to open surgical revision is slightly inferior (LE: 2b). However, due to the minimally invasive nature of the technique, laser endoureterotomy is associated with less morbidity and should be considered a first-line treatment option (LE: 3). When compared with other well-substantiated, endourological methods (e.g. hot-wire balloon catheter, endoincision with electrocautery or cold knife), laser endoureterotomy has been reported to have the same or superior long-term results (9). However, currently, there are no larger studies available presenting reliable long-term equivalence.

Holmium:YAG laser appears the only well tested-treatment modality (LE: 4). Currently, other laser energy sources are under evaluation which should still be considered experimental.

Since large studies are lacking and long-term studies are rare, the median time to failure has not yet been elucidated. Stricture recurrence as long as 18 months post-operatively has been reported. Yet, recurrence is most likely to be evident within the first 3 months (LE: 3). Balloon dilation after laser incision and post-operative placement of a ureteral stent for the duration of between 4 weeks to 6 months are common practices that
appear to aid long-term effectiveness (LE: 4). However, there remains a lack of studies comparing treatment failure with or without balloon dilation and post-operative ureteral stenting.

Table 14: Clinical experience with retrograde laser endoureterotomy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Disease</th>
<th>Success rate</th>
<th>Mean follow-up (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al. 2009 (2)</td>
<td>19</td>
<td>Benign ureteral strictures</td>
<td>52.6%</td>
<td>40.2</td>
<td>Stricture length and severity of hydronephrosis correlated with successful outcome</td>
</tr>
<tr>
<td>Gnnessin et al. 2009 (3)</td>
<td>35</td>
<td>Benign ureteral strictures</td>
<td>82% symptomatic, 78.7% radiographic</td>
<td>27</td>
<td>Success rate was higher for nonischaemic strictures (100% vs 64.7%, p = 0.027). Most failures occur within less than 9 months after surgery</td>
</tr>
<tr>
<td>Fu et al. 2009 (4)</td>
<td>18</td>
<td>Benign ureteral strictures, 6 cases complicated with ureteral calculus</td>
<td>88.8%</td>
<td>10.7</td>
<td>Post-operatively, an orthopaedic ureteral stent was left in place for 3-6 months</td>
</tr>
<tr>
<td>Corcoran et al. 2009 (5)</td>
<td>9</td>
<td>Benign ureteral strictures (20% idiopathic, 80% after calculi management or abdominal surgery)</td>
<td>85%</td>
<td>25.2</td>
<td>Laser urethrotomy was followed by balloon dilation in most cases</td>
</tr>
<tr>
<td>Gdor et al. 2008 (6)</td>
<td>13</td>
<td>Ureteral strictures associated with ureteral calculi (impacted ureteral calculi in 4)</td>
<td>62%</td>
<td>21</td>
<td>In case of impacted ureteral calculi, success rate was 56%. Without a history of impacted calculi, success rate was 75%</td>
</tr>
<tr>
<td>Hibi et al. 2007 (7)</td>
<td>20</td>
<td>80%</td>
<td>60.5</td>
<td></td>
<td>All failures occurred within 18 months</td>
</tr>
<tr>
<td>Lane et al. 2006 (8)</td>
<td>19</td>
<td>Non-obliterative iatrogenic ureteral strictures</td>
<td>68.4%</td>
<td>36</td>
<td>Failure was uniformly evident within the first 3 months</td>
</tr>
<tr>
<td>Razdan et al. 2005 (9)</td>
<td>17</td>
<td>Ureteral strictures of varying causes</td>
<td></td>
<td>40.8</td>
<td></td>
</tr>
<tr>
<td>Kourambas 2001 (10)</td>
<td>7</td>
<td>Ureteral strictures</td>
<td>91%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Singal et al. 1997 (1)</td>
<td>22</td>
<td>Ureteral strictures from a variety of causes and including ureteroenteric anastomoses</td>
<td>76%</td>
<td>9</td>
<td>Failure was uniformly evident within the first 3 months</td>
</tr>
<tr>
<td>Watterson et al. 2002 (11)</td>
<td>23</td>
<td>Ureterointestinal strictures</td>
<td>56%</td>
<td>36</td>
<td>Some recurrences occurred 16 months or longer postoperatively</td>
</tr>
<tr>
<td>Laven et al. 2001 (12)</td>
<td>19</td>
<td>Ureterointestinal strictures</td>
<td>57%</td>
<td>20.5</td>
<td></td>
</tr>
</tbody>
</table>
7.3 Conclusions and recommendations for retrograde laser endoureterotomy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde laser endoureterotomy is a feasible and safe treatment option</td>
<td></td>
</tr>
<tr>
<td>for ureteral strictures.</td>
<td>3</td>
</tr>
<tr>
<td>Open surgical revision remains the gold standard.</td>
<td>1a</td>
</tr>
<tr>
<td>Ureteral strictures of different aetiologies appear to respond differently</td>
<td>2b</td>
</tr>
<tr>
<td>to treatment.</td>
<td></td>
</tr>
<tr>
<td>In selected cases, success rate can reach 90%.</td>
<td></td>
</tr>
<tr>
<td>Ureteroenteric anastomosis strictures respond poorly to laser endoureterotomy.</td>
<td>3</td>
</tr>
<tr>
<td>Late stricture recurrence should be expected until as long as 18 months</td>
<td>3</td>
</tr>
<tr>
<td>post-operatively.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde endoureterotomy should be considered a first-line treatment</td>
<td>C</td>
</tr>
<tr>
<td>option for ureteral strictures.</td>
<td></td>
</tr>
<tr>
<td>Longer follow-up is needed.</td>
<td>C</td>
</tr>
</tbody>
</table>

7.4 References

8. RETROGRADE LASER ENDOPYELOTOMY FOR URETEROPELVIC JUNCTION OBSTRUCTION (UPJO)

8.1 Introduction
Initial experience with laser endopyelotomy for the treatment of ureteropelvic junction obstruction (UPJO) can be traced back to the early 1990s (1). Since then, laser retrograde endopyelotomy has been a well-established method for the treatment of primary or secondary ureteropelvic junction (UPJ) strictures. Publications concerning retrograde laser endopyelotomy are mostly based on retrospective analysis, i.e. single-institution studies resulting in level 3 and 4 evidence data (Table 15) (2-19).

8.2 Clinical application and results
The optimal indication for laser endopyelotomy is a short (< 2 cm) UPJO of intrinsic aetiology in the absence of a very large pelvis, high insertion of the ureter, renal split function below 20%, and ipsilateral renal calculi (LE: 4). When particular inclusion criteria are selected, success rates are reported to be around 80% or even higher in more selected cases in the hands of an experienced urologist (LE: 4). Inferior success rates have been reported in cases of extrinsic cause of UPJO and severe hydronephrosis and in poor renal function (16,17).

The outcome of retrograde laser endopyelotomy compared to open pyeloplasty is slightly inferior (LE: 2b). However, due to the minimally invasive nature of the technique, laser endopyelotomy is associated with minimum blood loss, reduced hospital stay and less post-operative pain and should be one of the first-line treatment options (LE: 2b). In addition, a failed endopyelotomy is not a contraindication for secondary open or laparoscopic pyeloplasty. When compared with other well-substantiated, endourological methods (e.g. hotwire balloon catheter, endoincision with electrocautery or cold knife), laser endopyelotomy is reported to have a similar or higher success rate and a lower rate of complications (8) (LE: 3). However, there are as yet no larger studies to provide reliable long-term equivalence.

The Ho:YAG laser appears to be the only well-tested treatment modality (LE: 4), with other laser energy sources under evaluation and still experimental. Complication rates associated with retrograde laser endopyelotomy have been reported as 12.5%, although the complications referred to are usually minor. More serious measures, such as conversion to open surgery, rarely need to be taken (LE: 3).

Despite the fact that long-term studies are rare, the median time to failure is reported to be as high as 7.7 months post-operatively (6). Post-operative placement of ureteral catheters, such as JJ stents for several weeks, is a common practice, despite the lack of studies comparing treatment failure with or without post-operative ureteral stenting.

Table 15: Clinical experience with retrograde laser endopyelotomy for ureteropelvic junction obstruction

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Disease</th>
<th>Success rate</th>
<th>Mean follow-up (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acher et al. 2009 (2)</td>
<td>15</td>
<td>Failed pyeloplasty</td>
<td>100%</td>
<td>6</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Stilling et al. 2009 (3)</td>
<td>44</td>
<td>Primary (n=37) and secondary (n=7)</td>
<td>Symptom relief complete 66%; improved 23%</td>
<td>27.5</td>
<td>Strict inclusion criteria</td>
</tr>
<tr>
<td>Savoie et al. 2009 (4)</td>
<td>27</td>
<td>Primary (n=16) and secondary (n=11)</td>
<td>PEJO</td>
<td>70%</td>
<td>Median time to failure: 2.7 months</td>
</tr>
<tr>
<td>Braga et al. 2007 (5)</td>
<td>10</td>
<td>Failed pyeloplasty in children</td>
<td>60% radiographic relief</td>
<td>47</td>
<td>Age &lt; 4 years and narrowed ureteral segment greater than 10 mm were associated with a poor outcome</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Outcome Description</td>
<td>Success Rate</td>
<td>Complication Rate</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>---------------------------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Doo et al. 2007 (6)</td>
<td>47</td>
<td>UPJO</td>
<td>67.5%</td>
<td>37.3</td>
<td>Median time to failure: 7.7 months</td>
</tr>
<tr>
<td>Rassweiler et al. 2007 (7)</td>
<td>113</td>
<td>Extrinsic as well as intrinsic UPJO</td>
<td>72.6% (85.7% intrinsic vs 51.4% extrinsic)</td>
<td>63 months</td>
<td>Complication rate of 5.3%</td>
</tr>
<tr>
<td>Ponsky et al. 2006 (8)</td>
<td>37</td>
<td>Primary and secondary UPJO</td>
<td>74.2%</td>
<td>75.6</td>
<td>No major complications reported</td>
</tr>
<tr>
<td>Geavlete et al. 2007 (9)</td>
<td>30</td>
<td>Failed pyeloplasty (n=17); failed endopyelotomy (n=13)</td>
<td>83.3% (at 18 months)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>el-Nahas et al. 2006 (10)</td>
<td>20</td>
<td>Primary and secondary UPJO</td>
<td>85%</td>
<td>29.9</td>
<td>10% complication rate</td>
</tr>
<tr>
<td>Minervini et al. 2005 (11)</td>
<td>30</td>
<td>UPJO</td>
<td>80% (at 10 months)</td>
<td>24</td>
<td>12.5% complication rate</td>
</tr>
<tr>
<td>Seveso et al. 2005 (12)</td>
<td>16</td>
<td>Primary (n=10) and secondary (n=6) UPJO</td>
<td>81%</td>
<td>18</td>
<td>One case of intra-operative haemorrhage</td>
</tr>
<tr>
<td>Matin et al. 2003 (13)</td>
<td>46</td>
<td>Primary (n=40) and secondary (n=6) UPJO</td>
<td>65.4% symptomatic and 73.1% radiographic</td>
<td>23.2</td>
<td>No intra-operative complications; 11.1% post-operative complications</td>
</tr>
<tr>
<td>Hibi et al. 2002 (14)</td>
<td>5</td>
<td>UPJO</td>
<td>80%</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>Giddens et al. 2000 (15)</td>
<td>23</td>
<td>Primary and secondary UPJO</td>
<td>83%</td>
<td>10</td>
<td>Repeat laser incision successful in 50% of primary failures</td>
</tr>
<tr>
<td>Biyani et al. 2000 (16)</td>
<td>22</td>
<td>Primary (n=16) and secondary (n=4) UPJO</td>
<td>75%</td>
<td>34</td>
<td>Success rate tends to be poor in patients with poor renal function</td>
</tr>
<tr>
<td>Renner et al. 1998 (17)</td>
<td>34</td>
<td>Primary (n=27) and secondary (n=7) UPJO</td>
<td>85%</td>
<td>18</td>
<td>Minor complications in 15%</td>
</tr>
<tr>
<td>Conlin et al. 1998 (18)</td>
<td>21</td>
<td>UPJO</td>
<td>81%</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Biyani et al. 1997 (19)</td>
<td>8</td>
<td>Primary (n=5) and secondary (n=3) UPJO</td>
<td>87.5%</td>
<td>12.4</td>
<td></td>
</tr>
</tbody>
</table>

**UPJO = ureteropelvic junction obstruction.**

### 8.3 Conclusions and recommendations for laser treatment for UPJO

**Conclusions**

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde laser endopyelotomy is a feasible and safe treatment option for the treatment of ureteropelvic junction obstruction.</td>
<td>3</td>
</tr>
<tr>
<td>Open or laparoscopic pyeloplasty remains the gold standard.</td>
<td>1a</td>
</tr>
<tr>
<td>In selected cases, success rate can reach 90%.</td>
<td></td>
</tr>
<tr>
<td>Treatment morbidity is minimal and major complications are rare.</td>
<td>3</td>
</tr>
<tr>
<td>Treatment failure may occur up to 1 year post-operatively.</td>
<td>3</td>
</tr>
</tbody>
</table>
Recommendations

Retrograde laser endopyelotomy could be one of the first-line treatment options. C
Follow-up should be prolonged for at least 1 year post-operatively. C
Open or laparoscopic pyeloplasty remain options in cases in which minimally invasive measures fail. C
Ensure identification of crossing vessels which is of particular relevance in reducing bleeding complications. B
Ureteric stent placement before the procedure is an option that may affect the post-operative success rate. C

8.4 References


9. TRANSURETHRAL LASER URETHROTOMY

9.1 Introduction
The introduction of transurethral laser urethrotomy using the Nd:YAG laser can be traced back to 1979 (1). Since then, laser urethrotomy has become a common urological practice worldwide in the management of urethral strictures. Publications concerning this approach are based on retrospective analysis, i.e. single-institution studies leading to level 3 or 4 evidence data (2-19) (Table 16).

9.2 Clinical application and results
Success rates of laser urethrotomy for urethral strictures are reported to be as high as 100% in selected cases (LE: 3). Short segment urethral strictures tend to respond excellently to this treatment modality (LE: 3). However, long (> 1.5 cm) or recurrent urethral strictures are reported to demonstrate inferior results (LE: 3). Periodic urethral dilatation is usually enough for the management of treatment failure (LE: 3).

The types of lasers tested on laser urethrotomy are the Nd:YAG, the KTP, the argon, the Ho:YAG and the diode laser. No superiority of one type of lasers has been demonstrated (LE: 3). There is a lack of large multicentre studies comparing the success rate of laser endourethrotomy with conventional optical urethrotomy. Currently, the midterm effectiveness of both treatment options is considered equal (LE: 3). However, in a randomised control study comparing the effectiveness of Nd:YAG laser with conventional cold-knife optical urethrotomy in the treatment of varying length urethral strictures (0.3-2.4 cm), laser treatment significantly decreased the probability of therapeutic failure and recurrence of strictures (20) (LE: 3).

Table 16: Clinical experience with transurethral laser urethrotomy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Disease</th>
<th>Success rate %</th>
<th>Mean follow-up (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo et al. 2010 (2)</td>
<td>238</td>
<td>Urethral strictures</td>
<td>81.9%</td>
<td>6</td>
<td>2-micron thulium laser</td>
</tr>
<tr>
<td>Guo et al. 2008 (3)</td>
<td>198</td>
<td>Urethral strictures (n = 179) or atresia (n = 13)</td>
<td>81.7%</td>
<td>6</td>
<td>2 micron thulium laser</td>
</tr>
<tr>
<td>Xiao et al. 2008 (4)</td>
<td>34</td>
<td>Urethral strictures</td>
<td>94.7%</td>
<td>3-18</td>
<td>Holmium laser: 4 received urethral dilatation and 2 underwent a second holmium laser urethrotomy</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Cases</td>
<td>Description</td>
<td>Success Rate</td>
<td>Duration</td>
<td>Laser Type</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>-------------</td>
<td>--------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>Eltahawy et al. 2008</td>
<td>24</td>
<td>Anastomotic stenosis following radical prostatectomy, 79% recurrent-resistant to other treatment modalities</td>
<td>83%</td>
<td>24</td>
<td>Holmium laser + steroid injection</td>
</tr>
<tr>
<td>Futoa et al. 2006</td>
<td>28</td>
<td>Paediatric patients with urethral strictures (n=25) and urethral atresias (n=3)</td>
<td>89.3%</td>
<td>(2-48)</td>
<td>Ho:YAG</td>
</tr>
<tr>
<td>Hossain et al. 2004</td>
<td>30</td>
<td>Short segment anterior urethral stricture</td>
<td>90%</td>
<td>6</td>
<td>Ho:YAG</td>
</tr>
<tr>
<td>Dogra et al. 2004</td>
<td>29</td>
<td>Urethral stricture (&lt; 2.5 cm)</td>
<td>65.51% excellent, 31.03% acceptable</td>
<td>15</td>
<td>Ho:YAG</td>
</tr>
<tr>
<td>Gürdal et al. 2003</td>
<td>21</td>
<td>Recurrent benign urethral strictures 5-20 mm in length</td>
<td>52%</td>
<td>24</td>
<td>Nd:YAG</td>
</tr>
<tr>
<td>Dogra et al. 2003</td>
<td>61</td>
<td>Obliterative post-traumatic urethral strictures in children</td>
<td>100%</td>
<td>24</td>
<td>Nd-YAG</td>
</tr>
<tr>
<td>Matsuoka et al. 2002</td>
<td>31</td>
<td>Ureteral stricture of varying lengths</td>
<td>74%</td>
<td></td>
<td>Ho:YAG</td>
</tr>
<tr>
<td>Dogra et al. 2002</td>
<td>65</td>
<td>Post-traumatic urethral strictures</td>
<td>95.3%</td>
<td>9-44</td>
<td>Nd- YAG</td>
</tr>
<tr>
<td>Kamal 2001</td>
<td>22</td>
<td>Urethral strictures (8 recurrent)</td>
<td>54% (78.5% in non recurrent strictures)</td>
<td>26.7</td>
<td>Diode laser</td>
</tr>
<tr>
<td>Schmidlin et al. 1997</td>
<td>20</td>
<td>Anterior urethral strictures</td>
<td>81%</td>
<td>6</td>
<td>KTP</td>
</tr>
<tr>
<td>Becker et al. 1995</td>
<td>900</td>
<td>Urethral strictures (most iatrogenic)</td>
<td>30%</td>
<td>15.2</td>
<td>Argon</td>
</tr>
<tr>
<td>Faerber et al. 1994</td>
<td>12</td>
<td>Paediatric urethral strictures</td>
<td>83%</td>
<td>12</td>
<td>Nd-YAG</td>
</tr>
<tr>
<td>Turek et al. 1992</td>
<td>37</td>
<td>Benign urethral strictures</td>
<td>59% complete, 20.5% partial success</td>
<td>9.7</td>
<td>KTP</td>
</tr>
<tr>
<td>Vicente et al. 1990</td>
<td>15</td>
<td>Benign urethral strictures</td>
<td>73.3%</td>
<td>12</td>
<td>Cold knife + Nd:YAG laser</td>
</tr>
<tr>
<td>Bloiso et al. 1988</td>
<td>115</td>
<td>31 short strictures 36 bladder neck 48 complicated</td>
<td>96.7% (short strictures); 100% (bladder neck); 22.91% (complicated)</td>
<td>10 (short strictures); 7 (bladder neck); 14 (complicated)</td>
<td>Nd:YAG</td>
</tr>
</tbody>
</table>

Ho:YAG = Holmium: yttrium aluminium garnet; KTP = potassium titanyl-phosphate laser; Nd:YAG = neodymium-doped yttrium aluminium garnet

9.3 Conclusions and recommendation for transurethral laser urethrotomy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transurethral laser urethrotomy is a feasible and safe treatment option for the treatment of urethral strictures.</td>
<td>3</td>
</tr>
<tr>
<td>Cold-knife optical urethrotomy remains the gold standard.</td>
<td>1a</td>
</tr>
<tr>
<td>Success rates as high as 100% are reported in selected cases</td>
<td>3</td>
</tr>
<tr>
<td>Treatment morbidity is minimal and major complications are rare.</td>
<td>3</td>
</tr>
</tbody>
</table>
Recommendation

Transurethral laser urethrotomy could be one of the first-line treatment options for benign urethral strictures.

9.4 References


10. LASER CLINICAL APPLICATIONS IN UPPER URINARY TRACT STONES AND TUMOURS

10.1 Introduction
The entire upper urinary tract can be accessed and explored with flexible endoscopes (1-3). Miniaturisation especially with laser fibres became an armamentarium in the endourological field. In Ho:YAG lasers, energy is delivered most commonly in a pulsatile manner, using a thermomechanical action. Absorption depth in tissue is about 1-2 mm, as long as it is used in a water-based medium. This specific light energy provides good homeostasis when used in a pulsed mode of 250-millisecond duration and at low pulse rate. At higher pulse rates, it may also be used for incisions. The frequency-doubled, double-pulse Nd:YAG (FREDDY) laser is a short-pulsed, double-frequency solid-state laser with wavelengths of 532 and 1064 nm. Although FREDDY laser is effective for lithotripsy, it does not have a soft-tissue application (e.g. tumours). The erbium laser (Er:YAG) laser may be superior to the Ho:YAG laser for precise ablation of strictures with minimal peripheral thermal damage and for more efficient laser lithotripsy (4). Er:YAG laser cuts urethral and ureteral tissues more precisely than Ho:YAG laser and produces less peripheral thermal damage. With any laser, all intra-operative personnel should wear proper eye protection to avoid corneal or retinal damage. This especially is true with Nd:YAG (FREDDY), which penetrates deeply and can burn the retina faster than the blink reflex can protect it. Ho:YAG does not penetrate as deeply, but it may cause corneal defects if aimed at the unprotected eye. An adequate draping should be used around external areas. Wet towels should be draped around cutaneous lesions. Reflective surfaces (e.g., metal instruments) should be kept away from the field if possible and, if not possible, should be draped with wet drapes. Furthermore, using laser where oxygen is in use anywhere near the operative field is dangerous. This can result in a laser fire and cause significant burns.

10.2 Upper urinary tract stones
Endoscopic intracorporeal laser lithotripsy is widely used as a treatment for upper urinary tract stone (5-7). Lasers are ideally suited for retrograde intra-renal surgery or percutaneous approach (8).

Flexible quartz fibres deliver laser energy to fragment all types of stones. That energy is delivered in a pulsatile fashion through low-water density quartz fibres. In water, a vaporisation bubble surrounds the fibre tip. This bubble actually destabilises stones, creating fine dust and small fragments. Accurate fibre contact against a calculus is the primary safety factor. Successful stone fragmentation is achieved in on average > 90% of cases (6). Stone fragmentation with Ho:YAG laser further minimises ureteral wall trauma; provided that, the distance between the tip of the fibre and ureter is greater than one mm. the risk of ureteral perforation during laser lithotripsy is negligible since the depth of thermal injury is 0.5 to 1 mm. Ho:YAG laser is fully absorbed within the first few millimetres of tissue; therefore, when applied in water or saline irrigant, minimal risk of surrounding thermal injury exists as compared to Nd:YAG (9,10). Ho:YAG has a minimal fragment migration and retrograde propulsion when low settings compared to Nd:YAG (9).

Hard stones in difficult locations (e.g., lower pole caliceal calculi, stone bearing caliceal stone) can be treated using a thin, 150 to 200-μm, that is easily deflected. Moreover, the type of eye protection used for Ho:YAG does not affect colour perception. Nd:YAG laser combines of solid and dye lasers. In vitro studies (11), It has been compared with Ho:YAG lasers across several parameters relating to stone treatment; fragmentation was significantly better with Nd:YAG laser than with Ho:YAG laser. Nevertheless, in 2006, a study reported Nd:YAG laser provided suspect fragmentation of calcium oxalate monohydrate stones and ineffective fragmentation of cystine stones (12). In addition to that, stone retropulsion was significantly greater (9,11,13). Alexandrite laser has been used, it is safe and effective, although it is rarely used in recent clinical practice (14).

All of the initial laser lithotrities (pulsed dye, Q-switched YAG and alexandrite) fragmented stones through the generation of a shock wave. Those waves disrupt the stone along fracture lines.
The Holmium laser works through a photo-thermal mechanism, which involves the direct absorption of the laser energy by the stone. The absence of strong wave in Holmium laser avoids the retropulsion phenomenon (15). Nevertheless, it is still strong enough to create stone dust and thereby facilitate stone fragmentation with smaller fragments than those produced by pulsed lasers or other devices. Residual fragments place patients at higher risk for recurrent stone formation or growth (16). Holmium laser energy is absorbed by all stone compositions; this laser can be used to fragment all stone types (17). Cyanide production was reported as a side effect of uric acid stones fragmentation (18).

10.2.1 Conclusions

<table>
<thead>
<tr>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsed lasers are an effective and safe treatment for UUT stones, using endoscopes.</td>
</tr>
<tr>
<td>Lasers present a safe option for fragmenting stones in the upper urinary tract.</td>
</tr>
</tbody>
</table>

10.3 Upper urinary tract urothelial tumours

The aim of the conservative management of upper tract urothelial tumours (UUT-UT) is to preserve renal function (19-21). This may be considered imperative or absolutely indicated in patients with a solitary anatomic kidney, solitary functioning kidney or limited renal function.

The development of sophisticated endourologic techniques for the treatment of benign urologic disease has translated to the treatment of malignant neoplasms, with the use of flexible ureteroscope and laser ablation becoming common place in urologic practice (19-23). Further, the cancer-control efficacy of this management approach has been established (20,21).

Even though nephro-ureterectomy is the gold standard; the current literature supports the use of lasers in patients with UUT-UT; however, meticulous and long-term follow up is needed (23,25). Ho:YAG and Nd:YAG lasers are presently the most commonly used lasers. The laser combining of both is convenient and effective but Ho:YAG can be used alone, preferentially with the variable pulse duration. Nd:YAG laser energy is used to coagulate with a thermal effect that extends deeper than other lasers. Holmium is more precise, with less of a coagulative effect. Laser therapy for tumour ablation is safe in patients with bleeding diathesis (25). In contrast to tumour ablation (Holmium/Thulium), in case of tumour vaporisation no pathology specimen will be available (Nd:YAG/Holmium/Thulium). Therefore multiple prior biopsy samples to determine depth of invasion should be obtained. Appropriate staging of the tumour (CT/biopsy) is important to allow selection of patients for nephron-sparing surgery. There are reports on percutaneous laser treatment of TCC of the kidney and this technique has been recognised in urological practice (26-28).

A true drawback with the Nd:YAG laser is that the area of destruction is deep and not fully visualised. Within the renal pelvis, the energy choice depends mainly upon the size of the lesion. Larger vascular tumours (> 1 cm) can be coagulated initially with the Nd:YAG and then ablated and cleared with the Holmium when a combination laser is available. Lower Holmium energy tends to maximise the coagulative effect and minimise the risk of bleeding (e.g. 0.5 to 0.6 joules and 5 hertz). The stricture rate in larger series has ranged from 5% to 13.7% (29). Because of the miniaturisation of instruments and development of laser fibres, the incidence of stricture rate is considered lower. Moreover, the stricture rate is considered lower due to minimal fibrotic reaction after laser use in comparison with electrocautery devices. To avoid urothelial damage and possible stricture, all endoscopic laser modalities should be used under direct vision, through the working channel of an endoscope.

10.4 Conclusion and recommendations for laser treatment of UUT urothelial tumours

<table>
<thead>
<tr>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephro-ureterectomy is still the gold standard for UUT urothelial tumours.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser ablation of small low-grade upper tract transitional cell carcinoma with close follow-up can be a safe alternative treatment to nephroureterectomy in patients with normal contralateral kidneys.</td>
</tr>
<tr>
<td>Endoscopic conservative treatment can be the preferred treatment in high-risk patients, as well as those with bilateral disease, solitary kidney or reduced renal function.</td>
</tr>
</tbody>
</table>
10.5 References


ABBREVIATIONS USED IN THE TEXT

(This list is not comprehensive for the most common abbreviations)

BPE    benign prostatic enlargement
BOO    bladder outlet obstruction
BPO    benign prostatic obstruction
CW     continuous wave
EAU    European Association of Urology
Er:YAG erbium: yttrium-aluminium-garnet laser
GR     grade of recommendation
HoLAP  Holmium laser ablation of the prostate
HoLEP  Holmium laser enucleation of the prostate
HoLRP  Holmium laser resection of the prostate
Ho:YAG Holmium: yttrium aluminium garnet
IIEF-5 international index of erectile function (abbreviated version)
KTP    laser potassium titanyl-phosphate laser
LBO    lithium triborate
LE     level of evidence
LNSRP  Laser-assisted laparoscopic nerve-sparing radical prostatectomy
LPN    laparoscopic partial nephrectomy
LTA    laser thermal ablation
MRI    magnetic resonance imaging
Nd:YAG neodymium-doped yttrium aluminium garnet
Nd:YAG (FREDDY) frequency-doubled, double-pulse laser
Nd:YAG laser (LBO) Lithium borat modulated Nd:YAG laser
NVB    prostate neurovascular bundle
OP     open prostatectomy
PN     partial nephrectomy
PSA    prostate specific antigen
PVP    photoselective vapourisation of the prostate
PVR    postvoid residual urine
Qmax   urinary peak flow
QoL    Quality of Life
Tm:YAG laser Thulium:Yttrium-Aluminium-Garnet laser
ThuWAP Tm:YAG Vaporisation of the prostate
ThuWARP Tm:YAG Vaporesection
ThuVEP Tm:YAG Vapoenucleation
ThuLEP Tm:YAG laser enucleation of the prostate
TUR    transurethral resection
TURB   TUR of the bladder
TURP   transurethral resection of the prostate
UPJO   ureteropelvic junction obstruction
UTI    urinary tract infection

Conflict of interest

All members of the New Technologies Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Robotic- and Single-site Surgery in Urology


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1. METHODOLOGY

1.1 Introduction

In 2011, the EAU Guidelines Office formed a working group to evaluate the current literature and the level of evidence (LE) of keyhole and robotic assisted surgery in urological procedures.

The panel members are surgeons with particular expertise in performing the procedures discussed in this document. All have been trained in traditional open and laparoscopic surgical approaches. Robotic assisted surgery is performed as a routine procedure by two expert panel members on a daily basis.

This document will not address economic evidence for robotic surgery in a systematic fashion. Resource limitations made it impossible for the panel to perform a comparative cost analysis (laparoscopic vs. robot assisted surgery). Doing so within a European-wide setting is not possible because national health policies determine the costs of clinical care. An analysis suggests that robotic surgery is more expensive than open surgery and laparoscopic surgery in approximately 75% of cases, with any cost-saving benefits of robotic surgery being largely attributed to variation in hospitalisation costs (1). Also, since robotic surgical devices are currently offered by one producer only, costs may decline in the future if there is more competition in the market for machines or related consumables (2).

1.1.1 Definitions

The following definitions are used here:

1. Single-site surgery is one single incision, with the addition of a maximum of one instrument (port) not larger than 5 mm.

2. Robotic surgery is the use of console-based laparoscopic telemanipulators.

1.2 Evidence acquisition

1.2.1 Literature search

Searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, Medline, and Embase on the Dialog-Datastar platform. The controlled terminology of the respective databases was used and both MesH and EMTREE were analysed for relevant entry terms.

1.2.2 Inclusion criteria

Case reports, congress proceedings, editorials, reviews and letters to the editor were not included. Publications reporting from the same institution and cohort were limited to the most recent or largest study. An online systematic review of the literature, according to Cochrane recommendations, was performed in July 2012 and identified data from 1990 to 2012. Manuscripts in languages other than English were included if data were extractable; these manuscripts were selected for inclusion in analysis using the criteria mentioned above.

1.2.3 Quality of evidence

There is still an on-going learning curve with this technique. It was therefore difficult to draw strong conclusions from the data currently available for analysis. There is a lack of multicentre, randomised, controlled studies producing conclusive evidence supporting open- vs. laparoscopic surgery.

In the absence of high-quality data, the expert panel came to the conclusion that providing guidance on the use of robotic-assisted surgery may even be more important. Except for a few procedures for which more mature data exist, recommendations are therefore generally based on the panel’s review of low-level evidence and expert opinion.

The only robotic system assessed in clinical studies is the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA). Most of the literature published discusses robotic assisted laparoscopic radical prostatectomy (RALP) and open radical prostatectomy (ORP). In renal cell cancer, bladder cancer and ureteropelvic junction obstruction only limited research was done assessing this novel technique.

1.3 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). Grading aims to provide transparency between the underlying evidence and the recommendation given.
Table 1: Level of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomised trials.</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomised trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well-designed controlled study without randomisation.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td>
</tr>
</tbody>
</table>

*Modified from (3).

It should be noted that when recommendations are graded, the link between the level of evidence (LE) and grade of recommendation (GR) is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as "upgraded based on panel consensus". The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (4-6).

Table 2: Grade of recommendation*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without randomised clinical trials.</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality.</td>
</tr>
</tbody>
</table>

*Modified from (3).

1.4 Of note

As with all technical equipment, malfunctions may occur; conversion to open procedure may be necessary in that case.

1.5 References


2. RENAL ROBOTICS - RADICAL NEPHRECTOMY, RECONSTRUCTIVE, AND PYELOPLASTY

2.1 Robotic radical nephrectomy (RRN)
Since its introduction in 1991, laparoscopic nephrectomy has been the gold standard for cases in which radical nephrectomy is indicated or nephron-sparing surgery is not possible (1). The first RRN was performed in 2000 (2). There are reports in the literature from 2001 for the use of robotic assisted surgery in donor nephrectomy and robot assisted laparoscopic nephrectomy (3,4).

Robotic radical nephrectomy is considered a safe procedure in selected cases. The reported complication rate of RRN in experienced hands is 18%, which is similar to the reported rate for laparoscopic radical nephrectomy (LRN) (5-9) (LE: 3; one prospective data evaluation). A longer operative time for RRN is reported, mainly due to the learning curve, robot dock time, and port placement. The use of the four-arm robot has been described to retract and position the kidney, independent of the assistant (10).

Few studies have evaluated the use of RRN due to the reduced advancement compared to standard laparoscopic surgery or non-robotic laparoscopic single site surgery (LESS), mainly due to the technical effort and additional cost per procedure and mostly not taking the initial costs for the robotic system into account. Robotic radical nephrectomy was performed either by a transperitoneal or retroperitoneal route. The available studies that compare RRN with LRN include cohorts of less than 50 patients (2,5,6,8,11).

Robotic assistance may be considered to be a ‘technical over-treatment’. It should therefore be weighed against a standard laparoscopic approach depending on the individual case. However, RRN serves as a useful training setting for robotic partial nephrectomy (RPN) (9). One publication has reported higher complication rates for RRN (5).

2.2 Robotic partial nephrectomy (RPN)
If feasible, for renal tumours ≤ pT1b, nephron-sparing surgery is the preferred surgical approach because it conserves renal function and potentially increases overall survival (1). The first report of RPN was in 2004 (12) (LE: 3). There has been evaluation of triangulation, sliding clip technique (13), reduction of warm ischaemia time and zero ischaemia (14). Triangulation and localisation of tumours are important reasons why laparoscopic partial nephrectomy (LPN) is still a challenging procedure in most cases (15,16).

The reported mean tumour size is usually small (mean 2.9 cm) and accounts for well-selected cases in reported studies, which might not reflect the real-world setting. Tumours > 4 cm treated with RPN have been associated with higher complication rates of 26.7% (17). A retrospective series to date comparing LPN with RPN in 261 consecutive patients found in a matched cohort analysis (150 patients) no difference in operative time (197 vs. 200 minutes), warm ischaemia time (20.3 vs. 18.2), length of hospitalisation (p = 0.84), percent change in renal function (p = 0.8) or adverse events (p = 0.52). However, the mean blood loss was higher in RPN cohort (323 vs. 222 ml, p = 0.01) (18). One of the largest comparative studies retrospectively evaluated 381 patients who underwent LPN (n = 182) or RPN (n = 199). The conversion rate was significantly lower (1%) in the RPN group compared to the LPN cohort (11.5%). In addition, a higher decrease in percentage of eGFR was noted (-16% vs. -12.6%) (19).

In the largest single centre series to date, which consists of 400 patients undergoing RPN, there were a total of 11 intraoperative complications (2.7%). There were 61 cases (15.3%) of postoperative complications, which were mainly low grade (grades 3 and 4 in 3.2%) (20).

Robot assisted partial nephrectomy is a safe and viable alternative to LPN. It provides equivalent early oncological outcomes and comparable morbidity to a traditional laparoscopic approach. Robot assisted partial nephrectomy appears to offer no difference, with regards to hospital stay, intraoperative blood loss, operative time or conversion rate, and a shorter warm ischaemia time. However, the RPN series reported significantly less warm ischaemic time than with an LPN procedure, as reported by a recently published systemic meta-analysis on RPN vs. LPN (21).

Table 3 lists selected studies on RPN. Further investigations defining RPN effects on renal preservation and long-term oncological outcomes are needed.
Table 3: The outcomes of selected studies on robotic assisted partial nephrectomy compared to laparoscopic partial nephrectomy.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>OR time LPN</th>
<th>EBL LPN</th>
<th>TF rate LPN</th>
<th>W-ischaemic LPN</th>
<th>Complications LPN</th>
<th>Hosp stay LPN</th>
<th>Study design</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aron, 2008 (22)</td>
<td>12</td>
<td>256</td>
<td>300</td>
<td>NA</td>
<td>22</td>
<td>NA</td>
<td>4.4</td>
<td>Retrospective, matched pair</td>
<td>3</td>
</tr>
<tr>
<td>Benway, 2009 (23)</td>
<td>118</td>
<td>174</td>
<td>196</td>
<td>2</td>
<td>28.4</td>
<td>12</td>
<td>2.7</td>
<td>Retrospective</td>
<td>3</td>
</tr>
<tr>
<td>Deane, 2008 (24)</td>
<td>11</td>
<td>289</td>
<td>198</td>
<td>NA</td>
<td>35</td>
<td>0</td>
<td>3.1</td>
<td>Retrospective</td>
<td>3</td>
</tr>
<tr>
<td>DeLong, 2010 (25)</td>
<td>15</td>
<td>253</td>
<td>NA</td>
<td>NA</td>
<td>39.9</td>
<td>NA</td>
<td>NA</td>
<td>Retrospective</td>
<td>3</td>
</tr>
<tr>
<td>Jeong, 2009 (26)</td>
<td>26</td>
<td>139</td>
<td>208</td>
<td>1</td>
<td>17</td>
<td>NA</td>
<td>5.3</td>
<td>Retrospective</td>
<td>3</td>
</tr>
<tr>
<td>Kural, 2009 (27)</td>
<td>20</td>
<td>226</td>
<td>387</td>
<td>2</td>
<td>35</td>
<td>2</td>
<td>4.2</td>
<td>Retrospective</td>
<td>3</td>
</tr>
<tr>
<td>Williams, 2011 (28)</td>
<td>59</td>
<td>221</td>
<td>146.3</td>
<td>NA</td>
<td>18.5</td>
<td>2.71</td>
<td>Prospective, single surgeon</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Wang, 2009 (29)</td>
<td>62</td>
<td>156</td>
<td>173</td>
<td>1</td>
<td>25</td>
<td>8</td>
<td>2.9</td>
<td>Comparative, retrospective</td>
<td>3</td>
</tr>
<tr>
<td>Ellison, 2012 (30)</td>
<td>108</td>
<td>162</td>
<td>400</td>
<td>19.3</td>
<td>2.2</td>
<td>2.2</td>
<td>Retrospective</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pierorazio, 2011 (31)</td>
<td>102</td>
<td>192</td>
<td>245.1</td>
<td>18</td>
<td>NA</td>
<td>Retrospective</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seo, 2011 (32)</td>
<td>14</td>
<td>117</td>
<td>264.1</td>
<td>36.4</td>
<td>5.3</td>
<td>Retrospective</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long, 2012 (19)</td>
<td>182</td>
<td>240.7</td>
<td>325.0</td>
<td>14.3%</td>
<td>23.2</td>
<td>1.36</td>
<td>Retrospective</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

N = nephrectomy; LPN = laparoscopic partial nephrectomy; RPN = robotic partial nephrectomy; OR time = operating time; EBL = estimated blood loss; TF = transfusion rate; W-ischaemic = warm ischaemic; Hosp stay = hospital stay; NA = not available.

2.3 Robotics reconstructive renal surgery

Initial experience of laparoscopic pyeloplasty performed with the da Vinci robotic system matched to procedures performed with standard laparoscopic techniques dates back to 1999 (33). The robotic platform is well suited for reconstructive procedures due to the number of degrees of freedom, superior optics, and reduction of tremor. Operative time, perioperative outcome and success rates are similar for laparoscopic pyeloplasty (LPP) and robotic assisted laparoscopic pyeloplasty (RLPP). The mean suturing time for RLPP seems shorter. Complications for both procedures are infrequent. Success rates, as measured by diuretic scintirenography, are high for the conventional and robotic approach. Most data on pyeloplasty robotic surgery are from the paediatric literature (34).

A recent meta-analysis on open vs. LPP in children demonstrated a cosmetic advantage with comparable long-term results and function (35). For the comparison of LPP and RLPP data are sparse, a meta-analysis on these comparators used the data of 8 studies valid enough for consideration (36) and concluded that both techniques had no major differences with regards to OR time, postoperative urine leakage, and function.
2.4 Conclusions and recommendations on RPN and LPN

**Conclusions on RPN and LPN**

<table>
<thead>
<tr>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conclusive long-term data are not available.</td>
</tr>
<tr>
<td>RPN and RRN are technically feasible.</td>
</tr>
<tr>
<td>No comparable long-term data on oncological, safety and functional outcomes are available. However, based on short-term data and panel expertise, no significant differences are expected.</td>
</tr>
<tr>
<td>In ablative surgery, robotics will produce no better outcomes compared to laparoscopy.</td>
</tr>
<tr>
<td>Possible benefit in reconstructive surgery, i.e. partial nephrectomy/pyeloplasty.</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use laparoscopy for simple or radical nephrectomy.</td>
</tr>
<tr>
<td>Use robotic assisted or laparoscopic surgery for partial or reconstructive renal surgery if technically feasible.</td>
</tr>
<tr>
<td>Use of minimal invasive techniques should not compromise nephron-sparing surgery in ≤ pT1b.</td>
</tr>
</tbody>
</table>

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### 2.5 Literature


3. LESS KIDNEY - RADICAL NEPHRECTOMY, PARTIAL NEPHRECTOMY, NEPHROURETERECTOMY, PYELOPLASTY AND (PARTIAL) ADRENALECTOMY

3.1 Terminology and technical principals
Laparoendoscopic single site surgery (LESS) was first suggested as a consensus nomenclature suggested by the Urologic NOTES Working Group in 2008. Laparoendoscopic single site surgery is now widely accepted as a general term for all new surgical procedures using one skin incision for access of camera and instruments, with or without an additional port of max 5 mm (1). Advantages of this new approach regarding minimal invasiveness over conventional laparoscopy are in discussion, but not yet proven (2), and cosmesis seems to be driving this technology to a considerable extent (3,4). Since advantages of NOTES techniques over conventional laparoscopy are not yet proven, personal and institutional expertise should guide the selection of surgical treatment. The first urological report on nephrectomy in humans was reported by Raman et al. (5) in 2007.

Although all the published studies have used only one single skin incision, three different trocar settings were reported. Raman et al. described the use of adjacent 5-mm trocars, resulting in one centre of rotation with skin incisions connected at the time of specimen extraction, while most other authors used a single port system with three or four instrument channels. Both approaches resulted in the need to use articulating and bent instrumentation to achieve triangulation intracorporeally, despite trocars being adjacent to one another (6).

Another study group used a small c-shaped incision in the umbilical fold, which was stretched to maximum length prior to the placement of three conventional trocars through the rectus fascia in a straight line, resulting in enough space for triangulation with straight instruments (single incision triangulated umbilical surgery = SITUS) (2,7). This approach was confirmed by a laboratory experiment addressing the problem of clashing of crossed bent and articulating instruments resulting in a loss of precision and time in a laboratory setting. The authors of this experiment setting concluded that coordinative abilities and time for the trained tasks were optimal, using straight followed by bent instruments and worst with articulating instruments. In 2009, Kaouk et al. (8) reported the first urological LESS procedures aided by the da Vinci system. In a multi-institutional analysis in 2011 of 1076 cases, the same author presented the use of this so called R(obotic)-LESS in 13% of all collected cases (9). Until then, there was no specific robotic platform for R-LESS on the market. Forced by positive reports concerning vision, limitation of instrumental movement, triangulation, suturing, etc.
using the conventional da Vinci System (11-13), several studies have demonstrated the innovative potential of novel robotic platforms (11,14). As in conventional laparoscopy, robotics has the potential to play a major role in LESS surgery.

3.2 Simple and radical nephrectomy

Laparoendoscopic single site nephrectomy was first described by Raman et al. in 2007 in three humans, without complications. Key steps of the new technology are shown in Table 3.

Table 4: Simple nephrectomy (SNX), radical nephrectomy (RNX)

<table>
<thead>
<tr>
<th>Author</th>
<th>n SNX</th>
<th>OR time SNX</th>
<th>EBL SNX</th>
<th>TF rate SNX</th>
<th>Conversion SNX</th>
<th>Hosp. stay RNX</th>
<th>Incision length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raman, 2008 (6)</td>
<td>2</td>
<td>Mean 133 min</td>
<td>Mean 30 mL</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2-4.5 cm</td>
<td>First multitrocar study</td>
</tr>
<tr>
<td>Desai, 2008 (21)</td>
<td>1</td>
<td>3.4 h</td>
<td>100 mL</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td>First single port study with curved instruments</td>
</tr>
<tr>
<td>Nagele, 2011 (7)</td>
<td>3 12</td>
<td>Mean 127 min</td>
<td>Mean 115 mL</td>
<td>n.c.</td>
<td>no</td>
<td>5</td>
<td>n.a.</td>
<td>First SITUS study</td>
</tr>
<tr>
<td>Kaouk, 2009 (8)</td>
<td>130 210</td>
<td>-161 -158</td>
<td>-166 -168</td>
<td>4.1</td>
<td>3.7</td>
<td></td>
<td></td>
<td>First robotic study</td>
</tr>
</tbody>
</table>

SNX = simple nephrectomy; RNX = radical nephrectomy; OR time = operating time; EBL = estimated blood loss; TF rate = transfusion rate; Hosp. stay = hospital stay; n.a. = not applicable.

There have been several comparative studies of LESS vs. conventional laparoscopy. A recent meta-analysis included 1,094 LESS nephrectomy cases and demonstrated a longer operative time and a higher conversion rate compared with conventional laparoscopic nephrectomy. However, LESS nephrectomy was associated with less postoperative pain, lower analgesic requirement, shorter hospital stay, shorter recovery time and a better cosmetic outcome. Furthermore, no significant differences were found in perioperative complications, estimated blood loss, warm ischaemia time, and postoperative serum creatinine levels of graft recipients (14).

3.3 Radical Nephroureterectomy

Nephroureterectomy using a single port inserted via Pfannenstiel incision was first reported by Ponsky et al. (16). Following LESS nephrectomy, the distal ureter was then resected through the 7.5 cm incision in two patients. The operating time (OR time) was 187 + 409 min, the estimated blood losses (EBL) were 50 mL and 200 mL, and the patients were discharged after 2 to 4 days. White et al. demonstrated 7 nephroureterectomies in his single centre 100 single port case series (17). Park et al. described 7 nephroureterectomies in two patients with OR times of 385 and 285 min, EBLs of 100 and 350 mL, and discharge at day 3 without perioperative complications (18). Laparoendoscopic single site nephroureterectomy using an endoloop for en-bloc bladdercuff excision was published by Chung et al. in two patients, with OR times of 165 and 325 min and EBLs of 30 mL and 65 mL. One patient was discharged at day 3 and the other patient at day 7 (19). Kaouk et al. reported 39 nephroureterectomies in a multicentre, retrospective trial (9). To date, neither long-term oncological data nor comparative studies are available.

3.4 Pyeloplasty

In the mostly young patient population needing reconstructive surgery for ureteropelvic junction obstruction, cosmesis seems to be of great importance.

A matched cohort study was reported by Stein et al. with 16 patients in each arm (20). The mean follow-up was 13 months in LESS and 17 months in the laparoscopic approach. All patients in both groups experienced clinical resolution of their symptoms; no difference in perioperative variables was noted between the groups. The authors noted no benefit for LESS, except aesthetic advantages.

Desai et al. performed 17 cases of LESS pyeloplasty. The mean OR time was 236 min and the EBL was 79 mL. One case was converted to conventional laparoscopy, while all other cases were aided by a 2-mm additional instrument for suturing. Fifteen of 16 available postoperative imaging demonstrated no obstruction.
Another series with 28 patients receiving LESS was published by Best et al. in 2011. This series reported a complication rate of 25% within the first 30 days (22). Seventy-one per cent of all these complications were reported in the first 10 cases. The authors concluded that the surgical challenge of this procedure might translate into a higher complication rate for LESS compared to conventional pyeloplasty in the early learning curve for this procedure.

3.5 (Partial-)adrenalectomy

Whereas Hirano et al. reported an retroperitoneal adrenalectomy using a rectoscope without gas insufflation in 2005 (23), Castellucci et al. described the first, transperitoneal, supraumbilical, single incision adrenalectomy using three ports in 2008 (24). Rane et al. reported results from a cumulative number of 59 functional adenomas, 28 pheochromocytomas and 15 miscellaneous in his review of LESS adrenalectomy (25). Rane et al. reported retroperitoneal and transperitoneal (umbilical, supraumbilical and subcostal) access.

Retroperitoneal access seems to have some advantages compared to transperitoneal access concerning body mass index (26) and avoidance of retraction of intraperitoneal organs (27). However, it is restricted by limited space resulting in an inability to use bent instruments and hampered triangulation. Agha et al. (28) compared 4 retro- and 4 trans-peritoneal adrenalectomies and concluded that both access techniques are safe and feasible in appropriate OR time.

Matched case control studies (26,29,30) showed a trend to longer OR time in LESS vs. conventional laparoscopy, but less postoperative pain and no significant difference in blood loss or complications. The first synchronous bilateral laparoendoscopic single site adrenalectomy in a patient with aldosterone-producing tumours was published by Jeong et al. with uneventful surgery and follow-up (29). Initial experience of transumbilical LESS surgery of partial adrenalectomy in patients with aldosterone-producing adenoma was contributed by Yuge et al. in a patient with both-sided disease using a multiport and ultrasound scalpel (31).

3.6 Complications and conversions in LESS surgery of the upper urinary tract

A multicentre study by Irwin et al. reporting results from transumbilical LESS procedures of the upper urinary tract. A total of 13.3 % (125 patients) of all laparoscopic procedures were done via a LESS approach (32). Conversion, defined as additionally placed 5- or 10-mm trocars (single 2-mm ports for reconstructive surgery were not considered conversion), was necessary in 5.6% of all LESS procedures due to facilitated dissection and reconstruction and control of bleeding. No conversion to open surgery was necessary. Complications occurred in 15.2% of all cases. The authors concluded that LESS was technically feasible for upper tract procedures, but was associated with a higher complication rate than in major conventional laparoscopic series. Kaouk et al. reported a total of 3.3% of intraoperative complications (1.7% vascular, 0.5% bowel, 0.2% splenic and diaphragmatic injuries) and 9.5% postoperative complications in an 18-institution multinational series with 1076 patients (9). Postoperative complications were 3.3% Dindo-Clavien grade 1, 3.8% grade 2, 1.9% grade 3 and 0.4% grade 4. An additional port was used in 23% of all cases. Conversion rate was 20.8% (1% to open surgery) and the overall transfusion rate was 6.1%.

3.7 Conclusions and recommendations

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LESS surgical procedures of the upper urinary tract are technically feasible but demanding.</td>
<td>3</td>
</tr>
<tr>
<td>Long-term oncological data are not yet available.</td>
<td></td>
</tr>
<tr>
<td>No proven or documented benefits over laparoscopic approach.</td>
<td></td>
</tr>
<tr>
<td>Cosmesis is a reported advantage.</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LESS surgery should be favoured in cases where cosmesis is of paramount importance.</td>
<td>A</td>
</tr>
<tr>
<td>Only experienced laparoscopic surgeons should embark on this technique.</td>
<td>A</td>
</tr>
</tbody>
</table>

LESS = Laparoendoscopic single site

3.8 Laparoendoscopic single site partial nephrectomy

The cumulative surgical experience of LESS partial nephrectomy is low and very few centres are using this challenging technique (Table 4). A total of 12 publications were identified. The studies included case series (LE: 3b) and prospective cohort studies (LE: 2a). Because the number of patients treated with this technique is low, studies often report data from LESS partial nephrectomy together with results from LESS procedures for other causes, or in multi-institutional evaluations (9, 10). One multi-institutional study reported 190 cases of patients who received LESS partial nephrectomy (10). Another multi-institutional study reported on 137 patients
out of a series of a total of 1076 patients (9).

In total, the results of the presented case series studies and multicentre studies (9,10) appear to match the findings of conventional laparoscopic approaches with regard to intraoperative and perioperative data. An observational study by Bazzi et al., which compared conventional laparoscopic vs. LESS partial nephrectomy, found a reduced mean use of postoperative analgesics in favour of LESS with no significant difference in the postoperative VAPS score (33). Long-term or intermediate-term follow-up is not available. In most cases, negative surgical margins could be achieved (21,34-37). One multi-institutional study demonstrated a positive surgical margin rate of 4.2% (10). Table 4 summarises these findings (9,17,21,34,38-42).
### Table 5: LESS in partial nephrectomy

BMI = body mass index; n.a. = not applicable; OT = operating time; WIT = warm ischaemia time.

<table>
<thead>
<tr>
<th>Authors</th>
<th>n / total</th>
<th>n / LESS</th>
<th>% / Robot LESS</th>
<th>Additional ports (%)</th>
<th>Diameter lesion (cm)</th>
<th>Estimated blood loss (EBL)</th>
<th>OT time (min)</th>
<th>BMI</th>
<th>WIT</th>
<th>Hospital stay (d)</th>
<th>Transfusion</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aron, 2008 (34)</td>
<td>5</td>
<td>5</td>
<td>0.00</td>
<td>1/5 (20%)</td>
<td>3.00</td>
<td>150.00</td>
<td>270.00</td>
<td>23</td>
<td>20 [11;29]</td>
<td>3.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Desai, 2009 (21)</td>
<td>100</td>
<td>6</td>
<td>0.00</td>
<td>6/6 (100%)</td>
<td>n.a.</td>
<td>525 [11-1000]</td>
<td>270 [240; 336]</td>
<td>25</td>
<td>n.a.</td>
<td>4 [2;22]</td>
<td>0</td>
<td>1 lap</td>
</tr>
<tr>
<td>Kaouk, 2009 (37)</td>
<td>7</td>
<td>5</td>
<td>0.29</td>
<td>1 Liver retraction</td>
<td>2.10</td>
<td>420±475 [50;1200]</td>
<td>160±25</td>
<td>27.5±1.1</td>
<td>16.00</td>
<td>3.2</td>
<td>1 (2 units)</td>
<td>1 lap</td>
</tr>
<tr>
<td>White, 2009 (17)</td>
<td>100</td>
<td>15</td>
<td>0.36</td>
<td>n.a.</td>
<td>3.01</td>
<td>422.00</td>
<td>196.00</td>
<td>n.a.</td>
<td>n.a.</td>
<td>4.5</td>
<td>2 open</td>
<td>1 lap</td>
</tr>
<tr>
<td>Cindolo, 2010 (38)</td>
<td>6</td>
<td>6</td>
<td>0.00</td>
<td>2 Suturing, 1 Liver retraction</td>
<td>1.85 [1;3,5]</td>
<td>201 [30; 550]</td>
<td>148 [115; 180]</td>
<td>26.35</td>
<td>n.a.</td>
<td>5.5 [3;10]</td>
<td>0.00</td>
<td>1 lap</td>
</tr>
<tr>
<td>Choi, 2011 (39)</td>
<td>171</td>
<td>3</td>
<td>0.95</td>
<td>1 Liver retraction</td>
<td>2.5</td>
<td>70.00</td>
<td>226.00</td>
<td>n.a.</td>
<td>29 [11;65]</td>
<td>4.3</td>
<td>n.a.</td>
<td>1 open</td>
</tr>
<tr>
<td>Han, 2011 (40)</td>
<td>14</td>
<td>0</td>
<td>14/14 100%</td>
<td>n.a.</td>
<td>3.2 [1,2; 6,5]</td>
<td>200 [30;1850]</td>
<td>205 [140;365]</td>
<td>23.4 [21.2; 28.3]</td>
<td>30 [16;43]</td>
<td>4 [3;11]</td>
<td>11/14</td>
<td>2 open</td>
</tr>
<tr>
<td>Kaouk, 2011 (9)</td>
<td>127</td>
<td>127</td>
<td>n.a.</td>
<td>n.a.</td>
<td>276.9 ± 294.3</td>
<td>208.3 ± 165.3</td>
<td>n.a.</td>
<td>18.4 ± 15.5</td>
<td>1.6 ± 1.7</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Cindolo, 2011 (41)</td>
<td>1</td>
<td>1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3.5</td>
<td>180</td>
<td>165</td>
<td>n.a.</td>
<td>0</td>
<td>6</td>
<td>n.a.</td>
<td>0.00</td>
</tr>
<tr>
<td>Ras-Bahrami, 2012 (42)</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>14.00</td>
<td>2.3 [0.7; 4.0]</td>
<td>293.3 [50; 1300]</td>
<td>167.3 [120; 267]</td>
<td>29.3 [23.9; 35.9]</td>
<td>14.7 [0; 37]</td>
<td>2.7 [2;5]</td>
<td>n.a.</td>
<td>1.00</td>
</tr>
</tbody>
</table>

BMI = body mass index; n.a. = not applicable; OT = operating time; WIT = warm ischaemia time.
Recommendations

LESS surgery or SITUS partial nephrectomy for renal cell cancer can provide an alternative surgical approach in experienced hands if all the factors involved in choosing open or laparoscopic partial nephrectomy are considered, especially with regard to warm ischaemia time (WIT) and organ sparing. Currently, LESS or SITUS practical nephrectomy are only advised as part of a clinical study.

Open or conventional laparoscopic partial nephrectomy is mandatory for patients with tumours smaller than 4 cm.

LESS = laparoendoscopic single site; SITUS = single-incision triangulated umbilical surgery

3.9 References


4. ROBOTIC-ASSISTED RADICAL PROSTATECTOMY

4.1 Literature search
A comprehensive PubMed search was conducted on publications related to the robot-assisted radical prostatectomy (RARP). No time frame was used. Key words included ‘robot assisted radical prostatectomy’ or ‘robotic prostatectomy’ and one of the following: ‘oncological outcome’, ‘continence’ and ‘potency’. Additional relevant literature was retrieved from references outlined by the initially harvested manuscripts. Literature was limited to human studies only and manuscripts published in English. Due to the wide extent of the robotic prostatectomy literature (more than 1,300 articles), review was restricted to comparative studies and meta-analyses that compared robot-assisted with open and conventional laparoscopic approaches. Review manuscripts were also excluded.

4.2 Introduction
Since its introduction in 2000 by Binder and Kramer, RARP has been adopted by many institutes worldwide as the standard care for the management of localised prostate cancer (1). Currently, there is a lack of multicentred, randomised, control studies (LE: 1a) comparing RARP with the gold-standard open retropubic radical prostatectomy (ORP). Additionally, only two, single-institute, randomised studies have been published comparing RARP with the well-established alternative conventional laparoscopic radical prostatectomy (LRP). Thus, current guidelines are based mostly on simple cohorts and meta-analyses derived from large volume centres and non-randomised, single-institute, prospective studies, resulting in LE 2 and 3 data.

4.3 Oncological outcome
There are very little data on the long-term oncological outcomes of RARP (biochemical recurrence and disease-free survival). Until such evidence is available, positive surgical margin (PSM) will remain the most valid oncological parameter available to justify the oncological effectiveness of the robotic approach in comparison with alternative radical prostatectomy techniques.

Comparative studies between RARP and RR or LRP demonstrate varying PSM outcomes. The
majority of such studies report equivalent or lower PSM rates for RARP than the other two approaches (Table 5). The two currently available, prospective, randomised studies, which compare RARP with LRP, found no differences in PSM between the two surgical groups (2,3) (LE: 2b). However, in the absence of large-scale, randomised, controlled trials, it is not possible to make a definite conclusion, regarding the superiority or not of RARP in cancer control.

Meta-analyses of published radical prostatectomy outcomes have reported equivalent or lower PSM rates than the gold-standard ORP and LRP (LE: 3a). Parsons and Bennett and Ficarra et al., in two meta-analyses of RARP studies published before 2006 and 2008, respectively, showed no significant differences in overall risk for PSM between ORP and LRP or RARP (4,5). In contrast, Coelho et al. in a comparative meta-analysis of ORP, LRP and RARP outcomes reported by high-volume centres (studies reporting population of more than 250 patients) revealed that RARP yielded a lower, overall, weighted, mean PSM rate than ORP and LRP (6). Finally, Novara et al. and Tewari et al, in two of the most recent meta-analysis on the subject reported similar PSM between RARP, ORP and LRP (7,8).

The biochemical recurrence-free survival for RARP is well documented for up to 5 years. Schroek et al. have documented no significant difference in early (1 year) prostate-specific antigen (PSA) recurrence between RARP and ORP (9). Similarly, Barocas et al. and Krambeck et al. have reported equivalent 3-year biochemical recurrence-free survival rates between the two techniques (10,11). In addition, Drouin et al. in a retrospective evaluation of 239 patients treated via ORP, LRP or RARP showed no difference in the 5-year PSA-free survival rates between the different approaches (12). Finally, Magheli et al. reported an analysis using propensity score matching, in which 522 RARP cases were matched with an equal number of patients who had undergone LRP and ORP. A higher overall PSM rate was observed for the RARP group compared to ORP and LRP. However, there was no difference with respect to a 5-year biochemical recurrence-free survival between the three surgical groups (13).

Surgical expertise appears to be a crucial factor in oncological outcomes of RARP. The rates for both PSM and biochemical recurrence have been reported to decrease significantly with increasing experience (14,15). Nevertheless, the exact number of cases required for a surgeon to achieve to sustain acceptable oncological outcomes remains to be defined.

Table 6: PSM rates of RARP in comparison with other techniques

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Type of study</th>
<th>Overall PSM</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porpiglia, 2012</td>
<td>60 (vs. 60 LRP)</td>
<td>Prospective randomised trial</td>
<td>26.6%</td>
<td>2a</td>
</tr>
<tr>
<td>Magheli, 2011</td>
<td>522 (vs. 522 ORP, vs. 522 LRP)</td>
<td>Retrospective matched pair comparison</td>
<td>19.5%</td>
<td>3a</td>
</tr>
<tr>
<td>Di Pierro, 2011</td>
<td>75 (vs. 75 ORP)</td>
<td>Prospective trial</td>
<td>16%</td>
<td>2c</td>
</tr>
<tr>
<td>Asimakopoulos, 2011</td>
<td>64 (vs. 64 LRP)</td>
<td>Prospective randomised trial</td>
<td>NS</td>
<td>2a</td>
</tr>
<tr>
<td>Doumerc, 2010</td>
<td>212 (vs. 502 ORP)</td>
<td>Prospective trial</td>
<td>21.2%</td>
<td>2c</td>
</tr>
<tr>
<td>Williams, 2010</td>
<td>604 (vs. 346 ORP)</td>
<td>Retrospective cohort</td>
<td>7.7-13.5%</td>
<td>4</td>
</tr>
<tr>
<td>Ficarra, 2009</td>
<td>103 (vs. 105 ORP)</td>
<td>Prospective trial</td>
<td>21%</td>
<td>2c</td>
</tr>
<tr>
<td>Drouin, 2009</td>
<td>71 (vs. 83 ORP, vs. 85 LRP)</td>
<td>Retrospective cohort</td>
<td>17%</td>
<td>4</td>
</tr>
<tr>
<td>White, 2009</td>
<td>50 (vs. 63 ORP)</td>
<td>Retrospective cohort</td>
<td>22%</td>
<td>4</td>
</tr>
<tr>
<td>Laurila, 2009</td>
<td>94 (vs. 98 ORP)</td>
<td>Retrospective cohort</td>
<td>13%</td>
<td>4</td>
</tr>
<tr>
<td>Rocco, 2009</td>
<td>120 (vs. 240 ORP)</td>
<td>Prospective matched pair comparison</td>
<td>22%</td>
<td>4</td>
</tr>
<tr>
<td>Krambeck, 2009</td>
<td>294 (vs. 588 ORP)</td>
<td>Retrospective matched pair comparison</td>
<td>15.6%</td>
<td>4</td>
</tr>
<tr>
<td>Schroek, 2008</td>
<td>362 (vs. 435 ORP)</td>
<td>Retrospective cohort</td>
<td>29%</td>
<td>4</td>
</tr>
</tbody>
</table>

ROBOTIC- AND SINGLE-SITE SURGERY IN UROLOGY - MARCH 2013
Chan, 2008 (23)  
660 (vs. 340 ORP)  
Retrospective cohort  
9.9-19% Significantly lower  
4

PSM = positive surgical margin; RARP = robotic assisted radical prostatectomy; LE = level of evidence; LRP = laparoscopic radical prostatectomy; ORP = retropubic radical prostatectomy; NS = non-significant difference with compared approach.

4.4 Conclusions and recommendation on robotic radical prostatectomy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARP for localised prostate cancer is now a well-established surgical approach offering similar positive surgical margin rates with ORP and LRP.</td>
<td>2a</td>
</tr>
<tr>
<td>Long-term PSA-free survival of patients treated with RARP as documented for up to 5 years is comparable with other radical prostatectomy approaches.</td>
<td>3b</td>
</tr>
<tr>
<td>In the absence of level 1a data and very limited long-term data, a firm conclusion regarding the oncological superiority of the technique over other techniques cannot be drawn.</td>
<td>2a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic surgery does not improve oncological outcomes in comparison to ORP and LRP; surgical expertise is the crucial factor. Use of the robot is not recommended to improve surgical outcomes.</td>
<td>A</td>
</tr>
</tbody>
</table>

4.5 References


4.6 RARP and urinary continence

As evidenced by numerous studies on RARP, there is a trend towards faster recovery of continence and higher overall continence rates in comparison to the gold standard ORP (Table 6). Nevertheless, this finding is questioned by the lack of randomised comparative studies between the two approaches. Coehlo et al. in a well-documented meta-analysis of comparative studies between ORP, LRP and RARP revealed that RARP was associated with higher continence rates at 12 months' postoperatively. The weighted mean continence rate was 79%, 84.8% and 92% for ORP, LRP, and RARP, respectively (1). Similarly, Ficara et al. in the most recent meta-analysis on the subject calculated a statistically significant advantage in favour of RARP compared with both ORP and LRP in terms of 12-month urinary continence recovery (2). In contrast, two other meta-analyses including 3893 and 44,702 patients, respectively, did not confirm the superiority of RARP at 12-month continence recovery, with equal continence calculated for all three approaches (3,4).
Tewari et al., in a non-randomised, prospective, comparison between ORP and RARP demonstrated an earlier continence recovery for RARP (median time 44 vs. 160 days; p < 0.05) (5). Similarly, Ficcarra et al., in a prospective study comparing ORP cases with RARP, demonstrated not only earlier recovery, but significantly higher continence rates at 1 year postoperatively after RARP (6). In addition, Rocco et al. in a matched-pair analysis of 120 prospectively evaluated RARP cases with a comparable population of ORP cases (n = 240) revealed superior continence rates for RARP at 6 and 12 months postoperatively (93% and 97% vs. 83% and 88% for RARP and ORP, accordingly) (7).

In contrast, no significant difference in continence was reported in a larger matched-pair analysis, reporting equivalent 1-year urinary continence rates for RARP and ORP, respectively (8). More recently, Pierro et al. in a prospective trial comparing consecutive series of ORP and RARP cases (including learning curve cases) revealed that RARP was associated with a faster recovery of continence but not with higher overall continence at 1 year postoperatively (9).

The two, currently available, randomised controlled trials between LRP and RARP have reported conflicting results. Porpiglia et al. in a recent, randomised, controlled study between LRP and RARP reported higher continence rates after RARP (10). In contrast, Assimacopoulos et al. revealed no differences in continence rates between the two approaches (11). Similarly, other non-randomised studies have revealed controversial results (12,13,14).

### Table 7: Continence outcomes of RARP in comparative studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>RARP cases</th>
<th>Type of study</th>
<th>Continence</th>
<th>Time of observation (mo)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tewari, 2003 (5)</td>
<td>200 (vs. 100 ORP)</td>
<td>Prospective trial</td>
<td>50% Higher than ORP</td>
<td>1.5</td>
<td>2c</td>
</tr>
<tr>
<td>Ficcarra, 2009 (6)</td>
<td>103 (vs. 105 ORP)</td>
<td>Prospective trial</td>
<td>97% Significantly higher</td>
<td>12</td>
<td>2c</td>
</tr>
<tr>
<td>Rocco, 2009 (7)</td>
<td>120 (vs. 240 ORP)</td>
<td>Prospective matched pair comparison</td>
<td>97% Significantly higher</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Kramberck, 2009 (8)</td>
<td>294 (vs. 588 ORP)</td>
<td>Matched pair analysis</td>
<td>92% NS</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Di Pierro, 2011 (9)</td>
<td>75 (vs. 75 ORP)</td>
<td>Prospective trial</td>
<td>89% NS</td>
<td>12</td>
<td>2c</td>
</tr>
<tr>
<td>Porpiglia, 2012 (10)</td>
<td>60 (vs. 60 LRP)</td>
<td>Prospective randomised trial</td>
<td>95% Significantly higher</td>
<td>12</td>
<td>2a</td>
</tr>
<tr>
<td>Park, 2011 (12)</td>
<td>44 (vs. 62 LRP)</td>
<td>Retrospective cohort</td>
<td>94.4% NS</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Hakimi, 2009 (13)</td>
<td>75 (vs. 75 LRP)</td>
<td>Retrospective cohort</td>
<td>93.3% NS</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Ploussard, 2013 (14)</td>
<td>1009 (vs. 1377 LRP)</td>
<td>Prospective trial</td>
<td>83.6% Significantly higher</td>
<td>12</td>
<td>2c</td>
</tr>
</tbody>
</table>

RARP = robotic assisted radical prostatectomy; LE = level of evidence; ORP = retropubic radical prostatectomy; NS = Non-significant difference with compared approach; LRP = laparoscopic radical prostatectomy.

### 4.7 Conclusions and recommendations RARP and incontinence

**Conclusions**

- RARP for localised prostate cancer is a surgical approach offering high continence rates, at least comparable with ORP and LRP. LE: 2a
- Experienced robotic surgeons achieve good early continence results. LE: 3b
- There is a trend towards faster recovery of continence after RARP in comparison to ORP and LRP. LE: 3b

**Recommendations**

- To achieve better early continence results, the use of robotic technique is recommended.* RECOMMENDED WITH RESERVATIONS: C

*The expert panel would like to stress that a well-done laparoscopy or open procedure would produce similar results.
4.8 References


4.9 RARP and potency

The significant variation on reported potency rates after RARP can be explained by the fact that different studies entail varying population characteristics, different potency assessment and the use of different potency aids. The majority of comparative studies between RARP and ORP favour the robotic approach in terms of potency. Faster recovery of intercourse (with or without phosphodiesterase type 5 inhibitors), faster return to intercourse and higher overall potency rates at 1 year postoperatively have been documented by several studies (1-4). In addition, two well-documented meta-analyses revealed that RARP was associated with higher potency rates than ORP(5,6). In contrast, comparable potency rates between RARP and ORP at 1-year follow-
up were reported in a large matched-pair analysis and an additional meta-analysis (7,8). Due to the lack of randomised comparative studies between RARP and ORP, it is not possible to make definite conclusions, regarding the superiority of RARP in terms of potency.

A direct comparison of RARP with LRP reveals a trend towards better potency outcomes for RARP. Asimacopoulos et al. and Porpiglia et al., in two, currently available, prospective, randomised studies comparing LRP with RARP, reported a significantly shorter time-to-capability for intercourse and a higher 12-month rate of capability for intercourse in the RARP arm and erection recovery, accordingly (9,10). Coelho et al. in a meta-analysis of high-volume comparative studies calculated weighted mean potency rates for patients who underwent unilateral or bilateral nerve sparing, at 12-month follow-up, of 31.1% and 54% for LRP, compared with 59.9% and 93.5% for RARP (5). In a recent meta-analysis, Ficarra et al. calculated a non-statistically significant trend in favour of RARP compared with LRP (6). Similarly, Plaussard et al. in a recent comparative investigation including 1,009 RARP and 1,377 LRP operations revealed higher potency rates in the RARP arm at both 6 and 12 months of follow-up (11). In contrast, comparable potency rates between RARP and LRP at 1-year follow-up were reported by other studies (12,13).

Table 8: Potency outcomes of RARP in comparative studies

<table>
<thead>
<tr>
<th>Author</th>
<th>RARP cases</th>
<th>Type of study</th>
<th>Potency rates</th>
<th>Time of observation</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tewary, 2003 (1)</td>
<td>200 (vs. 100 ORP)</td>
<td>Prospective trial</td>
<td>50% Significantly higher</td>
<td>6</td>
<td>2c</td>
</tr>
<tr>
<td>Di Pierro, 2011 (2)</td>
<td>75 (vs. 75 ORP)</td>
<td>Prospective trial</td>
<td>55% Significantly higher</td>
<td>12</td>
<td>2c</td>
</tr>
<tr>
<td>Ficarra, 2009 (3)</td>
<td>103 (vs. 105 ORP)</td>
<td>Prospective trial</td>
<td>81% Significantly higher</td>
<td>12</td>
<td>2c</td>
</tr>
<tr>
<td>Rocco, 2009 (4)</td>
<td>120 (vs. 240 ORP)</td>
<td>Prospective matched pair comparison</td>
<td>61% Significantly higher</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Krambeck, 2009 (7)</td>
<td>294 (vs. 588 ORP)</td>
<td>Matched pair analysis</td>
<td>70% NS</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Asimakopoulos, 2011 (9)</td>
<td>64 (vs. 64 LRP)</td>
<td>Prospective randomised trial</td>
<td>77% Significantly higher</td>
<td>12</td>
<td>2a</td>
</tr>
<tr>
<td>Porpiglia, 2012 (10)</td>
<td>60 (vs. 60 LRP)</td>
<td>Prospective randomised trial</td>
<td>80% Significantly higher</td>
<td>12</td>
<td>2a</td>
</tr>
<tr>
<td>Plaussard, 2013 (11)</td>
<td>1009 (vs. 1377 LRP)</td>
<td>Prospective trial</td>
<td>57.7% Significantly higher</td>
<td>12</td>
<td>2c</td>
</tr>
<tr>
<td>Park, 2011 (12)</td>
<td>44 (vs. 62 LRP)</td>
<td>Retrospective cohort</td>
<td>54.5% NS</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Hakimi, 2009 (13)</td>
<td>75 (vs. 75 LRP)</td>
<td>Retrospective cohort</td>
<td>76.5% NS</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

RARP = robotic assisted radical prostatectomy; LE = level of evidence; ORP = retropubic radical prostatectomy; NS = non-significant difference between compared groups; LRP = laparoscopic radical prostatectomy.

4.10 Conclusions and recommendations RARP and potency

Conclusions

Potency assessment after radical prostatectomy has many limitations, which partly explains the wide variation in potency outcomes among different studies.  
RARP is not inferior to ORP and LRP for potency rates.  
There is a trend towards faster recovery of potency after robotic assisted laparoscopic radical prostatectomy (RALP) in comparison to ORP and LRP.

Recommendations

To achieve better early potency results, the use of laparoscopy or robotic techniques are recommended.*  
To achieve better early potency results, a cautery-free (i.e. athermal) technique during neurovascular bundle dissection is recommended.

*The expert panel would like to stress that a well-done ORP or LRP, compared to RARP would produce similar results.
4.11 References


5. ROBOTIC ASSISTED PELVIC LYMPH NODE DISSECTION AT THE TIME OF RADICAL PROSTATECTOMY

5.1 Introduction
Pelvic lymph node (LN) dissection (PLND) is considered the most reliable staging method to access LN involvement in clinically localised prostatic cancer (GR: B). The EAU 2011 guidelines on prostate cancer have recommended that nodal evaluation can be spared in patients with stage T2 or less, PSA < 10, a Gleason score ≤ 6 and < 50% positive biopsy cores, since these patients have < 10% risk of LN metastases (GR: B) (1). In contrast, PLND may increase staging accuracy and influence decision-making with respect to adjuvant therapy in the treatment of a subset of intermediate-risk cases and in all high-risk prostatic cancer cases (GR: B) (2).

5.2 Outcomes
Published outcomes of PLND during RARP demonstrate significant variability in both the number of harvested LNs and LN invasion rates. Multiple factors are responsible for the latter, including the different PLND indications used, different levels of surgical experience among robotic surgeons and different PLND resection templates followed in each institution. Different indications for PLND lead to different rates of nodal involvement; higher rates would be expected when PLND is offered only in high-risk patients and lower rates when PLND is regularly offered to all RARP cases. The EAU 2011 guidelines recommended that when PLND is indicated, an extended dissection template should be offered, including the removal of nodes overlying the external iliac artery and vein, the nodes within the obturator fossa cranially and caudally to the obturator nerve, and the nodes medially and laterally to the internal iliac artery (GR: C) (2). The more extended the LN yield, the higher the probability of detecting a LN invasion (3-5). Finally, rates for LN yield and LN invasion are surgeon-related. Siberstein et al., in a retrospective comparative study between open, laparoscopic and robotic PLND, revealed wide variations in median LN yield between surgeons. This variation was much greater than the variation of LN yield between the different surgical approaches (6).

Di Pierro et al., in a prospective trial comparing consecutive series of 75 open retropubic and 75 RARP, revealed a significant (p< 0.001) difference compared with robotic assistance in the number of retrieved LNs. RARP retrieved a median of 12 LNs (range 9-17) in contrast to an open technique retrieving 18 (range 12-23) nodes, respectively (7). Most available studies comparing robotic-assisted PLND with its open counterpart support the open approach and demonstrate a lower LN yield for robotic-assisted PLND (Table 8). The inferior LN retrieval of RARP is most likely related to the comparison of a well-established technique (e.g. open) with a newly introduced approach incorporating data during the learning curve. Recent reports on robotic-assisted PLND verified that robotic assistance itself does not limit a surgeon’s ability to perform a complete extended pelvic lymph node dissection (8,9).

Table 9: Robot assisted PLND studies

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Type of study</th>
<th>LN yield (range of median)</th>
<th>Lymph node involvement; (LNI)</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siberstein, 2011 (6)</td>
<td>126 (vs. 126 open, vs. 78 laparoscopic)</td>
<td>Retrospective cohort</td>
<td>16 (11-21)</td>
<td>Significantly lower than open and laparoscopic</td>
<td>13%</td>
</tr>
<tr>
<td>Di Pierro, 2011 (7)</td>
<td>75 (vs. 75 open)</td>
<td>Prospective trial</td>
<td>12 (9-17)</td>
<td>Significantly lower than open</td>
<td>12%</td>
</tr>
<tr>
<td>Truesdale 2010 (10)</td>
<td>99 (vs. 217 open)</td>
<td>Retrospective cohort</td>
<td>6.35 (4.52)</td>
<td>Borderline difference</td>
<td>1%</td>
</tr>
<tr>
<td>Lallas, 2010 (11)</td>
<td>473 (vs. 343 open)</td>
<td>Retrospective cohort</td>
<td>7.1 (0-29)</td>
<td>Significantly higher than open</td>
<td>1.1%</td>
</tr>
<tr>
<td>Yee, 2010 (12)</td>
<td>32</td>
<td>Prospective case series</td>
<td>18 (12-28)</td>
<td>13%</td>
<td>2b</td>
</tr>
<tr>
<td>Cooperberg, 2010 (13)</td>
<td>562 (vs. 716 open)</td>
<td>Prospective case series</td>
<td>9.3 (5.4) Significantly lower than open</td>
<td>4.1%</td>
<td>2b</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>------</td>
<td>----</td>
</tr>
<tr>
<td>Yates, 2009 (14)</td>
<td>62 (vs. 61 open)</td>
<td>Retrospective cohort</td>
<td>3.3 Significantly lower than open</td>
<td>3.2%</td>
<td>2b</td>
</tr>
<tr>
<td>Feicke, 2009 (15)</td>
<td>99</td>
<td>Retrospective case series</td>
<td>19 (8-53) 16%</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Polcari, 2009 (16)</td>
<td>60 (vs. 64 open)</td>
<td>Retrospective cohort</td>
<td>8.2 NS</td>
<td>3.3%</td>
<td>2b</td>
</tr>
<tr>
<td>Zorn, 2009 (17)</td>
<td>226 (vs. 471 open)</td>
<td>Retrospective cohort</td>
<td>12.5 (7-16) Significantly lower than open</td>
<td>7.8%</td>
<td>2b</td>
</tr>
<tr>
<td>Atung, 2006 (18)</td>
<td>40 (vs. 75 LRP)</td>
<td>Prospective case series</td>
<td>14.08 (9-24) 5%</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

LN = lymph node; LNI = lymph node involvement; LE = level of evidence; NS = non-significant difference between compared groups.

5.3 Conclusions and recommendations on root-assisted pelvic lymph node dissection

**Conclusions**

| The reported number of lymph nodes removed in laparoscopic and robotic series is lower than in open surgical series. |
| 2a |

However, the same extent of lymphadenectomy can be safely performed by all techniques of radical prostatectomy including RARP.

**Recommendation**

| RARP, LRP and ORP achieve similar perioperative and oncological pelvic lymph node dissection outcomes so either technique can be used in lymphadenectomy. |
| A |

RARP = robotic-assisted radical prostatectomy; LRP = laparoscopic radical prostatectomy; ORP = open retropubic radical prostatectomy.

5.4 References


6. ROBOTIC-ASSISTED LAPAROSCOPIC SACROCOLPOPEXY

6.1 Introduction
Robotic-assisted laparoscopic sacrocolpopexy (RLAS) has emerged as a minimally invasive option for the treatment of vaginal vault prolapse, aiming to provide a similar anatomical outcome with the open technique, in addition to limited morbidity and faster recovery time, both associated with laparoscopy. The literature on RALS is almost entirely limited to a few case series with short-term outcome data leading to a low level of evidence. In addition, there are three comparative studies; one study is a retrospective cohort study comparing RALS with an open approach, while the other two studies are small, randomised controlled studies, comparing RALS with laparoscopic sacrocolpopexy (1,2,3). Table 9 summarises the studies reporting RALS clinical outcomes.
Table 10: Clinical studies in robot-assisted laparoscopic sacrocolpopexy

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Type of study</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geller, 2008</td>
<td>73</td>
<td>Retrospective cohort study</td>
<td>2b</td>
</tr>
<tr>
<td>(1)</td>
<td>(vs. 105 open)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraiso, 2011</td>
<td>40</td>
<td>Randomised controlled trial</td>
<td>2b</td>
</tr>
<tr>
<td>(2)</td>
<td>(vs. 38 laparoscopic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seror, 2012</td>
<td>20</td>
<td>Randomised controlled trial</td>
<td>2b</td>
</tr>
<tr>
<td>(3)</td>
<td>(vs. 47 laparoscopic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moreno, 2010</td>
<td>31</td>
<td>Prospective case series</td>
<td>2c</td>
</tr>
<tr>
<td>(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gocmen, 2011</td>
<td>12</td>
<td>Retrospective case series</td>
<td>4</td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kramer, 2009</td>
<td>21</td>
<td>Retrospective case series</td>
<td>4</td>
</tr>
<tr>
<td>(6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akl, 2009</td>
<td>80</td>
<td>Retrospective case series</td>
<td>4</td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daneshgari, 2007</td>
<td>12</td>
<td>Retrospective case series</td>
<td>4</td>
</tr>
<tr>
<td>Elliott, 2006</td>
<td>30</td>
<td>Retrospective case series</td>
<td>4</td>
</tr>
<tr>
<td>Benson, 2010</td>
<td>12</td>
<td>Retrospective case series</td>
<td>4</td>
</tr>
</tbody>
</table>

LE = level of evidence.

6.2 Outcomes
As demonstrated by all published series, RALS is highly effective in restoring the apical vaginal vault defect. Cure rates of 95-100% are comparable with those using an open technique. Geller et al., in a retrospective cohort study comparing 73 RALS to 105 abdominal sacrocolpopexies, reported similar short-term vaginal vault support between the two techniques (1). In addition, Paraiso et al. and Seror et al., in two studies providing data from randomised trials, compared the outcomes of laparoscopic vs. RALS and demonstrated significant improvement in vaginal support and functional outcomes 1 year after surgery with no differences between the groups (2,3) (LE: 2b). The anatomical outcome of the procedure is considered durable. Nevertheless, the true durability of RALS still requires documentation, given that only a few studies report long-term results. No recurrence was evident in 31 cases, after a mean follow-up of 24.5 months, while one recurrence was reported in 30 other cases after a mean follow-up of 24 months in two studies providing long-term data (4,5).

6.3 Conclusion and recommendation robotic-assisted laparoscopic sacrocolpopexy

<table>
<thead>
<tr>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>RALS is safe and effective in restoring vaginal vault prolapse with durability evidenced up to 24 months.</td>
<td>2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic and robotic colpopexy should be considered standard treatment options for the restoration of apical vaginal vault defects.</td>
<td>A</td>
</tr>
</tbody>
</table>

6.4 References


7. ROBOTIC-ASSISTED AND LESS CYSTECTOMY

7.1 Introduction
Open radical cystectomy (ORC) with PLND is the standard-of-care treatment for high-risk non-muscle-invasive and muscle-invasive urothelial carcinoma of the bladder (UCB), providing durable local cancer control (1-4). Even when performed by experienced surgeons, it is associated with significant morbidity, including bleeding, pain associated with the lengthy incision and prolonged abdominal wall retraction, and major fluid shifts related to prolonged exposure of the peritoneal surface. Additionally, visibility of the surgical field can be difficult in the deep pelvis and retrovesical space using the open approach (5-10). With the increasing adoption of robot-assisted laparoscopic techniques for prostate and kidney cancers, there has been growing interest in robot-assisted radical cystectomy (RARC). To date, there are only limited published data on robot-assisted or LESS simple cystectomy, which means we cannot make any evidence-based recommendations regarding their use. However, since simple cystectomy is usually not technically more difficult than radical cystectomy, the concepts discussed below regarding RARC should apply to simple cystectomy.

7.2 RARC Safety
It has been suggested that RARC results in less blood loss, reduced morbidity, improved convalescence, and earlier initiation of adjuvant systemic therapies (5,9,10). To date, there is no prospective randomised study, comparing the safety and complications of RARC to ORC. In the absence of randomised clinical trials, comparison to historical ORC series from high-volume centres is the only possible approach (Table 10). Taken together, complication rates of RARC in the literature range from 20-91% (Table 10). RARC has been suggested, in retrospective comparative studies, to result in a lower rate of postoperative complications than ORC. A recent population-based study comparing RARC to ORC confirmed these findings (10). However, these studies suffered from a retrospective uncontrolled design with significant selection bias. Risk factors associated with major complications after RARC are (11,12), age > 65 years, estimated perioperative blood loss > 500 mL and intraoperative intravenous fluid > 5000 mL. The cumulative data supports the finding that the perioperative and long-term safety of RARC is at least not inferior to that of ORC. However, the long-term oncological safety and efficacy of RARC are still under debate.

7.3 Oncological efficacy
Theoretically, RARC should be a safe procedure provided there is adherence to standard oncological principles. In the absence of long-term data, surgical factors, including quality-of-care indicators, such as the soft-tissue surgical margin rate and the extent of lymphadenectomy (13,14) have been used to assess the oncological safety of RARC (7,15,16). Herr et al. suggested benchmark recommendations of a positive soft-tissue surgical margin rate of < 10% and a lymph node yield of > 10-14, based upon the oncological outcomes of 16 experienced ORC surgeons (17). Although early RARC series met these benchmarks, these studies included lower-risk patients with a lower rate of extravesical disease and nodal metastasis (7,18-21).
In addition, early RARC cohorts seemed to select generally younger and healthier patients, often excluding patients with prior pelvic treatments (i.e. surgery and radiation). Indeed, generalisation from the largest, reported, single-centre RARC series (n = 100) is limited by its patient selection (22). Such selection biases in early RARC series have made it difficult to extrapolate their findings to the general bladder cancer population which is often older and iller. However, these early studies established RARC as a feasible and safe procedure when performed in selected patients. In the current phase of RARC evaluation, the inclusion criteria have been relaxed to include almost all candidates for RC.

In a comparison of 35 RARC consecutive cases and 35 ORC consecutive cases (no statistically significant differences in patient characteristics, tumour stage, and LN status), Richards et al. (23) reported the same median LN yield (15 vs. 16). There was also no difference in positive soft tissue surgical margin rates (one in the RARC group compared to three in the ORC group). Using a multi-institutional international RARC database, Hellenthal et al. found that 82.9% of 527 patients from 15 institutions underwent adequate lymphadenectomy, which was defined as having > 10 LNs removed (24). This rate was comparable to rates of historical ORC series, even at specialised academic centres (1-3). Furthermore, the authors identified the surgeon’s volume and sequential case number (two factors suggestive of the learning curve) were predictive of the probability of undergoing an adequate lymphadenectomy with RARC. However, there was no association between margin positivity (35/513 RARC cases, 6.8%) and sequential case number or institutional volume (25). Moreover, the soft tissue margin positivity rate was within the range of that of ORC series and standards proposed (17,26). Similarly to ORC series, advanced age, LN positivity, and advanced tumour stage were associated with an increased likelihood of a positive soft tissue surgical margin (26,27). Comparative retrospective studies confirmed these findings either in an unmatched (28) or in a matched study design (9). Finally, a small prospective randomised trial (n = 41) confirmed the non-inferiority of RARC to ORC with the primary endpoint of LN yield (mean of 19 vs. 18 LNs) (29). Although the sample size is small, the authors should be recognised for reporting the first prospective randomised controlled trial between RARC and ORC. Cumulatively, these data, similar to robot-assisted radical prostatectomy, support that RARC can achieve a similar oncological surgical quality to ORC, and that this depends more on the surgeon performing the surgery than the procedure used.

To date, early and mid-term oncological outcomes have been reported and are presented in Table 11 (28,30,31). Two-year, recurrence-free, cancer-specific and OS estimates (74%, 85%, and 79%, respectively) mirror those of large contemporary ORC series, suggesting an early oncological equivalency of RARC to ORC (1,2,4,32,33). Despite the potential perioperative benefits and promising surgical quality indicators, as well as the mid-term oncological control afforded by RARC, the long-term oncological efficacy of this relatively new technique has yet to be determined. Before widespread application of RARC, it needs to be further tested at high-volume centres within controlled clinical studies.

### 7.4 Learning curve

To date, there is no standard definition of what would be considered an adequate learning curve for RARC. A recent study from the International Robotic Cystectomy Consortium demonstrated that operative time, estimated blood loss, and lymph node yield are significantly associated with previous robot-assisted radical prostatectomy experience. Moreover, the authors defined a cut-off of 30 cases as sufficient for obtaining an adequate learning experience for RARC (34). The panel cannot establish the number of cases needed before to become proficient at performing RARC.

### 7.5 Diversion

Extracorporeal urinary diversion through a mini-laparotomy incision is to date the most widely used reconstructive approach. The intracorporeal technique has been shown to generate increased rates of major complications in retrospective mono-centric studies (35,36). Recently, Pruthi et al. compared the perioperative outcomes of 12 patients who underwent RARC with intracorporeal urinary diversion to 20 patients who underwent extracorporeal diversion (37). In this small sample size series, the intracorporeal technique was associated with a longer operative time. However, complication rates and length of stay were not different. The choice of urinary diversion depends on the skill and dedication of the surgeon. There is no recommendation that can be made, regarding the benefit of one over the other. However, the panel suggests it is best to start with extracorporeal urinary diversion in the early experience.

### 7.6 Cost-effectiveness

The rapid adoption of robot-assisted surgery for prostate cancer and other diseases has called into question whether the benefits of this technology justify the cost, as there is no clear evidence demonstrating superior clinical outcomes of these techniques over traditional surgical approaches (i.e. open or laparoscopy) (10,38,39). There are only few, small, single-centre studies on comparative costs of RARC vs. ORC (38-40). Similar to other diseases, RARC has been estimated to be more costly than ORC (i.e. approximately US$
1,600 difference per case in direct costs). A population-based study found that the inpatient cost difference exceeded the US$1600 figure (10).

However, RARC has been reported to result in potentially less perioperative complications and a shorter length of stay than ORC, thereby possibly lowering hospital costs (8,10,41). When perioperative complication costs were included in the cost-comparison analysis of RARC and ORC (40), Lee et al. found that RARC was indeed cheaper than ORC (83 vs. 103 consecutive cases, respectively). The generalisability of these single-institution analyses is limited as the data are from high-volume, tertiary care centres with significant robotic experience. The cost issue therefore remains unsettled.

### 7.7 LESS RC

Due to the lack of data available, we cannot recommend this approach, outside of properly designed clinical trials.

### 7.8 Conclusions robot-assisted radical cystectomy

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
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<tbody>
<tr>
<td>RARC is a feasible and safe approach with comparable perioperative and long-term complications to ORC.</td>
<td>1b</td>
</tr>
<tr>
<td>RARC can yield the same extent of lymphadenectomy than ORC.</td>
<td>1b</td>
</tr>
<tr>
<td>Initial RARC series had a high rate of positive soft tissue surgical margins. Experienced surgeons, however, can achieve similar margin rates, irrespective of the technique used.</td>
<td>1b</td>
</tr>
<tr>
<td>Short- and intermediate-term survival data from retrospective series suggest that the oncological efficacy of RARC is not inferior to that of ORC.</td>
<td>3</td>
</tr>
<tr>
<td>Urinary diversion can safely be performed extracorporeally or intracorporeally.</td>
<td>3</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
</tr>
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<td>-----------------</td>
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<tr>
<td>Retrospective single centre studies</td>
<td></td>
</tr>
<tr>
<td>Guru et al. [18]</td>
<td>2007</td>
</tr>
<tr>
<td>Dasgupta et al. [19]</td>
<td>2008</td>
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<tr>
<td>Murphy et al. [20]</td>
<td>2008</td>
</tr>
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<td>Pruthi et al. [22]</td>
<td>2010</td>
</tr>
<tr>
<td>Jonsson et al. [30]</td>
<td>2011</td>
</tr>
<tr>
<td>Khan et al. [42]</td>
<td>2011</td>
</tr>
<tr>
<td>Torrey et al. [43]</td>
<td>2012</td>
</tr>
<tr>
<td>Yuh et al. [44]</td>
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<td>Ng et al. [8]</td>
<td>2010</td>
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<tr>
<td>Yu et al. [10]</td>
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</tr>
<tr>
<td>Nix et al. [29]</td>
<td>2010</td>
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<td></td>
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</tbody>
</table>

EBL = estimated blood loss; OR = operation; BMI = body mass index; ASA = American Society of Anesthesiologists; NMIBC = non-muscle invasive bladder cancer.
### Table 12: Oncological outcomes of robot-assisted radical cystectomy studies

<table>
<thead>
<tr>
<th>Author</th>
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<th>NB</th>
<th>Follow-up</th>
<th>Lymph node yield (%)</th>
<th>STSM (%)</th>
<th>RFS (%)</th>
<th>CSS (%)</th>
<th>OS (%)</th>
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<td>-</td>
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<td>5</td>
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<td>2008</td>
<td>17</td>
<td>23</td>
<td>16</td>
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<td>90</td>
<td>90</td>
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<td>2008</td>
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<td>17</td>
<td>16</td>
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<td>96 (f/u)</td>
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<td>2010</td>
<td>100</td>
<td>21</td>
<td>19</td>
<td>0</td>
<td>85 (f/u)</td>
<td>94 (f/u)</td>
<td>90 (f/u)</td>
</tr>
<tr>
<td>Hellenthal et al.[24, 25]</td>
<td>2010 and 2011</td>
<td>527</td>
<td>17.8</td>
<td>17.8</td>
<td>6.8</td>
<td>-</td>
<td>-</td>
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<td>2010</td>
<td>59</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>82</td>
<td>71</td>
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<td>2011</td>
<td>45</td>
<td>25</td>
<td>19</td>
<td>2</td>
<td>84 (f/u)</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
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<td>2011</td>
<td>85</td>
<td>18</td>
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<td>5</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td>ORC</td>
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<td>-</td>
<td>18</td>
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</tr>
</tbody>
</table>

STSM = soft tissue surgical margin; RFS = recurrence-free survival; CSS = cancer-specific survival; OS = overall survival.

### 7.9 References


8. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

- EAU: European Association of Urology
- EBL: Estimated blood losses
- GR: Grade of recommendation
- LARP: Laparoscopic radical prostatectomy
- LE: Level of evidence
- LESS: Laparoendoscopic single-site
- LN: Lymph node
- LPN: Laparoscopic partial nephrectomy
- LPP: Laparoscopic pyeloplasty
- LRN: Laparoscopic radical nephrectomy
- LRP: Laparoscopic radical prostatectomy
- ORC: Open radical cystectomy
- ORP: Open retropubic radical prostatectomy
- PLND: Pelvic lymph node dissection
- PSA: Prostate-specific antigen
- PSM: Positive surgical margin
- RALP: Robotic-assisted laparoscopic radical prostatectomy
- RALS: Robot-assisted laparoscopic sacrocolpopexy
- RARC: Robot-assisted radical cystectomy
- RARP: Robot-assisted radical prostatectomy
- RC: Radical cystectomy
- RCT: Randomised controlled trial
- RLPP: Robot-assisted laparoscopic pyeloplasty
- RP: Radical prostatectomy
- RPN: Robotic partial nephrectomy
- RRN: Robotic radical nephrectomy
- SITUS: Single-incision triangulated umbilical surgery
- UCB: Urothelial carcinoma of the bladder
- VAPS: Visual analogue pain scale
- WIT: Warm ischaemia time

Conflict of interest

All members of the Urological Technologies Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.
Guidelines on Reporting and Grading of Complications after Urologic Surgical Procedures

D. Mitropoulos (chair), W. Artibani, M. Graefen, M. Remzi, M. Rouprêt, M.C. Truss

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<td>6. ABBREVIATIONS USED IN THE TEXT</td>
<td>16</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

Evidence of variations in clinical practice, together with rising costs associated with constrained resources in most health care systems over the past decade, has triggered growing interest in evaluating the quality of our surgical work (1-3). At present, the main methods of assessing surgical results for audit and quality assurance remain mortality and morbidity (4-6). Thus measurement of morbidity requires an accurate definition of a surgical complication. Although the incidence of postoperative complications is still the most frequently used surrogate marker of quality in surgery (1,3,7), the direct cause-and-effect relationship between surgery and complications is often difficult to assess. This uncertainty carries a risk of underreporting surgical complications, with substantial consequences.

Most published articles focus only on positive outcomes (e.g. trifecta in prostate cancer after radical prostatectomy) (8). There is a need to compare complications for each specific approach in a systematic, objective, and reproducible way. As yet, no definitions for complications or guidelines for reporting surgical outcomes have been universally accepted. Reporting and grading of complications in a structured fashion is only one aspect of the quality of outcome reporting. In 2002, Martin et al. proposed 10 criteria that should be met when reporting complications following surgery (9) (Table 1). Clavien and Dindo proposed a system for grading the severity of postoperative complications (10) that was subsequently revised and validated (11) (Table 2).

Table 1: Martin et al. criteria of accurate and comprehensive reporting of surgical complications (9)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of accruing data defined</td>
<td>Prospective or retrospective accrual of data are indicated</td>
</tr>
<tr>
<td>Duration of follow-up indicated</td>
<td>Report clarifies the time period of postoperative accrual of complications such as 30 days or same hospitalisation</td>
</tr>
<tr>
<td>Outpatient information included</td>
<td>Study indicates that complications first identified following discharge are included in the analysis</td>
</tr>
<tr>
<td>Definition of complications provided</td>
<td>Article defines at least one complication with specific inclusion criteria</td>
</tr>
<tr>
<td>Mortality rate and causes of death listed</td>
<td>The number of patients who died in the postoperative period of study are recorded together with cause of death</td>
</tr>
<tr>
<td>Morbidity rate and total complications indicated</td>
<td>The number of patients with any complication and the total number of complications are recorded</td>
</tr>
<tr>
<td>Procedure-specific complications included</td>
<td>Any grading system designed to clarify severity of complications including major and minor is reported</td>
</tr>
<tr>
<td>Severity grade utilised</td>
<td>Evidence of risk stratification and method used indicated by study</td>
</tr>
<tr>
<td>Length-of-stay data</td>
<td>Median or mean length of stay indicated in the study</td>
</tr>
</tbody>
</table>

Table 2: Clavien-Dindo grading system for the classification of surgical complications (11)

<table>
<thead>
<tr>
<th>Grades</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention</td>
</tr>
<tr>
<td>Grade III-a</td>
<td>Intervention not under general anaesthesia</td>
</tr>
<tr>
<td>Grade III-b</td>
<td>Intervention under general anaesthesia</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management</td>
</tr>
<tr>
<td>Grade IV-a</td>
<td>Single organ dysfunction (including dialysis)</td>
</tr>
<tr>
<td>Grade IV-b</td>
<td>Multi-organ dysfunction</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Suffix “d”</strong></td>
<td>If the patient suffers from a complication at the time of discharge the suffix “d” (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to evaluate the complication fully.</td>
</tr>
</tbody>
</table>

Despite these proposals, no current standard guidelines or criteria exist for reporting surgical complications in the area of urology. It appears important that the urologic community create universally accepted criteria for reporting surgical morbidity and outcomes to establish the efficacy of surgical techniques and improve the quality of patient care (12). Adopting an integrated method of characterising and reporting surgical morbidity has the potential to improve patient care on many levels:

- It enables better characterisation of surgical morbidity associated with various surgical techniques.
- It allows comparison of different surgical techniques, which is important due to the relative lack (< 1%) of randomised trials in the urologic literature.
- It allows the physician to portray more accurately to patients the risks of a procedure versus other surgical or medical options.
- It allows better sequencing of multimodality approaches.
- It allows earlier recognition of the pattern of complications, thereby allowing for pre-emptive changes in care in an effort to decline the incidence.
- It allows better comparisons between individual surgeons or between institutional experiences.
- It allows identification of quality-of-care measures for benchmarking.

The aim of our work was to review the available reporting systems used for urologic surgical complications; to establish a possible change in attitude towards reporting of complications using standardised systems; to assess systematically the Clavien-Dindo system (currently widely used for the reporting of complications related to urologic surgical interventions); to identify shortcomings in reporting complications, and to present recommendations for the development and implementation of future reporting systems that focus on patient-centred outcomes. The panel did not take intraoperative complications into consideration, which may be addressed in a follow-up project.

### 1.1 Publication history

This article presents a republication of a scientific paper published in European Urology, the EAU scientific journal (13). Prior to publication, the paper has been subjected to double blind peer review.

In the course of 2012 the authors aim to assess the usage and reproducibility of the proposed model for reporting of complications. These findings will be published upon completion of the assessment.

## 2. EVIDENCE ACQUISITION

Standardised systems for reporting and classification of surgical complications were identified through a systematic review of the literature. To establish a possible change in attitude towards reporting of complications related to urologic procedures and assessment of the Clavien-Dindo system in urology, two different strategies were used. For the first objective (reporting trends), papers reporting complications after urologic surgery published in European Urology, Journal of Urology, Urology, BJU International, and World Journal of Urology in 1999-2000 and 2009-2010 were reviewed. Selection criteria were the top five general urology journals (from major urologic societies) based on impact factor (IF) and English-language publications. The panel recognised that IF as a quality indicator was debatable but considered that it would have had no impact on the validity of the outcome of this review. Promising articles were identified initially through the tables of contents of the respective journals. All selected papers were full-text retrieved and assessed; papers not reporting complications and reviews were excluded from the analysis. Analysis was done based on a structured form, which was similar for each article and for each journal (Form 1).

Data identification for the second objective (systematic assessment of the Clavien-Dindo system currently used for reporting of complications related to urologic surgical interventions) involved a Medline/Embase search using Clavien, urology, and complications as keywords. This search produced 63 eligible papers reporting complications using the Clavien-Dindo system. A second search using the search engines of individual urologic journals and publishers that may identify Clavien or Dindo and urology within the full text of a paper produced
141 more papers. Thus the total number of eligible papers was 204. All selected papers were full-text retrieved for analysis, which was done based on a structured form (Form 2). All papers were evaluated by two authors independently, and in case of disagreement, the paper was presented to all members to reach consensus.

Form 1: Data extraction form to assess reporting of complications after urologic procedures using the Clavien-Dindo system

| Study title: | |
| The study is a: | ☐ Case series | ☐ Controlled study without randomisation | Prospective, randomised trial | ☐ Meta-analysis |
| Level of evidence (Oxford criteria, EAU modification): | ☐ 1a | ☐ 1b | ☐ 2a | ☐ 2b | ☐ 3 |
| The study reports complications after (define the procedure): | |
| Did the authors use standardised criteria? | ☐ Yes | ☐ No |
| In case standardised criteria were used, they were: | ☐ Predefined by authors | ☐ Clavien-Dindo system |
| No of Martin criteria met: | ☐ 0-2 | ☐ 3/4 | ☐ 5/6 | ☐ 7/8 | ☐ 9/10 |

Form 2: Data extraction form to assess reporting of complications after urologic procedures using the Clavien-Dindo system

| Study title: | |
| Published in: | |
| Year of publication: | Volume: | Page: | to |
| The study is a: | ☐ Case series | ☐ Controlled study without randomisation | Prospective, randomised trial | ☐ Meta-analysis |
| Level of evidence (Oxford criteria, EAU modification): | ☐ 1a | ☐ 1b | ☐ 2a | ☐ 2b | ☐ 3 |
| No of Martin criteria met (0-10): | |
| The study reports complications after (define): | |
| In your opinion, was the Clavien-Dindo system used correctly? | ☐ Yes | ☐ No |
| If NO, why not: | |
3. EVIDENCE SYNTHESIS

3.1 Systems used to report surgical complications
The systematic review of the literature for standardised systems used for reporting and classification of surgical complications revealed five standardised systems (Table 3).

Table 3: Available classification systems for reporting of complications

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical validation</th>
<th>Simplicity</th>
<th>Severity grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavien-Dindo</td>
<td>Yes</td>
<td>Easy</td>
<td>I-V</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Yes</td>
<td>Easy</td>
<td>5</td>
</tr>
<tr>
<td>Accordion</td>
<td>No</td>
<td>Easy</td>
<td>4</td>
</tr>
<tr>
<td>contracted</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>extended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSQIP</td>
<td>Yes</td>
<td>Complex</td>
<td>Major/minor</td>
</tr>
<tr>
<td>NCT-CTC</td>
<td>Yes</td>
<td>Complex</td>
<td>5</td>
</tr>
</tbody>
</table>

MSKCC = Memorial Sloan-Kettering Cancer Centre classification - modification of the original T92 Clavien classification (9,14); NSQIP = National Surgical Quality Improvement Programme (3); NCT-CTC = National Cancer Institute Common Toxicity Criteria (17).

In 1992, Clavien et al. proposed a classification for complications of surgery and introduced a severity grading system called T92 (10), which was based on the main criterion of the intervention needed to resolve the complication. Four grades containing five levels of complications were described. In 2004, Dindo et al. introduced a modification of the T92 classification using five grades containing seven levels (Table 2) (11). This modification was performed to add further precision and to characterise whether an intervention due to the complication led to general anaesthesia, intensive care unit admission, or organ failure, and again, it was based on the type of therapy required to treat the complication. This modified classification, which is known as the Clavien-Dindo system, was validated and tested for interobserver variation in 10 centres around the world (14). The Clavien-Dindo system is widely used, with an exponential increase in recent years, especially in general surgery but also in urology (see Fig. 3 and 4). A few authors have adapted both systems to analyse specific procedures such as living donor liver and kidney transplantation, which has led to confusion (14).

A less extensive modification of the T92 system was made by Martin et al. (9,15) and is referred to as the Memorial Sloan-Kettering Cancer Centre (MSKCC) severity grading system. Conceptually, it is very similar to T92 but differs in numbering (for details see Table 1 in Strasberg et al. [16]).

The Accordion classification was introduced in 2009 and represents a flexible system that can be used in studies of different size and complexity (17) (Table 4). It is available on an open Website (http://www.accordionclassification.wustl.edu).
Table 4: Accordion severity classification of postoperative complications: contracted and expanded classification (17)

<table>
<thead>
<tr>
<th>Contracted classification</th>
<th>Expanded classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild complication</td>
<td>1. Mild complication</td>
</tr>
<tr>
<td>Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed: antiemetics, antipyretics, analgesics, diuretics and electrolytes.</td>
<td></td>
</tr>
<tr>
<td>2. Moderate complication</td>
<td>2. Moderate complication</td>
</tr>
<tr>
<td>Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.</td>
<td></td>
</tr>
<tr>
<td>All complications requiring endoscopic or interventional radiology or re-operation, as well as complications resulting in failure of one or more organ systems.</td>
<td></td>
</tr>
<tr>
<td>4. Death</td>
<td>4. Death</td>
</tr>
<tr>
<td>Postoperative death</td>
<td>Postoperative death</td>
</tr>
</tbody>
</table>

*An example would be wound re-exploration under conscious sedation and/or local anaesthetic.
†Such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an ICU.

The National Surgical Quality Improvement Program was established in 1994 within the US Veterans Administration (VA) health care system, with the aim of identifying and reporting adverse events as one prerequisite for process improvement in health care (3). The system is validated, outcome based, and uses data adjusted for patient preoperative risk. It allows comparison of the performance of different hospitals performing major surgery by the ratio of observed to expected (O/E) adverse events. Statistically low (O/E < 1) or high (O/E > 1) outliers are then identified to support continuous quality improvement activities. The annual use of this system has contributed to the improvement of the standard of surgical care and to lower 30-d mortality and morbidity rates for major noncardiac surgery within the VA.

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) system (17) was first created in 1983, aimed at the recognition and grading of adverse effects of chemotherapy in cancer patients. The system was updated and expanded in 1998 (CTC v2.0), including acute effects of radiotherapy and limited criteria applicable to surgery. In 2003, Common Terminology Criteria for Adverse Events (CTCAE v3.0) was introduced for application to all possible modalities and is organised by organ system categories (all organs are included), with 370 different criteria. An adverse event is defined as any new finding or undesirable event that may not be attributed to treatment. Grading criteria are shown in Table 5. Late and acute effects criteria are merged into a single uniform system and applied without a predetermined time-based designation. The previously used “90-day rule” is not advised currently because each study is unique. The new CTC system was designed to be applied to all possible modalities, and it is organised by organ system categories (all organs are included) with 370 different criteria. The unexpected serious and life-threatening (grades 3 and 4) consequences of surgery are the focus of immediate surgical reporting. CTCAE v3.0 is available on the Cancer Therapy Evaluation Program Website (www.ctep.info.nih.gov).
Table 5: National Cancer Institute Common Toxicity Criteria grading system for the adverse effects of cancer treatment (17)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition of effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Minimal and usually asymptomatic effects that do not interfere with functional endpoints (interventions or medications are generally not indicated for these minor effects).</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate, are usually symptomatic. Interventions such as local treatment or medications may be indicated (they may interfere with specific functions but not enough to impair activities of daily living).</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe and very undesirable. There are usually multiple, disruptive symptoms (more serious interventions, including surgery or hospitalisation, may be indicated).</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Potentially life threatening, catastrophic, disabling, or result in loss of organ, organ function, or limb.</td>
</tr>
</tbody>
</table>

Most recently, the International Urogynecological Association (IUGA) and the International Continence Society (ICS) have established a joint working group on terminology for complications related to the insertion of prostheses and grafts in female pelvic floor surgery (18). The document proposes definitions of specific complications, distinguishing local complications, complications to surrounding organs, and systemic complications. New terms have been proposed and defined in detail such as contraction, prominence, separation, exposure, extrusion, perforation, dehiscence, and sinus tract formation. The classification is based on category, time, and site of complications, with the aim of summarising any of a large range of possible clinical scenarios into a code using as few as three numerals and three (or four) letters. Lowercase letters can be added, describing the presence and the type of pain. The ICS-IUGA classification appears at first sight to be complex and not immediately mastered, as outlined by the proponents. The main goal is to establish common language and to promote a homogeneous registry to improve the quality of pelvic floor surgical procedures using prostheses and grafts.

3.2 Attitude of urologists towards reporting complications

A total of 874 eligible papers of 1261 retrieved publications were included in the final analysis. The type of studies reporting complications did not vary between the two time frames selected (1999-2000 vs 2009-2010) (p > 0.1). Most of the papers identified were case studies (Fig. 1). However, a shift could be seen in the number of studies using most of the Martin criteria (Fig. 2), as well as in the number of studies using either standardised criteria or the Clavien-Dindo system to report complications (Fig. 3).

Fig. 1: Comparative distribution of papers reporting complications after urologic procedures by study type and time frame
3.3   Assessment of the Clavien-Dindo system for reporting complications after urologic procedures

The literature search identified 204 papers published in:

- Urology 38
- Journal of Urology 37
- Journal of Endourology 35
- European Urology 34
- BJU International 19
- World Journal of Urology 15
- and several others 26

The number of papers using the Clavien-Dindo system to report complications after urologic surgical interventions showed an exponential increase (Fig. 4). Most of the studies identified were, again, case series, and 77.9% of the studies fulfilled ≥ 7 of the Martin criteria (range: 3-10; mean: 7.5; standard deviation: 1.5). The
vast majority of papers referred to novel technologies (laparoscopy/robot-assisted procedures), whereas only 13.2% of papers discussed open procedures. The Clavien-Dindo system was not properly used in 72 papers (35.3%): Eight times it was also used to report/grade intraoperative complications; six times the authors used their own modification of the Clavien-Dindo system; in 27 studies, the authors grouped complications into major (Clavien-Dindo ≥ 3) and minor without mentioning specific complications; and in 31 papers, the authors did not assign a grade to the complications reported.

Fig. 4: Distribution of studies using the Clavien-Dindo system to report complications after urologic procedures

3.4 Discussion
The definition of surgical complications still lacks standardisation, which hampers the interpretation of surgical performance and quality assessment (5,7,19). Although many surgeons would argue that their subjective intuition is an appropriate guide to defining what a complication might be, the value of the surgeon’s intuition is unreliable in many situations because it lacks objective criteria and depends heavily on the experience of the individual clinician (4,7,20). Second, a surgical complication is not a fixed reality. Instead, it depends on the surgeon’s level of skill, the surgeon’s learning curve for the procedure, the patient’s comorbidity and risk factors, and the facilities available. A surgical complication in a Western country may not be perceived or subjectively weighted as a surgical complication in rural or less developed countries. Similarly, a complication in 2011 may be seen as obsolete in a few years’ time, with a better understanding of the pathophysiology of the underlying malady. As surgical techniques and equipment improve, what were once inevitable negative outcomes may acquire the status of mere surgical complications (2,5,7). Finally, and paradoxically, the higher the expectation of the surgeon and patient, the more potential surgical complications occur (21,22). The clinical relevance of reporting surgical complications is primarily related to the fact that the dissemination of technology is very rapid, with current grades of recommendations based on the level of evidence in their corresponding studies. However, in the surgical field, randomised controlled trials with high levels of evidence are uncommon, and this limitation naturally leads to a low number of recommendations. We have to keep in mind that the guidelines can only rely on the surgical evidence. Thus there is a real discrepancy between the reality of daily surgical practice and the relevance of the low-grade recommendations produced in this area. However, the scientific quality of an article is not only related to its level of evidence. The use of more rigorous methodology and the consensus-related complications of surgical techniques will probably improve the quality of the surgical scientific literature. It is likely that this improvement will renew interest in daily clinical practice in the minds of surgeons. In addition, it will allow recommendations that avoid complications, clearly the most relevant issue in improving patient care.

In defining surgical complications, subjectivity cannot always be avoided, but it should be reduced as much as possible (4). Additionally, different audiences (e.g. patients, nurses, health care providers, and third-party payers) and different surgical communities (e.g. urologists, orthopaedists, and vascular surgeons) view, define,
and perceive complications differently. Currently, no generally accepted standards or definitions exist with regard to the severity of surgical complications. Clavien-Dindo recommended the following definitions of surgical outcomes:

1. Surgical complication: any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure.
2. Failure to cure: diseases or conditions that remained unchanged after surgery.
3. Sequelae: conditions that are inherent in a procedure and thus would inevitably occur, such as scar formation or the inability to walk after an amputation.

Based on the review of the current literature, and with reference to the Accordion Severity Grading System (16), an appropriate definition of a complication is a combination of the following items: an event unrelated to the purposes of the procedure, an unintended result of the procedure, an event occurring in temporal proximity to the procedure, something causing a deviation from the ideal postoperative course, an event that induces a change in management, or something that is morbid (i.e. causes suffering directly by causing pain, or indirectly, by subjecting the patient to additional interventions).

In contrast to a complication, the sequelae of a procedure should be defined as an after-effect of that procedure. The risk of sequelae is inherent in the procedure (e.g. diabetes after pancreatic resection, rejection after transplantation, limp after amputation, dyspnoea after pneumonectomy, or impairment of renal function after tumour nephrectomy). Failure to cure should be defined as failure to attain or maintain the purpose of the procedure (e.g. failure to remove all stones during ureteroscopy or percutaneous stone surgery, tumour recurrence, stricture recurrence, or recurrence of patency when the purpose of the procedure is to occlude). Sequelae of procedures and failures to cure should be reported but presented separately from complications (14).

However, a complication that results in lasting disability is considered a sequela of a complication. Stroke or acute renal failure (ARF) occurring after a procedure is considered a complication and should be reported as such. However, long-term aphasia resulting from stroke or chronic renal failure after ARF is considered a sequela of that complication. Therefore, it should be reported in a special section devoted specifically to long-term disability.

Patients and their treating physicians do not necessarily mean the same thing when they use the term complication. Several studies have shown substantial discrepancies in the reporting of adverse events and sequelae of a treatment when the estimations of patients and physicians are compared (22). The usual information on potential complications that patients can obtain before a surgical procedure can be taken from the available literature, the specific information given by the treating centre (i.e. home page or patient information brochures), or from direct discussion with the treating surgeon. This information has the potential to be biased from the definition of what is considered a complication, and a standardised system that is not only used for complication reports in the literature but also for patient counselling is important for a realistic estimation of outcomes. In the present literature, patients often report a higher frequency and severity of adverse events compared with that reported by their physicians (23). However, in a recent randomised study, Steinsvik et al. showed that several adverse events, such as bowel problems, were overrated by the physician (24). Overrating and especially underrating of complications by the treating physician leads to confusion and a discrepancy between patient expectation and reality.

Schroeck et al. evaluated variables associated with satisfaction and regret after open and robotic radical prostatectomy (21). Patients who underwent robotic-assisted laparoscopic prostatectomy were more likely to be regretful and dissatisfied, which was not necessarily interpreted as caused by a worse outcome but potentially caused by the higher expectation associated with an innovative procedure. The authors therefore suggested that urologists should carefully portray the risks and benefits of new technologies during preoperative counselling to minimise regret and maximise satisfaction.

These examples support the notion that realistic counselling is crucial for the patient’s decision-making process and for satisfaction with the achieved result. However, a standardised reporting system for surgical complications can only try to standardise the reporting of the intraoperative and perioperative morbidity of the procedure itself. Short-, mid- or long-term sequelae of a surgical procedure, such as erectile dysfunction or urinary incontinence following radical prostatectomy, are not covered by this classification and need to be reported with other validated tools.

Standardised classification and severity grading of surgical complications is essential for proper interpretation
of surgical outcome data, for comparing the surgical outcomes between institutions or individual surgeons, and for comparing techniques in case randomised trials are either lacking or difficult to perform (i.e. comparison of minimally invasive techniques with open surgery). The urologic community seems to conform to the current demands because recent studies have more often used standardised criteria to report complications (48.3% vs. 35.3%) (Fig. 3). In urologic oncology reports published from January 1995 to December 2005, the corresponding percentage was 33%, with only 19% (6% of the total) using a numerical complication severity grading system (12). The Clavien-Dindo system has gained wide acceptance both in general surgery (14) and the urologic community (Fig. 3, and Fig. 4). Clinical databases designed and controlled by physicians may underreport complications (25). Similarly, a disadvantage of the Clavien-Dindo system is its unreliability when recording is performed by residents, although, when captured, grading of complications was correct in 97% of the cases. Consequently, the authors have proposed that dedicated personnel should evaluate surgical outcomes (2). Special attention should also be paid to proper use of the Clavien-Dindo system because it has not been designed/validated to grade intraoperative complications, and any modifications and revisions can be confusing (14).

Classification and severity grading of surgical complications is an important, albeit not the only criterion of quality when reporting surgical outcome. Approximately 40% of general surgery series and trials and 23% of studies reporting surgical complications in urologic oncology (2) fulfil seven or more Martin criteria. Interestingly, 77.9% of the papers that used the Clavien-Dindo system to report complications after urologic procedures fulfilled seven or more criteria, implying that its use contributes to higher quality reports.

Besides the efficiency of an individual surgeon and the function of an institution, surgical care outcomes also depend on the patient’s preoperative risk factors (26). Thus they should always be defined and used in the analysis and report. A substantial proportion of postoperative complications occur after hospital discharge (27); extension of the length of postoperative observation may therefore be necessary. Other quality-of-care indicators are readmissions and reoperations (28) and should be included in both preliminary and final reports.

4. CONCLUSIONS

There is an urgent need for uniform reporting of complications after urologic procedures, which will aid all those involved in patient care and scientific publishing (authors, reviewers and editors). Urologists have considerably changed their attitude towards using standardised criteria when reporting complications, and there has been an exponential increase of the number of papers using the Clavien-Dindo system. However, a certain number of papers (35.3%) did not use it properly. When reporting the outcomes of urologic procedures, the committee proposes the following:

- Define your complications.
- Preferentially use a standardised system; the Clavien-Dindo grading system is highly recommended.
- When using the Clavien-Dindo system, provide a table of all complications and corresponding grades or list the complications by grade.
- Use the NCI-CTC system in multimodality treatment.
- Improve reporting of complications by following the revised quality criteria (Table 6).
- Define the method of accruing data: retrospective/prospective; through chart review/telephone interview/face-to-face interview/other.
- Define who collected the data: medical doctor/nurse/data manager/other, and whether he or she was involved in the treatment.
- Indicate the duration of follow-up: 30, 60, 90, or >90 d.
- Include outpatient information.
- Include mortality data and causes of death.
- Include definitions of complications.
- Define procedure-specific complications.
- Use a severity grading system (avoiding the distinction minor/major); the Clavien-Dindo system is recommended.
- Include risk factors: American Society of Anaesthesiologists score, Charlson score, Eastern Cooperative Oncology Group, other.
- Include readmissions and causes.
- Include reoperations, types and causes.
- Include the percentage of patients lost to follow-up.
Finally, editors of urologic journals should demand the use of a standardised system to report complications after urologic surgery.

**Table 6: Quality criteria for accurate and comprehensive reporting of surgical outcome**

1. Define the method of accruing data:
   - retrospective _ prospective _ , through:
     - chart review _ telephone interview _ face to face interview _ other _
2. Define who collected the data:
   - medical doctor _ nurse _ data manager _ other _
   - and whether he/she was involved in the treatment: yes _ no _
3. Indicate the duration of follow-up:
   - 30 days _ 60 days _ 90 days _ > 90 days _
4. Include outpatient information
5. Include mortality data and causes of death
6. Include definitions of complications
7. Define procedure-specific complications
8. Report intraoperative and postoperative complications separately
9. Use a severity grading system for postoperative complications (avoiding the distinction minor/major) - Clavien-Dindo system is recommended
10. Postoperative complications should be presented in a table either by grade or by complication type (specific grades should always be provided; grouping is not accepted)
11. Include risk factors
   - ASA score _ Charlson score _ ECOG _ other _
12. Include readmissions and causes
13. Include re-operations, types and causes
14. Include the percentage of patients lost to follow-up

5. REFERENCES


6. **ABBREVIATIONS USED IN THE TEXT**

*This list is not comprehensive for the most common abbreviations*

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF</td>
<td>acute renal failure</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CTC AE</td>
<td>Common Terminology criteria for Adverse Events</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>IC(U)</td>
<td>intensive care (unit)</td>
</tr>
<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>IF</td>
<td>impact factor</td>
</tr>
<tr>
<td>IUGA</td>
<td>International Urogynecological Association</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Memorial Sloan-Kettering Cancer Centre classification</td>
</tr>
<tr>
<td>NSQIP</td>
<td>National Surgical Quality Improvement Programme</td>
</tr>
<tr>
<td>NCT-CTC</td>
<td>National Cancer Institute Common Toxicity Criteria</td>
</tr>
<tr>
<td>O/E</td>
<td>ratio of observed versus expected</td>
</tr>
<tr>
<td>VA</td>
<td>US Veterans Administration</td>
</tr>
</tbody>
</table>

**Conflict of interest**

All members of the ad hoc EAU Guidelines working panel on Reporting and Grading of Complications after Urologic Surgical Procedures have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.