European Association of Urology

Guidelines

2012 edition

European
Association
of Urology

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

Upper Urinary Tract Urothelial Cell Carcinomas

Muscle-Invasive and Metastatic Bladder Cancer

Prostate Cancer

Renal Cell Carcinoma

Testicular Cancer

Penile Cancer

Management of Male LUTS, incl. benign prostatic obstruction

Male Sexual Dysfunction: Erectile dysfunction and premature ejaculation

Penile Curvature

Male Infertility

Male Hypogonadism

Urological Infections

Urinary Incontinence

Neurogenic Lower Urinary Tract Dysfunction

Urolithiasis

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Pain Management

Chronic Pelvic Pain

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Reporting complications

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

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1. BACKGROUND

1.1 Publication history

The first European Association of Urology (EAU) Guidelines on Bladder Cancer were published in 2002 (1). It was later decided to develop separate guidelines for different categories of urothelial tumours:

- TaT1 papillary tumours (non-muscle-invasive bladder cancer);
- Carcinoma *in situ* (CIS);
- Muscle-invasive bladder tumours;
- Upper urinary tract tumours.

Separate guidelines have been published in European Urology for TaT1, CIS, and upper urinary tract tumours (2-4). For logistical reasons, the guidelines group on non-muscle-invasive bladder cancer decided to integrate the guidelines of TaT1 tumours and CIS in one issue. This overview represents the updated EAU guidelines for non-muscle-invasive bladder cancer (CIS, Ta, T1).

1.2 Methodology

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, the Medline, Web of Science, and Embase databases were used. For the current upgrade, all articles published between 2008 and 2010 on TaT1 tumours and between 2004 and 2010 on CIS were considered. Focus of the searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomised controlled trials [RCTs]) in accordance with EAU methodology. Panel members rated papers following a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence (LE) (5). Additionally, recommendations have been graded to provide transparency between the underlying evidence and a recommendation given.

Table 1: Level of evidence*

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

**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 (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. 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 (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 panel will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**Modified from Sackett et al. (5).*

2. EPIDEMIOLOGY

Bladder carcinoma is the most common malignancy of the urinary tract. The worldwide age standardised incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females (9). In Europe, the highest incidence has been reported in the Western (23.6 in males and 5.4 in females) and Southern (27.1 in males and 4.1 in females) regions, followed by Northern Europe (16.9 in males and 4.9 in females). The lowest incidence is observed in Eastern European countries (14.7 in males and 2.2 in females) (10).

The global world mortality rate among males is 4 per 100,000 versus 1.1 per 100,000 among females. The ASR (per 100,000) only varies between 5.6 in developed countries and 3.1 in developing countries for males. For females the ASR varies between 1.4 in developed countries and 0.9 in less developed areas (9). In Europe, mortality rates show a substantial decline over the last decade of about 16% in men and about 12% in women (11).

Approximately 75-85% of patients with bladder cancer 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.

3. RISK FACTORS

Many of the aetiological factors for the development of bladder tumours are known and urologists should be aware of the types of occupational exposure that might be related to urothelial carcinogens (12-14). Aromatic amines were the first to be recognised. At-risk groups include workers in the following industries: printing, iron and aluminium processing, industrial painting, gas and tar manufacturing (LE: 3).

Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer (15-17) (LE: 2a). Smoking leads to a higher mortality rate from bladder cancer during long-term follow-up, even though, in a multivariate analysis, the prognostic effect of smoking was weaker than that of other factors, such as stage, grade, size, and multifocality of the tumour (18).

4. CLASSIFICATION

4.1 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) (19).

Table 3: 2009 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

4.2 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 (20,21) (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 various grades has been developed to improve accuracy further in using the system.

Table 4: WHO grading in 1973 and in 2004 (20,21)

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading
Flat lesions
Hyperplasia (flat lesion without atypia or papillary aspects)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Papillary lesions
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

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 PUNLMP and low-grade and high-grade urothelial carcinomas.

Papillary urothelial neoplasm of low malignant potentials 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 (22,23) (Figure 1).

It was shown that the 2004 WHO classification has a better reproducibility than the WHO 1973 classification (24).

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one system over another, however, have yielded controversial results (22-25). 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 scheme. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications can be used.

Figure 1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications (26)*

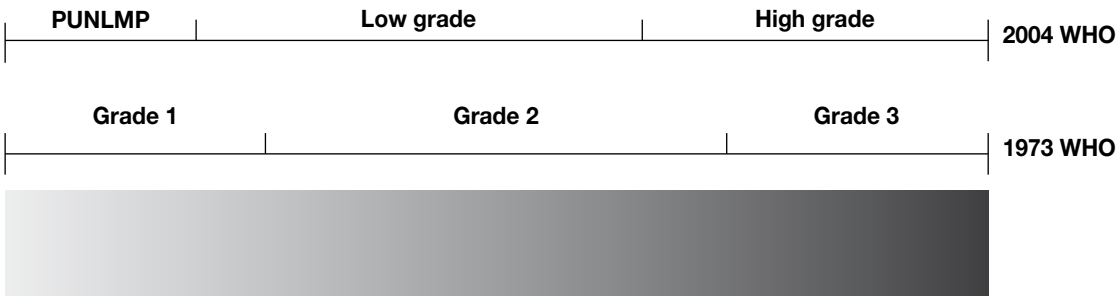

Fig. 1 - Comparison of the 1973 and 2004 WHO grading system. The 1973 WHO grade 1 carcinomas are reassigned, some to the PUNLMP category, and some to the low-grade carcinoma category. Similarly, 1973 WHO grade 2 carcinomas are reassigned, some to the low-grade carcinoma category, and others to the high-grade carcinoma category. All 1973 WHO tumours are assigned to the high-grade carcinoma category. WHO = World Health Organization; PUNLMP = papillary urothelial neoplasm of low malignant potential.

**Figure reproduced with permission from MacLennan GT, Kirkali Z, Cheng L. Histologic grading of noninvasive papillary urothelial neoplasms. Eur Urol 2007 Apr;51(4):889-98. Copyright 2007 Elsevier.*

4.3 Controversial definition of non-muscle-invasive ("superficial") tumours

The diagnosis of non-muscle-invasive bladder cancer requires consideration of all transurethral resection (TUR) samples.

A papillary tumour confined to the mucosa is classified as stage Ta according to the TNM system. Tumours that have invaded the lamina propria are classified as stage T1. Ta and T1 tumours can be removed by TUR, and therefore, they are grouped under the heading of non-muscle-invasive bladder cancer 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, invasive potential of CIS and T1 lesions. Therefore, the terms non-muscle-invasive and superficial bladder cancer are suboptimal descriptions.

Some promising prognostic factors that are based on pathological examination of resected tissue have been presented:

- In patients with T1 tumours, the depth of invasion into the lamina propria is considered. The depth of invasion is evaluated in relation to the muscularis mucosae layer. T1 tumours are substaged into T1a (tumours that extend into the lamina propria but above the level of the muscularis mucosae) and T1b (tumours that infiltrate into or below the level of the muscularis mucosae). The prognostic value of T1 substaging has been demonstrated by some retrospective cohort studies (27-29) (LE: 3).
- The presence of lymphovascular invasion has been recognised as an unfavourable prognostic factor in T1 tumours (29,30) (LE: 3).
- Detection of the micropapillary variant of urothelial carcinoma represents a poor prognostic factor (31) (LE: 3).

4.4 Inter- and intra-observer 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 (32,33). There is also important inter-observer variability in classification of stage T1 versus Ta tumours, and grading tumours with general conformity between 50 and 60% (24,32-36). The inter-observer variability is less with the 2004 WHO classification compared to the 1973 classification (23,24). However, a review of slides is recommended particularly in T1, CIS and high-grade lesions.

4.5 Specific character of CIS and its clinical classification

Carcinoma *in situ* is a flat, high-grade, non-invasive urothelial carcinoma. The term CIS might suggest that it is a precursor of cancer. Although it might be a precursor of invasive bladder cancer, the histological and cytological aspects of CIS make this an overtly malignant entity in itself.

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 in the upper urinary tract and in the prostatic ducts and urethra (37).

Carcinoma *in situ* is classified into one of three different clinical types (38):

- Primary: isolated CIS with no previous or concurrent exophytic tumours;
- Secondary: CIS detected during the follow-up of patients with a previous tumour;
- Concurrent: CIS in the presence of exophytic tumours.

5. DIAGNOSIS

5.1 Symptoms

Haematuria is the most common finding in non-muscle-invasive bladder cancer. TaT1 tumours do not cause bladder pain and rarely present with lower urinary tract symptoms. In patients who do complain of these symptoms, CIS might be suspected.

5.2 Physical examination

Physical examination does not reveal non-muscle-invasive bladder cancer.

5.3 Imaging

5.3.1 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 now questioned because of the low incidence of significant findings obtained with this method (39-41) (LE: 3). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (40). The risk of tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours (42).

In many centres, computed tomography (CT) urography is used as an alternative to conventional IVU (43). Especially in muscle-invasive tumours of the bladder and in upper tract tumours, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs) (LE: 4). However, CT urography has the disadvantage of higher radiation exposure compared to IVU.

*5.3.2 **Ultrasonography***

Ultrasonography (US) has been used with increasing frequency 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 hydronephrosis and visualisation of intraluminal masses in the bladder. It can be as accurate as IVU for diagnosis of upper urinary tract obstruction (39) (LE: 3). The US is thus a useful tool for investigation in patients with haematuria to detect obstruction, it cannot however exclude the presence of upper tract tumours. Imaging methods (IVU, CT urography or US) have no role in the diagnosis of CIS.

5.4 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 (LE: 2b). Due to a loss of cohesion of cells 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. Thanks to these conditions is the sensitivity of cytology in CIS detection > 90%. 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.

Cytological interpretation is user-dependent (44). Evaluation can be hampered by low cellular yield, urinary tract infections, stones or intravesical instillations. In experienced hands however, the specificity exceeds 90% (45) (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.

5.5 Urinary molecular marker tests

Extensive laboratory research has developed numerous urinary tests for diagnosis of bladder cancer based on detection of soluble or cell-associated markers (45-51).

Numerous reviews of urinary markers have appeared in recent years (45-59). A few of the markers have come into clinical application but none has been accepted as a standard diagnostic procedure in routine urology or in guidelines until now. Three tests are particularly promising: nuclear matrix protein 22 (NMP22), UroVysion®, and ImmunoCyt (49,50,60-64).

The following conclusions can be drawn about the existing tests. The bladder tumour antigen (BTA) test has a very limited role because of its high false-positive rate and low sensitivity for low-grade tumours (65,66). NMP22 similarly suffers from a high false-positive rate but has higher sensitivity than urinary cytology. With careful selection of patients, the specificity of NMP22 can be improved, and because of its high negative predictive volume (NPV), it can potentially be used during follow-up to delay cystoscopy control (60,62,67-69). ImmunoCyt has the highest sensitivity for detection of low-grade tumours and is less affected by other urological diseases. However, with a 60% detection rate for low-grade tumours, the test remains largely inadequate to replace cystoscopy (64,70). UroVysion® adds little to the surveillance of low-grade tumours. However, it can replace cytology for high-grade tumours when experience with urinary cytology is lacking or when its result is inconclusive. Some false-positive results arise because UroVysion® can detect occult disease and thus identify those patients who are more likely to experience recurrence. It might also be useful to predict response to intravesical therapy (63,71,72). Microsatellite analysis is the most promising of the methods listed in Table 5. It can predict recurrence of low-grade tumours in up to 80% of cases, but it still lacks sensitivity (73-75).

The sensitivity of tests can be improved by their combination, as suggested by the International Consensus Panel on Bladder Tumour Markers (45).

Although it is hoped that these tests can soon make the transition from the laboratory to the clinic, it is essential to evaluate their costs to determine whether they can provide a low-cost and reliable alternative to current cystoscopy methods (76).

Table 5 gives an overview of how far the available urinary markers correspond to some of these criteria (52).

Table 5: Summary of main urinary markers

Markers	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	Interference by BCG instillations and other bladder conditions	Comments
UroVysion®	30-72	63-95	66-70	No	No	Expensive and laborious
Microsatellite analysis	58	73	90	No	No	Expensive and laborious
Gene microarray	80-90	62-65	80	No	No	Expensive and laborious
Immunocyt/ uCyt +™	76-85	63-75	67-92	No	Yes	Good sensitivity in low-grade tumours, affected by BCG
Nuclear matrix protein 22	49-68	85-87.5	75-83	Yes	Yes	Low sensitivity, affected by benign conditions
BTA stat	57-83	68-85	61.5	Yes	Yes	Low sensitivity, affected by benign conditions and BCG
BTA TRAK	53-91	28-83	77	No	Yes	Low sensitivity, affected by benign conditions and BCG
Cytokeratins	12-85	75-97	33-82	No	Yes	Low sensitivity, affected by benign conditions and BCG
Survivin	53-90	88-100	50	No	No	Low sensitivity, expensive and laborious

BCG = Bacillus Calmette-Guérin; BTA = bladder tumour antigen.

5.6 Practical application of urinary cytology and markers

There are specified general requirements for good markers for bladder cancer (45):

- The test must be as simple as possible technically (preferably a point-of-care test, with readily available results, easy to perform, with a short learning curve);
- Low cost;
- Reliable and reproducible results;
- High diagnostic accuracy (high sensitivity and specificity);
- For individual patient populations and clinical situations, the test should have a high positive predictive value to avoid unnecessary workup because of false-positive results, and high NPV to avoid the risk of failing to detect tumours. These parameters vary between populations with different incidences of bladder cancer and cannot be used for general comparison of methods;
- For clinical settings, it is of utmost importance to detect reliably all high-grade tumours before they escape curative treatment.

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

- *Screening of the population at risk of bladder cancer.*
  The application of haematuria dipstick, NMP22 or UroVysion® in bladder cancer screening in high-risk

populations has been reported (60,61). However, concerns about feasibility and cost-effectiveness mean that routine application of screening has not yet been established.

- *Exploration of patients after haematuria or other symptoms that are suggestive of bladder cancer.*
  It is generally accepted that none of the tests can replace cystoscopy. However, urinary cytology or markers can be used as adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, the method should have high sensitivity and specificity for high-grade tumours. Urinary cytology is highly specific and sensitive in this regard. Most commercially available urinary markers are even slightly more sensitive than cytology, the problem is however their lack of specificity.

- *Facilitate surveillance of non-muscle-invasive bladder cancer to reduce the number of cystoscopies (48,52,62,65).*
  To reduce the number of cystoscopies, 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 recurrences. Several urinary markers are better but still do not detect half of the low-grade tumours that are detected by cystoscopy. Among the commercially available tests, the best performance for detecting recurrence of low-grade tumours is by immunocytology. Large prospective studies on recurrence of low-grade tumours are still lacking, thus, urinary markers cannot safely replace cystoscopy in this setting.

5.7 Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. The diagnosis of CIS is made by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies (77).

Cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualised in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo TUR.

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.

5.8 Transurethral resection (TUR) of TaT1 bladder tumours

The goal of the TUR in TaT1 bladder tumours is to make the correct diagnosis and remove all visible lesions.

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm) can be resected *en bloc*, the specimen contains the complete tumour plus a part of the underlying bladder wall. Some experts believe that deep resection is not necessary in small, apparently low-grade lesions with a previous history of TaG1 tumour. Larger tumours should 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. The specimens from different fractions must be referred to the pathologist in separate containers to enable him/her to make a correct diagnosis. Cauterisation should be avoided as much as possible during TUR to prevent tissue destruction.

Complete and correct TUR is essential to achieve a good prognosis (78). 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 (79) (LE: 2).

5.9 Bladder and prostatic urethral biopsies

Carcinoma *in situ* can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it might not be visible at all. It can be present as an isolated lesion without exophytic tumour, or it can accompany TaT1 tumours.

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 biopsies (R-biopsies), should be performed in patients with positive urinary cytology and absence of visible tumour in the bladder. It is recommended to take R-biopsies from the trigone, bladder dome and from right, left, anterior and posterior bladder walls.

In patients with TaT1 tumours, R-biopsies are not routinely recommended. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) (80) (LE: 2a). Cold cup biopsies from normal-looking mucosa should be performed when cytology is positive or when exophytic tumour has a non-papillary appearance. Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers. In CIS, the coherence and adherence of epithelial cells is decreased, and this feature often

results in denuded biopsies when taken by cold cup or a resection loop (81).

Involvement of the prostatic urethra and ducts in male patients with non-muscle-invasive bladder cancer has been reported. Although the exact risk of prostatic urethra or ducts involvement is not known, it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours (82,83) (LE: 3). In these cases and when cytology is positive, with no evidence of tumour in the bladder, or when abnormalities of prostatic urethra are visible, biopsies of the prostatic urethra are recommended. The biopsy is taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock position) using a resection loop.

5.10 Photodynamic diagnosis (fluorescence cystoscopy)

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. 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 (84-86) (LE: 2a). The additional detection rate with PDD was 20% for all tumours and 23% for CIS in a cumulative analysis of prospective trials (87). However, false-positivity can be induced by inflammation or recent TUR, and during the first 3 months after BCG instillation (88).

The benefit of ALA fluorescence-guided TUR for recurrence-free survival has been demonstrated in several small, randomised clinical trials (89-91). Cumulative analysis of three trials has shown that the recurrence-free survival was 15.8-27% higher at 12 months and 12-15% higher at 24 months in the fluorescence-guided TUR groups compared to the white light cystoscopy alone groups (87) (LE: 2) However, a large Swedish study could not detect any advantage in using ALA fluorescence-guided TUR routinely in all patients with non-muscle-invasive bladder cancer (92). A recent large, multicentre, prospective randomised trial that compared HAL fluorescence-guided TUR with standard TUR reported an absolute reduction of no more than 9% in the recurrence rate within 9 months in the HAL arm (93) (LE: 1b).

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

Photodynamic diagnosis is most useful for detection of CIS, and therefore it should be restricted to those patients who are suspected of harbouring a high-grade tumour, e.g. for biopsy guidance in patients with positive cytology or with a history of high-grade tumour. Because of conflicting data on recurrence rate this panel restricts the indication for PDD more than experts in a recently published review (94).

The additional costs of the equipment and instillation for PDD should be taken into account.

5.11 Second resection

The significant risk of residual tumour after initial TUR of TaT1 lesions has been demonstrated (78,95) (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-53% of patients (95-100).

Moreover, the tumour is often under-staged by initial resection. The likelihood that a T1 tumour has been under-staged and muscle-invasive disease is detected by second resection ranges from 4 to 25%. This risk has increased up to 50% in some cystectomy series, although these studies have only enrolled selected patients (96,101,102) (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; therefore, correct staging is important.

A second TUR should be considered when the initial resection is incomplete, for example, when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contains no muscle tissue (TaG1 excluded). Furthermore, a second TUR should be performed when a high-grade or T1 tumour has been detected at initial TUR (103). It has been demonstrated that a second TUR can increase the recurrence-free survival (98,99,104) (LE: 2a). There is no consensus about the strategy and timing of second TUR. Most authors recommend resection at 2-6 weeks after initial TUR. The procedure should include resection of the primary tumour site.

5.12 Pathological report

Pathological investigation of the specimen obtained by TUR and biopsies is an essential step in the diagnosis of bladder cancer. The pathological report should specify the grade of the lesion(s) and the depth of tumour invasion into the bladder wall, and should give information about whether the lamina propria and sufficient muscle are present in the specimen (104).

Essential for correct pathological assessment is the high quality of resected tissue. The presence of sufficient muscle is necessary for correct assignment of T-category. Close cooperation between urologists and pathologists is recommended.

5.13 Recommendations for primary assessment of non-muscle-invasive bladder tumours

	GR
The renal and bladder US may be used during initial work-up in patients with haematuria.	C
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).	B
Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology nor by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Voided urine cytology or urinary markers are advocated to predict high grade tumour before TUR.	C
It is recommended to perform TUR in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
It is recommended to perform TUR in fractions (including muscle tissue) for tumours > 1 cm in diameter.	B
It is recommended to take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome and from right, left, anterior and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a non-papillary appearance.	C
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. The biopsy should be taken from the precollicular area between 5 and 7 o'clock using a resection loop.	C
If equipment is available, fluorescence-guided (PDD) biopsy should be performed when bladder CIS is suspected (e.g. positive cytology, recurrent tumour with previous history of a high-grade lesion).	B
A second TUR should be performed at 2-6 weeks after initial resection when the latter is incomplete (in large and multiple tumours, no muscle in the specimen), or when an exophytic high-grade and/or T1 tumour is detected.	A
The pathological report should specify the grade, depth of tumour invasion, and whether the lamina propria and sufficient muscle are present in the specimen.	A

CIS = carcinoma in situ*; CT = computed tomography; IVU = intravenous urography; PDD = photodynamic diagnosis; TUR = transurethral resection; US = ultrasound.*

6. PREDICTING RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

The classic way to categorise patients with TaT1 tumours 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-risk, intermediate-risk and high-risk groups (105). When using these risk groups, however, no distinction is usually drawn between the risk of recurrence and progression. Although prognostic factors indicate a high risk for recurrence, the risk of progression might still be low, and other tumours might have a high risk of recurrence and progression.

In order to predict separately the short-term and long-term risks of recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary (GU) group has developed a scoring system and risk tables (106). 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-GU group trials. Patients with CIS alone are not included. Seventy-eight percent of patients have received intravesical treatment, mostly chemotherapy. However, they have not undergone a second TUR or received 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 (106), into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years. By combination of two of the four categories for recurrence and progression, the EAU working group suggests the use of a three-tier system that defines low-, intermediate- and high-risk groups for recurrence and progression, as shown in the rightmost column in Table 7.

Table 6: Weighting used to calculate recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CIS = carcinoma in situ*; WHO = World Health Organization.*

Table 7: Probability of recurrence and progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years		Recurrence risk group
	%	(95% CI)	%	(95% CI)	
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk

Progression score	Probability of progression at 1 year		Probability of progression at 5 years		Progression risk group
	%	(95% CI)	%	(95% CI)	
0	0.2	(0-0.7)	0.8	(0-1.7)	Low risk
2-6	1	(0.4-1.6)	6	(5-8)	Intermediate risk
7-13	5	(4-7)	17	(14-20)	High risk
14-23	17	(10-24)	45	(35-55)	

Note: Electronic calculators for Tables 6 and 7 are available at http://www.eortc.be/tools/bladdercalculator/.

The scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has recently been presented by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on 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 were performed in these patients. The scoring system is based on evaluation of seven prognostic parameters:

- patients' sex;
- patients' age;
- 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 probabilities, it is lower only in high-risk patients (107). The lower risks in the CUETO tables may be attributed to using a more effective instillation therapy in the individual studies on which the CUETO tables are based. The validation of the EORTC scoring system in an independent patient population with long-term follow-up has confirmed its prognostic value (108).

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease (109). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease and specify the most dangerous cases. The publications are based on a retrospective analysis of small series of patients and their conclusions are not homogeneous. Some studies have reported worse prognosis in concurrent CIS and T1 tumours compared to primary CIS (110,111) and in extended CIS (112) (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 (113-115) (LE: 2).

7. ADJUVANT TREATMENT

7.1 Intravesical chemotherapy

Although state-of-the-art TUR by itself can eradicate a TaT1 tumour completely, these tumours recur in a high percentage of cases and progress to muscle-invasive bladder cancer in a limited number of cases. The high variability in the 3-month recurrence rate indicates that TUR is incomplete or provokes recurrences in a high percentage of patients (78). It is therefore necessary to consider adjuvant therapy in all patients. The absolute risks of recurrence and progression do not always indicate the risk at which a certain therapy is optimal. The choice of therapy may be considered differently according to what risk is acceptable for the individual patient and the urologist.

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

In a meta-analysis of seven randomised trials (1,476 patients with a median follow-up of 3.4 years), one immediate instillation of chemotherapy after TUR significantly reduced recurrence rate compared to TUR alone (LE: 1a) (117). In absolute values, the reduction was 11.7% (from 48.4% to 36.7%), which implies a 24.2%

decrease in the corresponding relative risk. The majority of patients (> 80%) in the meta-analysis had a single tumour, but an almost significant and even greater reduction in recurrence was noted among the limited number of patients with multiple tumours. The efficacy of the single instillation has been confirmed also by two recently published studies (118,119). In one of these (119), the benefit was mainly seen in primary and single tumours and was in these tumour categories even greater than the 11.7%. By stratification according to EORTC recurrence scores, the benefit was observed in patients with scores 0-2, but not with scores ≥ 3. However, the study was not sufficiently powered for subgroup analyses. Despite stratification at randomisation, no separate analysis was made for primary or recurrent tumours in the other study (118).

No prospective data are available showing that the single instillation significantly reduces recurrence rates in patients with recurrent tumours. Nevertheless, there is significant evidence from one subgroup analysis that an immediate instillation might have an impact on the repeat instillation regimen for treatment of patients who are at intermediate- and high risk of recurrence (120) (LE: 2a). There are no statistically relevant data that address the role of immediate chemotherapy instillation in tumours at high risk of progression before further BCG intravesical treatment.

In summary, one immediate instillation significantly reduces the risk of recurrence in TaT1 bladder tumours. Further studies are required, however, to determine the definitive role of immediate chemotherapy before BCG or further chemotherapy instillations in intermediate- and high-risk groups.

The effect of early instillation can be explained by the destruction of circulating tumour cells immediately after TUR, or as an ablative effect (chemoresection) of residual tumour cells at the resection site. 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 (121-124). In all single instillation studies, the instillation was administered within 24 h. Subgroup analysis of one study has shown that, if the first instillation was not given on the same day as TUR, there was a twofold increase in the relative risk of recurrence (120) (LE: 2a). Moreover, a study in which the instillation was not given strictly on the same day did not find any advantage (125). To maximise the efficacy of the immediate instillation, every effort should be made to create flexible practices that allow the instillation to be given when necessary and as early as possible, that is, in the recovery room or even in the operating theatre.

There is no single drug that is superior with regard to efficacy. Mitomycin C, epirubicin, and doxorubicin have all shown a beneficial effect (117) (LE: 1a). In one study, gemcitabine plus 24 h bladder irrigation with physiological saline was not superior to irrigation with physiological saline alone (126) (LE: 1b).

The guidelines expert panel recommends immediate instillation in tumours at low risk of progression (single, primary, papillary lesions) as the only intravesical treatment and in those presumably at intermediate risk, for which a single instillation is considered as the initial stage of further intravesical therapy. In tumours that are presumably at high risk of progression (solid lesions, positive urinary cytology), immediate instillation is an option because it can have a positive impact on recurrence rate through prevention of tumour cell implantation. However, there is no doubt that subsequent BCG intravesical immunotherapy is essential treatment in these patients (see lower).

The immediate post-operative chemotherapy instillation 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 requiring bladder irrigation. Severe complications have been reported in patients in whom extravasation of the drug occurs (127).

Clear instructions should be given to the nursing staff to control the free flow of the bladder catheter at the end of the instillation. It has been demonstrated that administration of instillation is possible in the majority of cases (128).

7.1.2 ***Additional adjuvant intravesical chemotherapy instillations***

The need for further adjuvant intravesical therapy depends on the patients' prognosis. In patients with a low risk of tumour recurrence (see Table 7), a single immediate instillation reduces the risk of recurrence and is considered as the standard treatment (117) (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 the likelihood of recurrence and/or progression is considerable.

The effect of the immediate instillation of chemotherapy occurs during the first and second year (129,130) (LE: 1b). It has been calculated from the data of five randomised trials (130) that the reduction of recurrence lasts for a period of approximately 500 days.

The choice between further chemotherapy or immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. A combined analysis of EORTC and Medical Research Council data, comparing intravesical chemotherapy to TUR alone, has demonstrated that chemotherapy prevents recurrence but not progression (131) (LE: 1a). The efficacy of intravesical chemotherapy in reducing the risk of tumour recurrence has been confirmed by two other meta-analyses in primary (132) and recurrent tumours (133).

It is still controversial how long and how frequently instillations of intravesical chemotherapy have to be given. From a systematic review of the literature of randomised clinical trials, which have 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 (134). Nevertheless, the available evidence does not support any treatment longer than 1 year.

*7.1.3 **Optimising intravesical chemotherapy***

One randomised trial has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduce the recurrence rate (135) (LE: 1b).

Another randomised trial has documented that concentration is more important than duration of the treatment (136) (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***

Several meta-analyses have addressed important questions concerning the efficacy of BCG in non-muscle-invasive bladder tumours. Four 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 (137-140) (LE: 1a). Since the publication of these meta-analyses, three randomised studies of intermediate- and high-risk tumours have been presented. In these studies, BCG was compared with the combination of epirubicin and interferon (141), mitomycin C (MMC) (142) or epirubicin (143) alone. All of these studies have confirmed the superiority of BCG for prevention of tumour recurrence. It has been shown that the effect was long lasting (142,143) and was also observed in a separate analysis of patients with tumours at intermediate risk (143).

One recently published meta-analysis (144) has evaluated the individual data from 2,820 patients enrolled in nine randomised studies 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 (145,146) (LE: 1a). A meta-analysis carried out by the EORTC-GU group has evaluated data from 4,863 patients enrolled in 24 randomised trials. A total of 3,967 (81.6%) patients had only papillary tumours and 896 (18.4%) had primary or concurrent CIS. Five different BCG strains were used, and in 20 out of the 24 trials, some form of BCG maintenance was used. In four trials only, a 6-week induction course was used. Based on a median follow-up of 2.5 years and a maximum of 15 years, 260 out of 2,658 patients (9.8%) on BCG 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 is similar in patients with TaT1 papillary tumours and in those with CIS (146). A recent randomised study 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 (143) (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 (144). In summary, in spite of these conflicting results, the majority of data was able to show the reduction in the risk of progression in tumours at high and intermediate risk if the BCG including maintenance schedule was used.

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 (147,148). In the most recent meta-analysis, however, BCG maintenance was more effective than MMC also in patients who were previously treated with chemotherapy (144).

*7.2.2 **Optimal BCG schedule***

For optimal efficacy, BCG must be given in a maintenance schedule (140,144-146) (LE: 1a). In the EORTC-GU group meta-analysis, only patients who received maintenance BCG benefited. In the four trials in which no maintenance was given, no reduction in progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the odds of progression was observed ($p = 0.00004$). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective (146). In their meta-analysis, Böhle et al. have concluded that at least 1 year of maintenance BCG is required to obtain the superiority of BCG over MMC for prevention of recurrence or progression (140,145). Although some modifications have been tried, induction BCG instillations are classically given according to the empirical 6-weekly induction schedule that was introduced by Morales in 1976 (149). However, many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 27

instillations over 3 years (150). The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown (151).

7.2.3 ***Optimal dose of BCG***

To reduce BCG toxicity, a number of authors have proposed one-third and one-quarter dose instillations of BCG. Comparing one-third dose to full-dose BCG in 500 patients, CUETO has found no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours (152,153) (LE: 1b). Although fewer patients have reported toxicity with the reduced dose, the incidence of severe systemic toxicity has been similar in the standard- and reduced-dose groups. The same Spanish group has shown in a prospective randomised trial that one-third of the standard dose of BCG might be the minimum effective dose in 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 (154).

7.2.4 ***BCG toxicity***

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. As a result of the more pronounced side effects of BCG compared to intravesical chemotherapy, there is still reluctance about the use of BCG. Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis and allergic reactions have compromised its use (155). However, with increased experience in using BCG, the side effects now appear to be less prominent. Serious side effects are encountered in < 5% of patients and can be effectively treated in virtually all cases (155) (LE: 1b). Major complications can appear after systemic absorption of the drug. Thus, BCG should not be administered during the first 2 weeks after TUR, in patients with macroscopic haematuria or urinary tract infection, or after traumatic catheterisation. It should not be used in immunocompromised patients (immunosuppression, human immunodeficiency virus [HIV]) (156).

The management of side-effects after BCG should reflect their type and grade. Recommendations for individual situations were provided by the International Bladder Cancer Group and by a Spanish group (157,158). Before applying intravesical BCG therapy the urologist should be aware how to treat BCG-induced complications.

7.2.5 ***Indications for BCG***

Although BCG is a very effective treatment, there is a consensus that not all patients with non-muscle-invasive bladder cancer should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patients' risk of recurrence and progression (*see* Table 7). The use of BCG does not alter the natural course of tumours at low risk of recurrence (*see* Table 7), and could be considered to be over-treatment for this patient category. In patients with tumours at high risk of progression, for whom cystectomy is not carried out, BCG including at least 1 year maintenance is indicated. In patients at intermediate or high risk of recurrence and intermediate risk of progression, 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 patients' 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 muscle-invasive bladder cancer, 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 (106,107) and further treatment is mandatory. The treatment strategy is generally based on the criteria that are summarised in Sections 7.1, 7.2, 7.4 and Chapter 8.

Carcinoma *in situ* cannot be cured by an endoscopic procedure only. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy (LE: 2). No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (cystectomy) should be done, especially when there are concurrent high-grade papillary tumours. There has been a lack of randomised trials of instillation therapy and early cystectomy as immediate primary treatment. Tumour-specific survival rates after early cystectomy for CIS are excellent, but as many as 40-50% of patients might be over-treated (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 (109-112,159) (LE: 2). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence (112,150,159,160).

*7.3.3 **Prospective randomised trials***

Unfortunately, there have been few randomised trials in patients with CIS alone. Most trials have included patients with either papillary tumours or CIS, which has resulted in only a small number of CIS patients being entered. Thus, the power to detect differences of treatment results has been low and the reliability of the conclusions is limited (3).

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) (161).

In an EORTC-GU group 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) (146) (LE: 1b). There has been no single trial that has demonstrated superiority of combined BCG and MMC over BCG alone (162) (LE: 1).

In summary, as compared to chemotherapy, treatment of patients with CIS using BCG 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 (163). Patients with extravesical involvement had worse survival than those with bladder CIS alone (163) (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts (3). These situations should be distinguished from tumour invasion into the stroma of the prostate, which is staged as T4a, and for which immediate cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillations of BCG. Transurethral resection of the prostate can improve the contact of BCG with the prostatic urethra (3,164,165) (LE: 3). In patients with prostatic duct involvement, the data are insufficient to provide clear treatment recommendations. As no conclusive results have been attained with regard to the use of conservative therapy, radical surgery should be considered in these patients (165) (LE: 3).

The treatment of CIS that involves the upper urinary tract is discussed in the upper urinary tract guidelines.

7.4 Treatment of failure of intravesical therapy

*7.4.1 **Failure of intravesical chemotherapy***

Patients with non-muscle-invasive recurrence of urothelial bladder carcinoma after intravesical chemotherapy can profit from BCG instillations (147) (LE: 1a).

*7.4.2 **Failure of intravesical BCG immunotherapy***

Treatment with BCG is considered to have failed in following situations:

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 (166). 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 (37,166), but with increasing risk of progression (167,168).
c. Any worsening of the disease under BCG treatment, such as a higher number of recurrences, higher T- stage or higher grade, or appearance of CIS, in spite of an initial response (LE: 3).

Changing from BCG to intravesical chemotherapy, device-assisted chemotherapy instillations, or additional interferon α-2b immunotherapy can yield responses in selected cases with non-muscle-invasive BCG treatment failure (169-178). However, experience is limited and these strategies are considered experimental. As a result of the high risk of development of muscle-invasive tumour in these patients (166-168) (LE: 3), cystectomy is strongly advocated upon early BCG failure in fit patients.

Patients with a recurrence at > 1 year after completion of BCG therapy can be treated according to the risk classification (*See Tables 6, 7 and 8*) (169).

Table 8: Treatment recommendations in TaT1 tumours according to risk stratification

Risk category	Low	Intermediate	High
Recurrence	One immediate instillation of chemotherapy	One immediate instillation of chemotherapy, followed by further instillations, either chemotherapy or a minimum 1 year of BCG (the final choice is determined by the risk of tumour progression)	One immediate instillation of chemotherapy, followed by further instillations, either chemotherapy or a minimum of 1 year of BCG (the final choice is determined by the risk of tumour progression)
Progression	One immediate instillation of chemotherapy (it can be followed by further chemotherapy instillations if the patients has at the same time an intermediate risk of recurrence)	One immediate instillation of chemotherapy, followed by a minimum of 1 year of BCG or further chemotherapy instillations	Intravesical BCG for at least 1 year, or immediate cystectomy

BCG = bacillus Calmette-Guérin.

7.5 Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS

	GR
The type of intravesical therapy should be based on the risk groups shown in Table 7.	A
In patients with TaT1 tumours at low risk of recurrence and progression, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with TaT1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, one immediate instillation of chemotherapy should be followed by a minimum 1 year of BCG treatment, or by further instillations of chemotherapy.	A
If 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. The optimal schedule and the duration of the chemotherapy instillations remain unclear, but it should be given no more than 12 months.	B
In patients with TaT1 tumours at high risk of progression, intravesical BCG for at least 1 year is indicated.	A
In patients with bladder CIS, intravesical BCG for at least 1 year is indicated.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillations of BCG could be an option.	C
Immediate radical cystectomy may be offered to patients at highest risk of tumour progression.	C
In patients with BCG failure, cystectomy is indicated.	B

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ*; TUR = transurethral resection.*

8. CYSTECTOMY FOR NON-MUSCLE-INVASIVE BLADDER CANCER

Some experts consider it is reasonable to propose immediate cystectomy to those patients with non-muscle-invasive tumour who are at high risk of progression. According to the risk tables of the EORTC (*see* Tables 6 and 7) these are:

- multiple recurrent high-grade tumours;
- high-grade T1 tumours;
- high-grade tumours with concurrent CIS.

With these patients, it is recommended to discuss both treatment options: immediate cystectomy and conservative treatment with BCG instillations. Patients should be informed about the benefits and risks of both approaches.

Cystectomy is advocated in patients with non-muscle-invasive tumours with BCG treatment failure, as mentioned above. Delay of cystectomy in these patients might lead to decreased disease-specific survival (179). In patients in whom cystectomy is performed at the time of pathological non-muscle-invasive disease, the 5-year disease-free survival rate exceeds 80% (180-185).

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 need to be followed; however, the frequency and duration of cystoscopy and imaging should reflect the individual patients' degree of risk. Using risk tables (see Tables 6 and 7), we are able to predict the short-term and long-term risks of recurrence and progression in individual patients, and can adapt the follow-up schedule accordingly (106). By planning the follow-up schedule the following aspects should be considered:

a. *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 to the patient.*

b. *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 (186-193) (LE: 2b). In these patients, fulguration of small papillary recurrences on an outpatient basis could be a safe treatment option that reduces the therapeutic burden (194) (LE: 3). Some authors even defend temporary surveillance (192,193,195).

c. *The result of the first cystoscopy after TUR at 3 months is a very important prognostic indicator for recurrence and progression* (106,168,196,197) (LE: 1a). The first cystoscopy should thus **always** be performed 3 months after TUR in all patients with TaT1 bladder tumour.

d. *The risk of upper urinary tract recurrence increases in patients with multiple and high risk tumours* (42) (LE: 3).

As there has not been presented any non-invasive method that could replace endoscopy, the follow-up is based on regular cystoscopies (see 5.5). There has been a lack of randomised studies that have investigated the possibility of safely reducing frequency of follow-up cystoscopies. The following recommendations are therefore based only on retrospective experience.

9.1 Recommendations for follow-up in patients after TUR of non-muscle-invasive bladder cancer

	GR
Patients with TaT1 tumours at low risk of recurrence and progression should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with TaT1 tumours at high risk of progression and those with CIS should have a cystoscopy and urinary cytology at 3 months. If negative, the following 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. Yearly imaging of the upper tract is recommended.	C
Patients with TaT1 tumours at intermediate risk of progression (about one-third of all patients) should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
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.	B

CIS = carcinoma in situ*; PDD = photodynamic diagnosis.*

10. REFERENCES

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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

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

Conflict of interest

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all the relationships that they have and which might be perceived as a potential source of conflict of interest. This information is kept on file in the EAU Central Office database. This guidelines document was developed with the financial support of the EAU. 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

Upper Urinary Tract Urothelial Cell Carcinomas

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European Association of Urology

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1. INTRODUCTION

The most recent summary of the European Association of Urology (EAU) guidelines on upper urinary tract urothelial cell carcinomas (UUT-UCCs) was published in 2004 (1). The EAU Guideline working group for UUT-UCCs has prepared 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

A Medline search was performed on urothelial malignancies and UUT-UCC management using combinations of the following terms: *urinary tract cancer, urothelial carcinomas, upper urinary tract, carcinoma, transitional cell, renal pelvis, ureter, bladder cancer, chemotherapy, nephroureterectomy, adjuvant treatment, neoadjuvant treatment, recurrence, risk factors,* and *survival*. The publications concerning UUT-UCCs 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).

3. EVIDENCE SYNTHESIS

3.1 Epidemiology

Urothelial carcinomas are the fourth most common tumours after prostate (or breast) cancer, lung cancer, and colorectal cancer (3,4). They can be located in the lower urinary tract (bladder and urethra) or the upper urinary tract (pyelocaliceal cavities and ureter). Bladder tumours account for 90-95% of urothelial carcinomas (4) and are the most common malignancy of the urinary tract and the second most common malignancy of the urogenital tract after prostate cancer (5,6). However, UUT-UCCs are uncommon and account for only 5-10% of urothelial carcinomas (3,7-9). The estimated annual incidence of UUT-UCCs in Western countries is about one or two new cases per 100,000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 8-13% of cases, concurrent bladder cancer is present. Recurrence of disease in the bladder occurs in 30-51% of UUT-UCC patients (10,11), whereas recurrences in the contralateral upper tract are observed in 2-6% (12,13).

The natural history of UUT-UCCs differs from that of bladder cancer: 60% of UUT-UCCs are invasive at diagnosis compared with only 15% of bladder tumours (5,7,9). Upper urinary tract urothelial cell carcinomas have a peak incidence in people in their 70s and 80s, and UUT-UCC is three times more prevalent in men than in women.

There are familial/hereditary cases of UUT-UCCs linked to hereditary nonpolyposis colorectal carcinoma (HNPCC) (14). Among patients with UUT-UCCS, these cases can be detected during a medical interview. Indeed, the cancer is likely to be hereditary if the patient is < 60 yr of age and/or has a personal or family history of an HNPCC-type cancer (15,16). These patients should undergo DNA sequencing to identify hereditary cancers that have been misclassified as sporadic cancers by insufficient clinical data. The presence of other HNPCC-associated cancers should also be evaluated. These patients should be closely monitored, and genetic counselling is advocated (15,16).

3.2 Risk factors

Many environmental factors contribute to the development of UUT-UCCs. Some are similar to those associated with bladder cancer, whereas others are more specific for UUT-UCC. Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Exposure to tobacco increases the relative risk of developing a UUT-UCC from 2.5 to 7 (17,18). UUT-UCC “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, UUT-UCCs are secondary to an amino tumour of the bladder. The average duration of exposure needed to develop a UUT-UCC is approximately 7 yr, with a latency period of about 20 yr following the termination of exposure. The estimated risk (odds ratio) of developing UCC after exposure to aromatic amines is 8.3 (17,19).

Upper urinary tract tumours resulting from phenacetin consumption almost disappeared (17) after the product was banned in the 1970s.

Although the incidence of Balkan endemic nephropathy is also on the decline (20,21), roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the physiopathology and induction, respectively, of this nephropathy (22-24). Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis* (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 nonexposed population and is predominant in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UUT-UCC.

A high incidence of UUT-UCC has also been described in Taiwan, especially in the population of the southwest coast of the island, and represents 20-25% of UCCs in the region (16). The association of UUT-UCC with blackfoot disease and arsenic exposure remains unclear in this patient population (25).

Differences in the ability to counteract carcinogens may contribute to host susceptibility and the risk of developing urothelial carcinomas. Because certain genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, there is variability in interindividual susceptibility to the risk factors just mentioned. Only one polymorphism specific to UUT-UCC has been reported so far. A variant allele, SULT1A1*2, which reduces sulfotransferase activity, enhances the risk of developing UUT-UCC (26). Epidermoid carcinoma of the UUT is associated with chronic inflammatory and infectious disease arising from stones in the UUT (27,28).

3.3 Histology and classification

*3.3.1 **Histologic types***

More than 95% of urothelial carcinomas are derived from the urothelium and correspond to UUT-UCCs or bladder tumours (1,5,28). With regard to UUT-UCCs, morphologic variants have been described that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours, and such urothelial carcinomas are associated with one of the following variants: micropapillary, clear cell, neuroendocrine, and lymphoepithelial (9,27). Collecting-duct carcinoma has similar characteristics to UUT-UCCs because of its common embryologic origin (29).

Upper urinary tract tumours with nonurothelial histology are exceptions (30). Epidermoid carcinomas of the upper urinary tract represent < 10% of pyelocaliceal tumours and are even more rare within the ureter. Other histologic subtypes are adenocarcinomas (< 1%), neuroendocrine carcinomas, and sarcomas.

*3.3.2 **Classification***

The classification and morphology of UUT-UCCs are similar to those of bladder carcinomas (5,28). It is possible to distinguish between noninvasive papillary tumours (papillary urothelial tumours of low malignant potential, low-grade papillary urothelial carcinoma, high-grade papillary urothelial carcinoma), 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.

3.3.2.1 Tumour Node Metastasis (TNM) staging

Table 1 presents the Union Internationale Contre le Cancer (UICC) 2009 TNM classification used throughout these guidelines (31). 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.

Table 1: TNM classification 2009 for UUT-UCC (31) *

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma
	(Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

**All EAU guidelines advocate the TNM system of tumour classification.*
UUT-UCC = urethelial cell carcinoma of the upper urinary tract.

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) (32). In recent years, molecular biologic 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 (33). Thus the 2004 WHO classification now takes histologic data into account to distinguish among three groups of noninvasive 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 (9,27,28).

3.4 Symptoms

The diagnosis of a UUT-UCC may be fortuitous or related to the exploration of symptoms (1,6). The symptoms are generally restricted (34). The most common symptom of UUT-UCC is gross or microscopic haematuria (70-80%). Flank pain occurs in up to 20-40% of cases, and a lumbar mass is present in 10-20% of cases (1,7). However, systemic symptoms (altered health condition including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UUT-UCC should prompt consideration of a more rigorous metastatic evaluation or perioperative chemotherapy regimens (34).

3.5 Diagnosis

*3.5.1 **Imaging***

3.5.1.1 Multidetector computed tomographic urography

Multidetector computed tomographic urography (MDCTU) is the gold standard for exploration of the upper urinary tract and has replaced intravenous excretory urography (35-38). It must be conducted under optimal conditions, particularly with acquisition of an excretory phase. Multiple protocols from two helical computed tomography acquisitions (at least millimetric) are necessary before and after the injection of contrast.

The detection rate of UUT-UCC is satisfactory for this type of imaging: 96% sensitivity and 99% specificity for polypoid lesions between 5 and 10 mm. Sensitivity drops to 89% for polypoid lesions < 5 mm and 40% for polypoid lesions < 3 mm (16,17). Multidetector computed tomographic urography can also detect thickening of the wall of the renal pelvis or ureter as a sign of UUT-UCC. The main difficulty remains identifying

flat lesions that are undetectable until they evolve towards a massive infiltration.

Lastly, it was shown that hydronephrosis on preoperative imaging was associated with advanced pathologic disease and poorer oncologic outcomes (39).

3.5.1.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) urography is indicated in patients who cannot be subjected to an MDCTU (40). The detection rate of MRI is 75% after contrast injection for tumours < 2 cm (41). Magnetic resonance urography with contrast injection, however, remains contraindicated in selected patients with severe renal impairment (< 30 ml/min creatinine clearance) due to the risk of nephrogenic systemic fibrosis. Magnetic resonance urography without contrast is less helpful compared with MDCTU in diagnosing UUT-UCCs.

*3.5.2 **Cystoscopy and urinary cytology***

Positive urine cytology is highly suggestive of UUT-UCC when bladder cystoscopy is normal and if CIS of the bladder or prostatic urethra has been excluded. Cytology is less sensitive for UUT-UCC than for bladder tumours, even for high-grade lesions, and it should ideally be performed *in situ* (i.e. in the renal cavities). A positive cytology may be valuable in staging because it has been associated with muscle-invasive and non-organ-confined disease (42).

The detection of molecular abnormalities by fluorescence *in situ* hybridisation (FISH) is becoming more popular for UCC screening, but results are still preliminary (43,44). The sensitivity of FISH for the identification of UUT-UCCs parallels its performance in bladder cancer; however, the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UUT-UCCs may limit its usefulness (45). In addition, FISH appears to have limited value for upper urinary tract tumour surveillance (46,47).

*3.5.3 **Diagnostic ureteroscopy***

Ureteroscopy is a better approach to diagnose UUT-UCCs (42,48,49). A flexible ureteroscope can explore the ureter macroscopically and reach renal cavities in 95% of cases, and it can assess the aspect of the tumour, obtain tumour biopsy, and determine tumour grade in 90% of cases with a low false-negative rate (50). It also facilitates performing a selective ureteral cytology and a retrograde pyelogram.

Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, when conservative treatment is being considered, or in patients with a solitary kidney. The possible advantages of ureteroscopy should be discussed in the preoperative assessment of any UUT-UCC patient. Combining ureteroscopic biopsy grade, ipsilateral hydronephrosis, and urinary cytology may help decision making on radical nephroureterectomy (RNU) versus endoscopic treatment (42). Table 2 lists the recommendations.

Table 2: Guidelines for the diagnosis of UUT-UCC

Recommendations	GR
Urinary cytology	A
Cystoscopy to rule out a concomitant bladder tumour	A
MDCTU	A

UUT-UCC = urethelial cell carcinoma of the upper urinary tract; MDCTU = multidetector computed tomographic urography.

3.6 Prognostic factors

Upper urinary tract urothelial cell carcinomas that invade the muscle wall usually have a very poor prognosis. The 5-yr specific survival is < 50% for pT2/pT3 and < 10% for pT4 (51,52). This section briefly describes the currently recognised prognostic factors.

*3.6.1 **Tumour stage and grade***

According to the most recent classifications, the primary recognised prognostic factors are tumour stage and grade (8,31,53-55).

*3.6.2 **Age and gender***

The effect of gender on UUT-UCC mortality has been disputed recently and is no longer considered an independent prognostic factor (56-58). 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) (59). However, advanced age alone should not be an exclusion criterion for the aggressive treatment of potentially curable UUT-UCC. A large proportion of elderly patients can be cured with RNU (59). This suggests that

chronologic age alone is an inadequate indicator of outcomes in older UUT-UCC patients (59).

*3.6.3 **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 no longer accepted as a prognostic factor (11,60,61), contrary to previously published reports (LE: 3) (62). It seems there is no longer a prognostic impact for tumour location (i.e. ureteral vs. pyelocaliceal tumours) when adjusted for tumour stage (11,63).

*3.6.4 **Lymphovascular invasion***

Lymphovascular invasion is present in approximately 20% of UUT-UCCs and an independent predictor of survival. Lymphovascular invasion status should be included in the pathologic report of RNU specimens (LE: 3) (64-66). However, only in patients with negative lymph nodes does lymphovascular invasion add prognostic information beyond that obtained with standard features (64).

*3.6.5 **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) (67,68).
The tumour architecture (e.g., papillary vs. sessile) of UUT-UCCs appears to be associated with prognosis after RNU. A sessile growth pattern is associated with worse outcomes (LE: 3) (8,63,69).

The presence of concomitant CIS in patients with organ-confined UUT-UCC is associated with a higher risk of recurrent disease and cancer-specific mortality (LE: 3) (70). Similar to lower tract urothelial carcinoma, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease (71).

*3.6.6 **Molecular markers***

Several research groups are working on upper urinary tract tumour characteristics and carcinogenesis pathways. Specific markers that could aid in the prognosis of UUT-UCCs have been investigated. Microsatellite instabilities (MSIs) are independent molecular makers used for tumour prognosis (72). In addition, MSIs can help detect germ-line mutations, allowing for the detection of possible hereditary cancers (14,16,72).

E-cadherin has been shown to be a useful independent marker for prognosis, as have hypoxia-inducible factor (HIF)-1α and telomerase RNA component (73). Furthermore, HIF-1α appears to be significantly associated with tumour grade and growth pattern, and the telomerase RNA component could possibly be used for UUT-UCC diagnosis and prognostication. However, to date, none of the markers has been externally validated, and none has fulfilled the clinical and statistical criteria necessary to support its introduction in daily clinical decision making.

3.7 Treatment

*3.7.1 **Localised disease***

3.7.1.1 Radical nephroureterectomy

Radical nephroureterectomy with excision of the bladder cuff is the gold standard treatment for UUT-UCCs, regardless of the location of the tumour in the upper urinary tract (LE: 3) (8). The RNU procedure must comply with oncologic principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection (8,69).

Resection of the distal ureter and its orifice is performed because it is a part of the urinary tract with considerable risk of 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 nephroureterectomy have concluded that removal of the distal ureter and bladder cuff is beneficial (74-77).

McDonald et al. presented the pluck technique in 1952, but it was not until 1995 (78) that the usefulness of an endoscopic approach to the distal ureter was really 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 (12). Apart from ureteral stripping, none of these techniques have demonstrated inferiority to excision of the bladder cuff (LE: 3) (75-77,79). A delay > 45 d between diagnosis and resection of the tumour constitutes a risk for disease progression (LE: 3) (80).

Lymph node dissection associated with RNU is of therapeutic interest and allows for optimal staging of the disease (LE: 3) (81-83). Lymphadenectomy in pN+ allows for reduction of the tumour mass to guide patients towards adjuvant treatments (LE: 3) (82). However, the anatomic sites of lymphadenectomy have not yet been clearly defined. The number of lymph nodes to be removed depends on the tumour location. No trial so far has shown its direct impact on survival (82). Lymphadenectomy appears to be unnecessary in cases of TaT1 UUT-UCCs because it was reported to be retrieved in 2.2% T1 versus 16% pT2-4 tumours (82). In addition, authors have described a continuous increase in the probability of lymph node-positive disease related to pT classification (81). Lastly, lymphadenectomy appears to be a prognostic variable within a model in

patients with histologically confirmed node-negative (pN0) disease (83). However, these data are retrospective; it is not possible to standardise either indication or the extent of lymphadenectomy. Consequently, underreporting of the true rate of node-positive disease is likely.

The safety of laparoscopic RNU has not yet achieved final proof (84,85). In early experience, there were reports of retroperitoneal metastatic dissemination and dissemination along the trocar pathway when large tumours were manipulated in a pneumoperitoneal environment (86,87).

Recent data, however, show a tendency towards equivalent oncologic results between laparoscopic RNU and open surgery. In addition, the laparoscopic approach appears to be superior to open surgery only with regard to functional outcomes (LE: 3) (88-91). Only one prospective randomised study of 80 patients did not provide evidence that laparoscopic RNU is inferior to open RNU for noninvasive UUT-UCC (LE: 2) (92). 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, large (T3/T4 and/or N+/M+), or multifocal tumours are contraindications for laparoscopic RNU, until proven otherwise.

Recommendations are listed in Table 3.

Table 3: Guidelines for radical management of UUT-UCC: radical nephroureterectomy

Indications for RNU for UUT-UCC	**GR**
Suspicion of infiltrating UUT-UCC on imaging	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Techniques for RNU in UUT-UCC	
Open and laparoscopic access are equivalent in terms of efficacy	B
Bladder cuff removal is imperative	A
Several techniques for bladder cuff excision are acceptable except stripping	C
Lymphadenectomy is recommended in case of invasive UUT-UCC	C

RNU = radical nephroureterectomy; UUT-UCC = urethelial cell carcinoma of the upper urinary tract.

3.7.1.2 Conservative surgery

Conservative surgery for low-risk UUT-UCCs allows for preservation of the upper urinary renal unit while sparing the patient the morbidity associated with open radical surgery (93,94). Conservative management of UUT-UCCs can be considered in imperative cases (renal insufficiency, solitary functional kidney) or in elective cases (i.e. when the contralateral kidney is functional) for low-grade, low-stage tumours (LE: 3) (76,95). The choice of technique depends on technical constraints, the anatomic location of the tumour, and the experience of the surgeon.

3.7.1.2.1 Ureteroscopy

Endoscopic ablation can be considered in highly selected cases (96,97,98) and in these situations:

- A flexible rather than a rigid ureteroscope, laser generator, and pliers (pluck) for biopsies are available (LE: 3) (96,99).
- The patient is informed of the need for closer, more stringent surveillance.
- A complete resection is advocated.

3.7.1.2.2 Segmental resection

Segmental ureteral resection with wide margins provides adequate pathologic specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Segmental resection is possible for the treatment of low- and high-risk tumours of the distal ureter (LE: 3) (100,101). 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 (100,102).

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.

3.7.1.2.3 Percutaneous access
Percutaneous management can be considered for low-grade or noninvasive UUT-UCCs in the renal cavities (LE: 3) (97,103,104). 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.

3.7.1.3 Adjuvant topical agents
The instillation of bacillus Calmette-Guérin or mitomycin C in the urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete eradication of the tumour), or even through a ureteric stent (105), is technically feasible after conservative treatment of UUT-UCCs or for the treatment of CIS. 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) (1,106,107). Table 4 reports the recommendations.

Table 4: Guidelines for conservative management of UUT-UCC

Indications for conservative management of UUT-UCC	**GR**
Unifocal tumour	B
Small tumour	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on MDCTU	B
Understanding of close follow-up	B
Techniques used in conservative management of UUT-UCC	
Laser should be used in case of endoscopic treatment	C
Flexible ureteroscopy is preferable over rigid ureteroscopy	C
Open partial resection is an option for pelvic ureteral tumours	C
A percutaneous approach remains an option in small low-grade caliceal tumours unsuitable for ureteroscopic treatment	C

MDCTU = multidetector computed tomographic urography; UUT-UCC = urethelial cell carcinoma of the upper urinary tract.

3.7.2 ***Advanced disease***
3.7.2.1 Nephroureterectomy
There are no benefits of RNU in metastatic (M+) disease, although it can be considered a palliative option (LE: 3) (8,81).

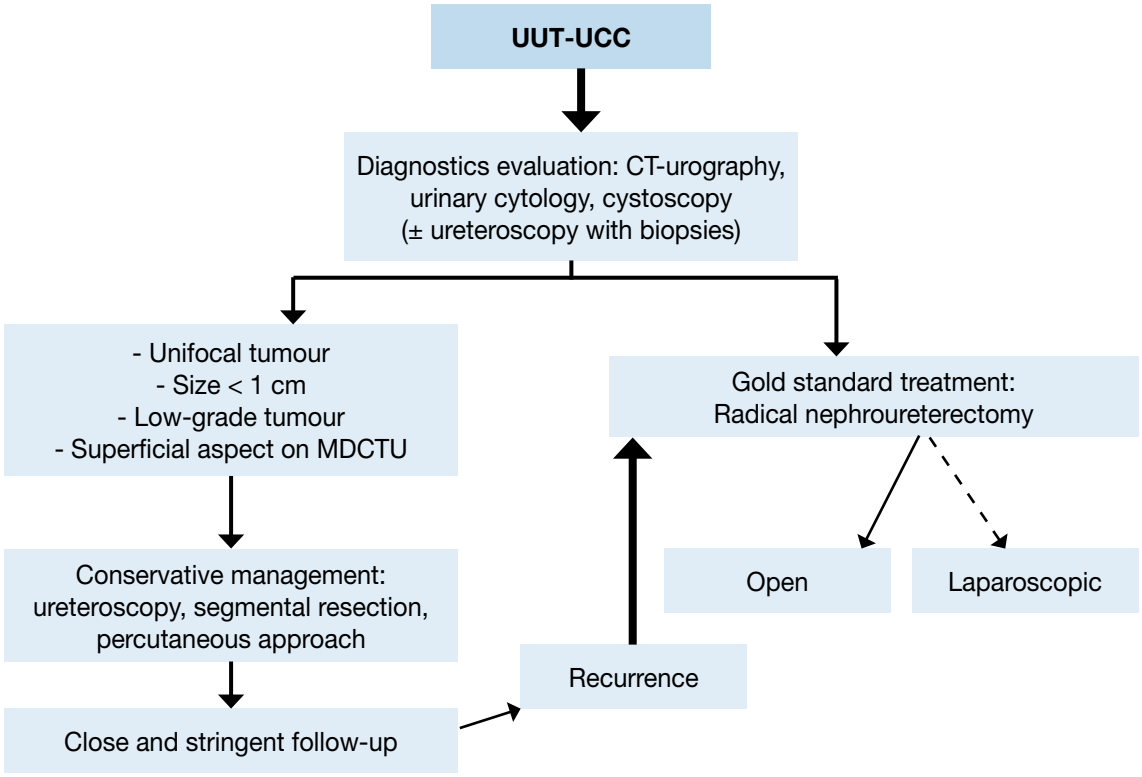
3.7.2.2 Chemotherapy
Because UUT-UCCs are urothelial tumours, platinum-based chemotherapy is expected to produce similar results to those seen in bladder cancer. Several platinum-based chemotherapy regimens have been proposed (108-111).

Only one study has reported the effect of neoadjuvant chemotherapy in contrast to what has been demonstrated in the bladder. While 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 UUT-UCCs (112).

Adjuvant chemotherapy achieves a recurrence-free rate of up to 50% but has minimal impact on survival (108-111). Not all the patients receive this treatment because of comorbidities and impaired renal function after radical surgery. Data are currently insufficient to provide any recommendations.

3.7.2.3 Radiation therapy
Adjuvant radiotherapy may improve local control of the disease (113). When given in combination with cisplatinum, it may result in a longer disease-free survival and longer overall survival (114) (LE: 3). Radiation therapy appears to be scarcely relevant nowadays both as a unique therapy and associated with chemotherapy as a tumour adjuvant (Fig. 1).

Fig. 1 Proposed flowchart for the management of UUT-UCC



UUT-UCC = urethelial cell carcinoma of the upper urinary tract; MDCTU = multidetector computed tomographic urography.

3.8 Follow-up

Strict follow-up of UUT-UCC 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 UUT-UCC varies considerably from 15% to 50% (10,115,116). Thus the bladder should be observed in all cases. A prior history of bladder cancer and upper tract tumour multifocality are the risk factors most often reported for bladder tumours following UUT-UCCs. The surveillance regimen is based on cystoscopy and urinary cytology for at least 5 yr (10,115,116). A bladder recurrence should not be considered a distant recurrence.

When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence. Despite notable improvements in endourologic technology, the follow-up of patients treated with conservative therapy is difficult, and minimally invasive procedures are often necessary (96,98,117,118). Table 5 lists the recommended follow-up schedules.

Table 5: Guidelines for follow-up of UUT-UCC patients after initial treatment

After RNU, over at least 5 yr	**GR**
Noninvasive tumour	
Cystoscopy/urinary cytology at 3 mo and then yearly	C
MDCTU every year	C
Invasive tumour	
Cystoscopy/urinary cytology at 3 mo and then yearly	C
MDCTU every 6 mo over 2 yr and then yearly	C

After conservative management, over at least 5 yr	
Urinary cytology and MDCTU at 3 mo, 6 mo, and then yearly	C
Cystoscopy, ureteroscopy and cytology *in situ* at 3 mo, 6 mo, and then every 6 mo over 2 yr, and then yearly	C

RNU = radical nephroureterectomy; MDCTU = multidetector computed tomographic urography.

4. CONCLUSIONS

These 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, physicians must take into account each individual patient's specific clinical characteristics with regard to renal function including medical comorbidities; tumour location, grade, and stage; and molecular marker status.

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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
FISH	fluorescence *in situ* hybridisation
GR	grade of recommendation
HIF	hypoxia-inducible factor
HNPCC	hereditary nonpolyposis colorectal carcinoma
LE	level of evidence
MDCTU	multidetector computed tomographic urography
MRI	magnetic resonance imaging
MSIs	microsatellite instabilities
RNU	radical nephroureterectomy
TNM	Tumour Node Metastasis
UUT-UCCs	upper urinary tract urothelial cell carcinomas
WHO	World Health Organization

Conflict of interest

All members of the Upper Urinary Tract Urothelial Cell Carcinomas guidelines working group have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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

Bladder Cancer Muscle-invasive and Metastatic

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European
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1. INTRODUCTION

1.1 The guideline

The European Association of Urology (EAU) Guideline Panel for Muscle-invasive and Metastic 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 three EAU guidelines documents (EAU Guidelines on Non-muscle-invasive (TaT1 and CIS) Bladder Cancer and EAU Guidelines on Upper urinary tract urothelial call carcinomas) which, together, present a comprehensive overview of the management of urothelial neoplasms (1,2).

1.2 Methodology

*1.2.1 **Data identification***

Comprehensive literature searches were designed for each section of the MIBC guideline 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 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; 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 guideline by an expert panel. It must be emphasised that the current guideline contains 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 (3). 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 (4-6).

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 a first guideline 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 guideline in 2004, with subsequent updates in 2007, 2009, 2010, 2011 and this 2012 update. A quick reference document presenting the main findings is also available alongside several scientific publications (7-9).

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.

1.3 Summary of updated information

For all Sections, the literature has been assessed and the guideline updated whenever relevant information was available.

Of note are changes in sections:

Chapter 2 “Epidemiology and risk factors”;

- Sections 2.2.5 (Bladder Schistosomiasis) and 2.2.6 (Chronic urinary tract infection) have been updated.

Chapter 3 “Classification”;

- Section 3.3.2 (Pathologist’handling of specimens); has been expanded.

Chapter 4 “Diagnosis and staging”;

- Section 4.2.1.1. (MR imaging for local staging of invasive bladder cancer); literature was revisited, resulting in amended recommendations.

Chapter 8 “Non resectable tumours”;

- A new section 8.3 on Supportive care has been included.

Chapter 10 “Bladder-sparing treatments for localised disease”

- Additional supportive evidence for TURB for selected patients has been added.
- Additional supportive evidence for EBRT monotherapy in highly selected patients
- The multimodality bladder-preserving (10.4) treatment section has been expanded; potential benefit will depend on low stage and complete TUR as important prognostic factors.

Chapter 12 “Metastatic disease”;

- Section 12.9 (Treatment of bone metastases - bisphosphonates); new literature has been added, resulting in amended recommendations.
- The available new evidence on quality-of-life (Chapter 13) has been added.

Chapter 14 “Follow up”;

- Additional data included on recurrences and secondary urethral tumours. Also a new follow-up table has been added.

Table 1: Level of evidence*

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

**Modified from Sackett, et al. (3).*

Table 2: Grade of recommendation*

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

**Modified from Sackett, et al. (3).*

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2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology

Bladder cancer is the 9th 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 disease. Among patients treated with radical cystectomy because of MIBC, 57% had muscle invasion at presentation, while 43% had been initially diagnosed with NMIBC that progressed despite organ-preserving treatment (2). Approximately one-third of patients diagnosed with MIBC have undetected metastasis at the time of treatment of the primary tumour (3), while 25% of patients subjected to 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 casual 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 alleged carcinogenic constituents of tobacco smoke include arylamines, particularly the potent carcinogen 4-aminobiphenyl (4-ABP), polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, heterocyclic amines, and various epoxides.

The incidence of bladder cancer is directly related to the duration of smoking and 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]: 2.17-3.54), while an analysis of 15 studies showed that the

overall relative risk calculated for former smokers was 1.72 (95% CI: 1.46-2.04) (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). The promotion of smoking cessation 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 accounted for 20-25% of all bladder cancer cases in several series. The substances involved in chemical exposure have been benzene derivatives and arylamines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline 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 higher after 10 years, or more; the mean latency period usually exceeds 30 years (10,11). These chemicals 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 established carcinogens for urothelium 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 was included in 1987 among proven human carcinogens by the International Agency for Research on Cancer (IARC). 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 ***Radiation therapy***

Increased rates of secondary bladder malignancies have been reported after external beam radiation therapy (EBRT) for gynaecological malignancies, with relative risks of 2 to 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, compared with the general US 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). As bladder cancer requires a long time to develop, patients treated with radiation and a long life-expectancy are at highest risk and should be followed up closely (17).

2.2.4 ***Dietary factors***

Several dietary factors had been believed to be related to bladder cancer; however, a link remains 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 reduced the risk of bladder cancer (18). For bladder cancer, there seems 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) Cairo, the largest tertiary cancer hospital in Egypt, showed that patients diagnosed in 2005 had a six-fold higher chance of developing transitional cell carcinoma (TCC) compared with patients diagnosed in 1980 (21). This shift from squamous cell carcinoma to TCC 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) different from schistosomiasis. A direct association between bladder cancer and UTIs has been observed in several case–control studies, reporting 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 for treatment of lymphoproliferative diseases and other non-neoplastic diseases, has been correlated with posterior development of MIBC with a period of latency 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 mercaptoethanesulfonate (mesna) (29).

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

In some cases, there is an association between upper urinary tract tumours (UUTT) and bladder cancer. The incidence of UUTT after diagnosis of NMIBC has been reported to be between 1.7% and 26%. Although synchronous UUTT and NMIBC are uncommon, 46% 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 6 times more likely to develop a synchronous tumour in the upper urinary tract (30). Examination of the upper urinary tract only in patients with a tumour in the trigone or with multiple bladder tumours could diagnose 41% or 69% of UUTT, respectively. In multiple and high-risk tumours, there is an increased risk of tumour recurrence in the UUT.

In addition, the overall incidence of bladder cancer development after treatment of UUTT has been reported in the literature as 15-50%. No level 1 evidence from prospective randomised trials is available, as yet. 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 upper urinary tract urothelial cell carcinoma (UUT-UCC) management. However the risk is life-long and repeat episodes are common. No variables can be used to predict future bladder cancer recurrence in UUT-UCC patients reliably. A history of bladder cancer prior to UUT-UCC management and upper tract tumour multifocality are the only commonly reported clinical risk factors in the current literature (31).

2.2.9 ***Gender***

In a retrospective study of patients who underwent radical cystectomy, it was demonstrated that women were more likely to be diagnosed with primary muscle-invasive disease than men (85% vs 51%) (2). It has been proposed 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, because the differential diagnosis in women includes diseases more prevalent than bladder cancer (32).

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, post-menopausal status was associated with an increase in bladder cancer risk even after adjusting for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women could be responsible for some of the difference in the gender prevalence of bladder cancer (33-35). Recently a study in Egyptian women was conducted and younger age at menopause (< 45y) was a factor associated with increasing risk of bladder cancer, while multiple pregnancies and use of oral contraceptives were associated with decreased odds of having bladder cancer. The magnitude of associations was higher in the urothelial carcinoma group (36). A recent publication mentions that female gender has a significant negative impact on CSS in patients younger of age and with positive LVI status, possibly suggesting different clinical phenotypes (37).

2.2.10 ***Race and socio-economic status***

Limited data exists on this topic, but a study based on 13,234 cases diagnosed in the SEER database in the period 1979-2003 showed that survival time from diagnosis was significantly decreased 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 compared to whites for eight of the most common types of cancers combined, lost statistical significance after adjusting for SES factors and treatments. But blacks still had unfavourable prognoses compared with whites even after adjustment for SES and treatment for tumours such as breast-, colorectal-, and urinary bladder cancer (38).

2.3 Conclusions and recommendations for epidemiology and risk factors

Conclusions	LE
The incidence of muscle-invasive disease has not changed for 5 years.	
Active and passive tobacco smoking continues to be the main risk factor, while exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients submitted to external beam radiation therapy, brachytherapy or a combination of external beam radiation therapy 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.	3
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.	
Currently, treatment decisions cannot be based on molecular markers.	

Recommendations	GR
The principle preventable risk factor for muscle-invasive bladder cancer is active and passive smoking.	B
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.	A

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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). There are no significant modifications to this for bladder cancer compared with the previous (2002) edition.

Table 3: 2009 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall

N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

3.2 Histological grading of non-muscle-invasive bladder tumours

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). It was published by the WHO in 2004 (2,3) (Table 4). Its major contribution is a detailed histological description of the various grades using specific cytological and architectural criteria. A website (http://www.pathology.jhu.edu/bladder) illustrating examples of various grades was developed to improve accuracy in using the system.

Table 4: WHO grading in 1973 and 2004 (2,3)

1973 WHO grading	
Urothelial papilloma	
Grade 1:	well differentiated
Grade 2:	moderately differentiated
Grade 3:	poorly differentiated
2004 WHO grading	
Urothelial papilloma	
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	
Low-grade papillary urothelial carcinoma	
High-grade papillary urothelial carcinoma	

*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.

The papilloma is composed of a delicate fibrovascular core covered by normal urothelium. A PUNLMP is defined as a papillary fibrovascular growth covered by 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. The low-grade papillary urothelial carcinoma group includes all former grade 1 (WHO 1973) cases and some former grade 2 cases (if a variation of architectural and cytological features exist 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 risk potential. However, until the 2004 WHO classification has been validated by more 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 2012 edition of the guidelines.

3.3 Pathology

*3.3.1 **Urologist handling of specimens***

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 the 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 ***Pathologist handling of specimens***

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists (6). 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 compulsory to study the urethra, the ureter, the prostate in men and the radial margins (7). In urethra-sparing cystectomy, the level of urethral dissection, 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 labelled containers. In case of doubt, or adipous differentiation of the lymph node, the entire specimen is to be included.

Lymph nodes should be counted and measured on slides, capsular effraction and percentage of lymph node invasion should be reported as well as vascular embols. In case of metastatic spread in the perivesical fat without real lymph node structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Fresh frozen sections are helpful to determine treatment strategy. A recent study confirmed reliability of fresh frozen sections of obturator lymph nodes, but similar studies are warranted to confirm these results (8). As yet, the use of fresh frozen section is generally used within a clinical study setting.

3.3.3 ***Pathology of muscle-invasive bladder cancer***

In muscle-invasive bladder cancer there are usually no cases of PUNLMP and low-grade carcinoma. All cases are high-grade urothelial carcinomas (grade II or grade III). For this reason, no more prognostic information can be provided by grading muscle-invasive bladder cancer (9). However, some morphological subtypes can be important for helping with prognosis and treatment decisions. Currently the following differentiation is used:

1. urothelial carcinoma (more than 90% of all cases)
2. urothelial carcinomas with squamous and/or glandular partial differentiation (10,11);
3. micropapillary urothelial carcinoma;
4. small-cell carcinomas (12);
5. some urothelial carcinomas with trophoblastic differentiation;
6. nested carcinoma (13):
7. spindle cell carcinomas.

For staging, TNM 2002/2009 (6^{th} or 7^{th} edition) is recommended (both editions are identical for bladder cancer). The pattern of muscular invasion can provide some prognostic information. Most cases show nodular or cordonal growth, but about 44% have an infiltrative pattern. According to some authors (9), the median survival time of a patient with an infiltrative pattern is lower than that for an individual with other pattern types ($p = 0.06$). Blood vessel invasion and lymph node infiltration have an independent prognostic significance (14). It seems that the pN category is closely related to the number of lymph nodes studied by the pathologist (15). For this reason, some authors have observed that more than nine lymph nodes have to be investigated to reflect pN0 appropriately (16).

New prognostic markers are under study (17). Currently, insufficient evidence exists to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient data upon which to base treatment in an individual patient.

3.3.4 ***Recommendations for the assessment of tumour specimens***

Mandatory evaluations
Depth of invasion (categories pT2 vs pT3a, pT3b or pT4);
Margins with special attention paid to the radial margin, prostate, ureter, urethra and peritoneal fat;
Histological subtype, if it has clinical implications;
Extensive lymph node representation (more than nine);
Optional evaluations
Bladder wall blood vessel invasion;
Pattern of muscle invasion.

3.4 References

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4. DIAGNOSIS AND STAGING

4.1 Primary diagnosis

4.1.1 Symptoms

Painless haematuria is a common finding. In addition, some patients complain of urgency, dysuria, increased frequency and pelvic pain. Pelvic pain and all the symptoms related to urinary tract obstruction are found in more advanced tumours.

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 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).

4.1.3 Bladder imaging

A bladder mass identified by diagnostic imaging such as ultrasonography (US), intravenous urography (IVU), computed tomography (CT) or magnetic resonance (MR) imaging should be confirmed with cystoscopy and histology.

4.1.4 Urinary cytology and urinary markers

Examination of a voided urine or bladder-washing specimen for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3). It is therefore useful when a high-grade malignancy or carcinoma *in situ* (CIS) is suspected.

Positive urinary cytology may indicate a urothelial tumour anywhere in the urinary tract from the calix, through the ureters, into the bladder and proximal urethra. Cytological interpretation is user dependent (3). The evaluation can be hampered by low cellular yield, urinary tract infections, stones or intravesical instillations. In experienced hands, however, specificity exceeds 90% (4) (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable as cytolysis may often be present. No urinary marker is registered specifically for the diagnosis of invasive bladder cancer. However, as most invasive tumours are of high grade the positive predictive value of markers may be greater in this setting (5).

4.1.5 Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the 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 CT, MR imaging, or US, a diagnostic cystoscopy may be omitted as the patient will undergo TUR for a histological diagnosis.

A careful description of the finding is necessary. It 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, in order to find associated CIS. The additional presence of a CIS could lead to a more aggressive treatment plan (*see* also section 5.1). Photodynamic Diagnosis has proven a great sensitivity for the detection of CIS and in experienced hands the rate of false positives may not be higher than seen in regular white light cystoscopy (6).

4.1.6 Transurethral resection (TUR) of invasive bladder tumours

The goal of TUR is to enable a correct diagnosis by the pathologist, which means including bladder muscle in the adequately sized 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 deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him to make a correct diagnosis. Cauterisation has to be avoided as much as possible during the resection to prevent tissue destruction. In case 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. Moreover tumours can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas, indistinguishable from inflammation, or may be not 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 (7). Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitiser initially experimentally 5-aminolevulinic acid (5-ALA) and lately after approval by the EMA hexaminolaevulinate (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumours, particularly CIS (8-11) (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 (6). 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 has been reported. Although the exact risk is not known, 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 (12,13) (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. Although a frozen section has a higher negative predictive value and is more accurate, neither technique is 100% sensitive (14-16).

*4.1.8 **Second resection***

There is a significant risk of residual tumour after the initial TUR (17,18) (LE: 1). Persistent disease was observed in 33-53% of patients (18-24). Moreover, the tumour may be understaged by the initial resection. There is a 4-25% probability that tumours initially staged as being of a lower stage are in fact muscle-invasive (19,20). Correct staging is extremely important since it will directly affect the treatment modality. A second TUR should always be performed when the initial resection has been incomplete, e.g. when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contained no muscle tissue. Furthermore, a second TUR should be performed when a high-grade, non-muscle-invasive tumour or a T1 tumour has been 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 progressive prostate cancer should be considered since 25-46% of patients submitted to cystectomy for bladder cancer (25,26) appear to have prostate cancer on final pathology. Unless the entire prostate is to be removed during cystectomy, any type of prostate cancer should be excluded.

*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)

Recommendations	GR
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
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.	C
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.	C
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.	C

4.2 Imaging for staging in verified bladder tumours

Imaging is indicated only if there is a clinical consequence. The treatment and prognosis for invasive bladder cancer is determined by tumour stage and grade (27). Tumour staging must be accurate for selecting the

correct treatment in clinical practice. The use of CT and MR imaging has largely replaced other imaging modalities for staging of invasive bladder cancer.

The purpose of imaging for staging invasive bladder cancer is to:

- Assess the extent of local tumour invasion;
- Detect tumour spread to lymph nodes;
- Detect tumour spread to the upper urinary tract and other distant organs (liver, lung, bones, peritoneum, pleura, adrenal gland and others).

*4.2.1 **Local staging of invasive bladder cancer***

Both CT and MR imaging may be used for assessment of local invasion but they are unable to detect microscopic invasion of perivesical fat (T3a) (28). The aim of CT and MR imaging is therefore to detect T3b disease, or higher.

4.2.1.1 MR imaging 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 CT imaging, MR imaging was reported to be more accurate for local assessment. The accuracy of MR imaging for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT (29).

Fast dynamic contrast-enhanced MR imaging helps to differentiate bladder tumour from surrounding tissues because enhancement of the tumour occurs earlier than the normal bladder wall due to neovascularisation (30,31). Fast dynamic MR imaging with images acquired at one image per second helps to distinguish tumour from post-biopsy reaction (30).

In 2006 a link between gadolinium-based contrast agents (Gd-CA) and nephrogenic systemic fibrosis (NSF) was established. NSF may result in a fatal or debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF. For this group of patients, non-ionic linear Gd-CAs should be avoided (gadodiamide, gadopentetate dimeglumine, and gadoversetamide) and a stable macrocyclic contrast agent used (gadobutrol, gadoterate meglumine, or gadoteridol). Alternatively, contrast enhanced CT could be performed using iodinated contrast media (32) (LE: 4).

4.2.1.2 CT imaging for local staging of invasive bladder cancer

The advantages of CT include shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to various patient factors.

Computed tomography imaging is unable to differentiate between stages Ta to T3a, but it is useful clinically 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% (33) and increases with more advanced disease (34).

*4.2.2 **Imaging of nodal involvement***

The assessment of nodal status based simply on size is limited by the inability of both CT and MR imaging to identify metastases in normal sized or minimally enlarged nodes. Sensitivities for detection of lymph node metastases are low, ranging from 48% to 87%. Specificities are also low as nodal enlargement may be due to benign pathology. Overall, the results of CT and MR imaging for detection of lymph node metastases in a variety of primary pelvic tumours are similar (35-40). Pelvic nodes greater than 8 mm and abdominal nodes greater than 10 mm in maximum short axis diameter (MSAD) should be regarded as enlarged on CT and MR imaging (41,42).

Currently there is no evidence supporting routine use of positron emission tomography (PET) CT in nodal staging of bladder cancer, although the method has been evaluated with varying results in small prospective trials (43,44).

*4.2.3 **Extravesical urothelial carcinoma***

Computed tomography urography is the preferred imaging modality for the diagnosis and staging of upper urinary tract and bladder cancer (45,46). Computed tomography urography has a higher diagnostic accuracy for urothelial cancers compared to IVU (LE: 2b). For UUT-UCC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results. (47-50).

*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. CT and

MR imaging are the diagnostic tools of choice to detect metastases to lung and liver. Metastases to bones or brain at presentation of invasive bladder cancer are rare. 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 (51,52. MR imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy (53,54) (LE: 2b).

*4.2.5 **Conclusions and recommendations for staging of verified bladder tumour***

Conclusions	**LE**
Imaging is used for formal staging only if it will make a difference to the selection of treatment options.	
Magnetic resonance (MR) imaging has some advantages over computed tomography (CT) for local staging, without being able to guide future treatment in most cases.	
If the patient is evaluated for radical treatment, multidetector computed tomography (CT) due to its higher specificity may be equivalent to magnetic resonance (MR) imaging regarding local staging.	
A positron emission tomography computed tomography (PET/CT) examination does not offer additional information but this is still under investigation.	

Recommendations	**GR**
Computed tomography or magnetic resonance imaging is recommended if there is suspicion of locally advanced or metastatic disease precluding radical treatment.	
In patients considered eligible for radical treatment, for optimal T-staging, either MR imaging with fast dynamic contrast-enhancement or multidetector computed tomography (CT) with contrast enhancement are recommended.	B
In patients with confirmed muscle-invasive bladder cancer, computed tomography (CT) of the chest, abdomen and pelvis is the optimal form of staging, including CT urography for complete examination of the upper urinary tracts. If CT is not available, lesser alternatives are excretory urography and a chest X-ray.	B
In patients with a verified muscle invasive lesion (TUR), abdominal pelvis and chest imaging is mandatory. MR imaging and CT are equivalent in diagnosing local and distant abdominal metastases.	C
Computed tomography (CT) is preferred to magnetic resonance (MR) imaging for the detection of pulmonary metastases.	C

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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 as well as staging and completeness of TUR are key variables confounding the results of present long-term studies of TUR, with or without intravesical therapy.

The understaging error in TaT1 tumours of 35% to 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% to 49% T2 tumours diagnosed initially as non-muscle-invasive tumours (4,5) (LE: 3). However, in spite of these disadvantages, recent meta-analyses have shown that intravesical therapy with Bacillus Calmette-Guérin (BCG) maintenance therapy prevents recurrence (6,7), but not progression. So far, no significant overall- or disease-specific survival advantages have been proven 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).

Initial cystectomy can be considered based on tumour multiplicity, size, concomitant *in situ* cancer, and urothelial tumour of the prostatic urethra (13) (GR: C). 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 (1,3,14,15) (LE: 3). In case of recurrent TaT1, mostly associated with CIS, the understaging at time of cystectomy is 34%, but the 10-year survival is not significantly different for patients with pT1 and pT2 tumours (16) (LE: 3). This is in contrast to an earlier report indicating a significant worse outcome for patients with previous TUR(s) (17) (LE: 3).

Undoubtedly, patients with muscle-invasive recurrence are best treated with radical cystectomy. However, the outcome in terms of 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 (18) (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 (19) (LE: 3). Solsona, et al. demonstrated that 80% of patients who had persistent disease at 3 months progressed to muscle invasive disease (20) (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 (21) (LE: 3). However, with careful selection and surveillance a durable complete response can be achieved also in patients diagnosed with superficial bladder transitional cell carcinoma involving the prostatic urethra (22). 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% to 51% and of unknown duration (23,24) (GR: C). Salvage chemotherapy is associated with limited response and should not be offered (25,26) (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 case of non-muscle-invasive disease (18) (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% (27,28) (LE: 2). CIS associated with TaT1 is treated according to the overt tumour.

Approximately 50% of patients develop recurrent disease with muscle invasion or extravesical tumour (27,29) (LE: 2). Between 11% and 21% die of the disease within 5-7 years after an initial complete response (27,30) (LE: 2). Non-responders or incomplete responders have a significant risk of tumour progression of 33% to 67% (20,31) (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.

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.

5.3 Recommendations for treatment failure of non-muscle-invasive bladder cancer

Recommendations	GR
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 [32]), immediate radical cystectomy is an option.	B
In all T1 patients failing intravesical therapy, cystectomy should be performed.	B

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6. NEOADJUVANT CHEMOTHERAPY

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 neoadjuvant chemotherapy, i.e. administering chemotherapy to patients with operable urothelial carcinoma of the urinary bladder before the planned definitive surgery (or radiation), 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 favourable pathological status determined mainly by negative lymph node status and negative surgical margins.

The disadvantages of neoadjuvant chemotherapy include:

- For clinical staging with CT or MR imaging, over- and under-staging is likely to happen with a staging accuracy of only 70% (6,7). Overtreatment is the possible negative consequence;
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (8,9).

The side-effects of neoadjuvant chemotherapy affecting outcome of surgical morbidity need to be considered. In one randomised trial (10), the same distribution of post-operative complications grade 3-4 was seen in both trial arms (10). However, generally, pre-operative anaemia and neuropathy was more common in the chemotherapy group. 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. Still, in crude figures, 218 of 306 experimental and cystectomised patients received all 3 chemotherapy cycles (71%). Further 23 patients 1 or 2 cycles and 3 patients with greater than 25% dose reduction of cisplatin, translating into 78% receiving any neoadjuvant treatment (11).

Several randomised phase III trials investigated the question of whether or not neoadjuvant chemotherapy improved survival, with conflicting results (12-28). Most patients were ≤ 70 years old, had a performance status (PS) of 0-1 and a creatinine clearance of > 50-60 mL/minute, due to the kind of chemotherapy (single-agent cisplatin or cisplatin combination chemotherapy) scheduled.

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 kind of definitive treatment allowed (cystectomy or radiotherapy or both).

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 (29-31).

- The first meta-analysis, published in 2003 (29), included 10 randomised trials (except for results of the INT 0080-study [20]) and showed a 13% reduction in the risk of death, equivalent to 5% absolute benefit at 5 years (increased overall survival from 45% to 50%).
- The second meta-analysis, published in 2004 (30), included 11 of 16 randomised trials with overall survival data of 2,605 patients. A statistically significant decrease in the risk of death (10%) was seen, corresponding to an absolute improvement in overall survival of 5% (from 50% to 55%).
- In the most recent meta-analysis, published in 2005 (32), with updated independent patient data of 11 randomised trials (3,005 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 (11). Of note, only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful benefit (29,31); 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 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 macrometastic nodal deposits are detected more often in post-cystectomy specimens of these extensive tumours (32). Further data is in support 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.

6.1 Conclusions and recommendations for neoadjuvant chemotherapy

Conclusions	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival, irrespective of the type of definitive treatment used.	1a
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations.	

Recommendations	GR
Neoadjuvant chemotherapy should always be cisplatinum based.	A
Neoadjuvant chemotherapy is not recommended in patients with PS $\geq$ 2 and/or impaired renal function.	B

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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 muscle-invasive bladder cancer in most countries of the Western Hemisphere (1,2). New interest in quality-of-life issues 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 type of urinary diversion with cystectomy being reserved for younger patients without concomitant disease and better performance status. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a recent multivariate analysis, which demonstrated an association between co-morbid disease and adverse pathological and survival outcome following radical cystectomy (3).

There is still controversy 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 demonstrated that patients above 80 years did have an increased postoperative morbidity but not an increased mortality. Some patients even successfully underwent a neobladder procedure in this group, but the majority of patients were treated with an ileal conduit diversion (4).

*7.1.2 **Timing and delay of cystectomy***

In a retrospective series of 153 patients with a clear indication for radical surgery of locally advanced bladder cancer, a delay of treatment beyond 90 days of primary diagnosis caused a significant increase in extravesical disease (81 vs 52%) (5).

The delay of cystectomy not only affects the outcome but also the type of urinary diversion. In organ-confined urothelial cancer of the bladder the average time from the primary diagnosis to cystectomy was 12.2

months in neobladder and 19.1 months in ileal conduit patients. It was even more striking for those patients who had an organ-confined invasive cancer diagnosed; in neobladder patients the average time to surgery was 3.1 and in ileal conduit patients 15.1 months (6). Similar results have been observed in a series of 247 patients where superior recurrence-free survival and overall survival was significantly better in those treated within the 90 day period compared to others who were treated after a longer period (7).

7.1.3 ***Indications***

Traditionally radical cystectomy is recommended for patients with muscle-invasive bladder cancer 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 for e.g. fistula formation, pain or recurrent macrohaematuria (*see* Section 8.1 Palliative cystectomy).

7.1.4 ***Technique and extent***

Radical cystectomy includes the removal of the bladder and adjacent organs, that is prostate and seminal vesicles in men, and uterus and adnexa in women (8). The inclusion of the entire prostate in male patients, and the extent of urethrectomy and vaginal resection in female patients, however, has recently been questioned (9,10).

Various techniques of partial prostate-sparing cystoprostatectomy in male patients with localized tumours have been proposed and results of series with a longer follow-up have been published (11-13). A randomised study comparing patients with and without remnant portions of the prostate is lacking and will be difficult to perform. Autopsy studies as well as studies looking at the unsuspected incidence of prostate cancer in cystoprostatectomy specimens suggest that in approximately 23-54% of patients a prostate cancer is found in the cystoprostatectomy specimen. Up to twenty-nine percent of these cancers may be clinically significant, locally recurrent or even metastatic in patients with prostatic tissue preserving radical cystectomy (14-16).

Furthermore urothelial cancer in the prostate was detected in 32 and 33% (69/240 cases and 77/235 cases, resp.) of patients undergoing radical cystoprostatectomy (15,17). In another study 50/121 of the cystoprostatectomy specimens (41%) removed for urothelial cancer had unsuspected prostate cancer. Twenty-four of these 50 tumours (48%) were clinically significant. In the same study 58/121 patients (48%) had urothelial carcinoma in the prostate of which 19 (33%) had apical involvement (18). Overall in the above mentioned series only 26 to 33% of the patients undergoing cystoprostatectomy for bladder cancer had neither prostate cancer nor prostatic urothelial cancer in the specimen.

However, by individualising the indication to spare seminal vesicles and the prostatic capsule in a group of 31 patients the oncological risk was small with a high probability of preserving potency (19).

Radical cystectomy also includes the dissection of regional lymph nodes. There is substantial data on the extent of lymphadenectomy. However, controversies in evaluating the clinical significant of lymphadenectomy relates to two main aspects of nodal dissection; postulated therapeutic procedure and/or staging instrument.

More recently, it has been attempted to categorize 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 (20). 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 in addition to the area described in the standard lymphadenectomy (21-23).

A recent study comparing the results of a high volume centre performing mainly a standard lymphadenectomy vs. a high volume centre performing an extended pelvic lymph node dissection in patients undergoing radical cystectomy revealed that there was no difference with regards to overall survival and recurrence (24) although the mean number of lymph nodes was 22 in one institution and 38 in the other institution. In another study looking at the SEER data did show a survival benefit in patients with the removal of more than 10 lymph nodes in patients with lymph node metastasis (25). It seems clear, however, that a more limited field of lymph node dissection in the pelvis than the standard lymphadenectomy as outlined above is associated with suboptimal staging and also with a poorer outcome for patients both with node positive and node negative disease (26,27).

There are several localisation studies with regards to lymphadenectomy (28-33) which 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 accurate anatomic assignment of removed lymph nodes is sometimes difficult and varies with different surgeons.

In the only autopsy investigation yet performed, it was shown that in 215 patients with 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 sole metastatic manifestation (34). It has been suggested that progression free survival as well as overall survival might be correlated with the amount of lymph nodes removed during surgery. Removal of more than 10-15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as being beneficial for overall survival in retrospective studies (25,33,35). No evidence exists of a minimum number of lymph nodes on the contrary to other cancers. Nevertheless the probability of survival increases with the number of dissected lymph nodes (36).

Inter-individual differences in the number of pelvic and retroperitoneal lymph nodes and difficulties in processing of the removed tissue by pathologists were not taken into account in these studies (37-39).

A distal ureteral segment (length not specified) should be resected and in case of bladder CIS a frozen section for evaluation of the surgical margins should be performed (8,40). Urethrectomy is recommended if there are positive margins at the level of urethral dissection, positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate (1,41,42).

*7.1.5 **Laparoscopic/robotic-assisted laparoscopic cystectomy (RALC)***

Laparoscopic cystectomy and RALC have been shown to be feasible both in male and female patients (43,44). 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 (45). 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 (46,47).

Laparoscopic intracorporeal construction of urinary diversion with or without robotic assistance has been tested in small series only (46,48,49). 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).

7.2 Urinary diversion after radical cystectomy

From an anatomical standpoint three alternatives are presently used after cystectomy:

- Abdominal diversion such as uretherocutaneostomy, 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 (50). Several studies have compared certain aspects of health-related quality of life, 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, socio-economic status, time interval to primary surgery, etc.

*7.2.1 **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 (51). Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary (52). Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation and gastrointestinal stimulation with metoclopramide and chewing gum (53).

Patients undergoing continent urinary diversion have to be motivated both to learn about their diversion and

to be manually skilful in manipulating their diversion. Contra-indications 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 preoperative radiation therapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence (54-56).

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 (57,58). 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 (4).

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 (57).

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 (59). Despite the limited comparative data available it has to be taken into consideration however, that older data and clinical experience suggest stricturing on skin level and ascending urinary tract infection are more frequent complications as compared to ileal conduit. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders (60).

7.2.3 ***Ileal conduit***

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of the patients develop early complications including urinary tract infections, pyelonephritis, uretero-ileal leakage and stenosis (60). 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% (61-63). 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) (61): the rate of complications increased from 45% at 5 years to 94% in those surviving longer than 15 years. In the latter group, 50% and 38% of the patients developed upper urinary tract changes and urolithiasis, respectively.

7.2.4 ***Continent cutaneous urinary diversion***

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for selfcatheterisation; gastric, ileocecal and sigma pouches have also been described (64-66). Different antireflux techniques can be used (8). Most patients have a well-functioning reservoir with daytime and night time continence approaching 93% (67). A stomal stenosis in 23.5% of patients with 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 (67-69). In a small series of previously irradiated female patients incontinence and stomal stenosis was 18% (8/44 patients) (70).

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 rectosigmoideum (uretero[recto]sigmoidostomy) (71,72). Most of the 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 (73,74). 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 a direct interaction between urothelium, colonic mucosa, together with faeces and urine (75).

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 (1,56,76). In elderly patients

(> 80 years), however, it is very rarely performed, even in high-volume expert centres (77,78).

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 (1). 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 (79,80). Long-term complications include diurnal (8-10%) and nocturnal incontinence (20-30%), ureterointestinal stenosis (3-18%), urinary retention (4-12%) both in males and female patients, metabolic disorders and vitamin B12 deficiency in series with 1,054 and more than 1,300 patients (56,81). In a recent study, which compared cancer control and 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 (82). Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) (56,83). 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 quality of life compared to a non-continent urinary diversion (84-86).

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 (69,80). 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 (9,87). 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% (76,81). 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 (88). In general, a lower morbidity and mortality has been observed by surgeons and by hospitals with a higher case load and therefore more experience (89).

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 (90).
- The recurrence-free and overall survival in a large single centre study of 1,054 male and female patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively (2).
- In node-positive patients, 10-year disease-specific and overall survival rates in another study have been reported to be 27.7% and 20.9%, respectively (91). In this cohort, 10-year disease-specific and overall survival rates were 72.9% versus 49.1% for organ-confined disease (defined as ≤ pT3a), and 33.3% versus 22.8% for non-organ-confined disease (91).
- 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 (92). Tumour stage and nodal involvement are the only independent predictors of survival (93).

7.5 Conclusions on urinary diversion after radical cystectomy

Conclusions	LE
For muscle-invasive bladder cancer radical cystectomy is the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes, the anatomical extent of which has not been sufficiently defined.	3
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.	3
Terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic and robotic-assisted laparoscopic cystectomy is feasible but still investigational.	3
In patients with invasive bladder cancer older than 80 years cystectomy is an option.	3
Co-morbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volume of cystectomy, and type of urinary diversion influence surgical outcome.	2
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.	2

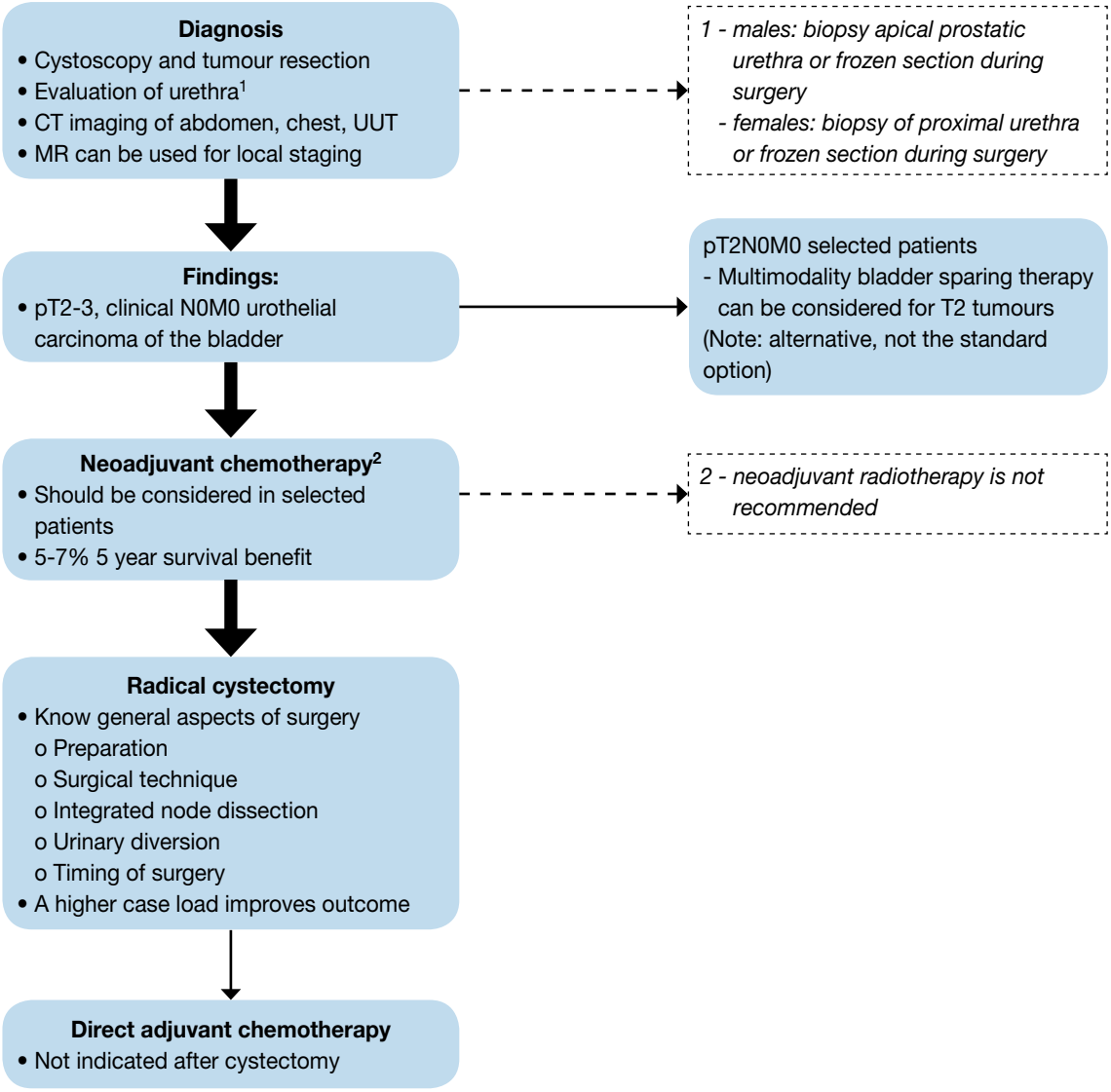
7.6 Recommendations for radical cystectomy and urinary diversion

*7.6.1 **Recommendations for radical cystectomy***

Recommendations	GR
Radical cystectomy is recommended in T2-T4a, N0 M0, and high risk non-muscle-invasive BC (as outlined above).	A*
Do not delay cystectomy more than 3 months since it increases the risk of progression and cancer-specific death.	B
Pre-operative radiotherapy is not recommended in case of subsequent cystectomy with urinary diversion.	A
Lymph node dissection should be an integral part of cystectomy, but the extent of the dissection has not been established.	B
The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly.	B
Laparoscopic and robot-assisted laparoscopic cystectomy are both 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.	C
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.	B
Pre-operative bowel preparation is not mandatory, ‘fast track’ measurements may reduce the time of bowel recovery.	C
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.	B

**Upgraded following panel consensus*

Figure 1: Flowchart for the management for T2-T4a N0M0 urothelial bladder cancer



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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 blockage 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	LE	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliatative option and cannot be offered as curative treatment.		B
In patients with symptoms palliative cystectomy may be offered.		
Prior to any further interventions, surgery-related morbidity and quality-of-life should be fully discussed with the patient.	3	B

8.3 Supportive care

Severe, localized 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 anesthesia. 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 embolization 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.

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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 gastero-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 down-staging in 73% of cT3 patients versus 29% of patients who were not given preoperative 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 versus 5-20 Gy versus 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):
  - down-staging 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% versus 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 than in patients given pre-operative radiotherapy (25-52%). pCR 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 down-staging and found an increase in pCR following preoperative 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) versus not pre-treating with radiotherapy (n = 97). The clinical stage of tumours was T1-3. Down-staging to T0 after cystectomy occurred in 7% (7/97) without radiotherapy versus 57% (51/90) with radiotherapy. In cT3 tumours, these results were 0% (0/16) versus 59% (19/34), respectively. Down-staging 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

Conclusions	LE
No data exist to support that pre-operative radiotherapy for operable muscle-invasive bladder cancer increases survival.	2
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 down-staging after 4-6 weeks.	2
Pre-operative radiotherapy with a dose of 45-50 Gy in fractions of 1.8-2 Gy does not significantly increase toxicity after surgery.	3
There are suggestions in older literature that pre-operative radiotherapy decreases local recurrence of muscle-invasive bladder cancer.	3

Recommendations	GR
Pre-operative radiotherapy is not recommended to improve survival.	B
Pre-operative radiotherapy for operable muscle-invasive bladder cancer results in tumour downstaging after 4-6 weeks.	C

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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 TURBT, 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 CSS of 81.9%, 79.5% and 76.7%, and a 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***

Conclusion and recommendation	LE	GR
Transurethral resection of bladder tumour (TURB) alone is not a curative treatment option in most patients.	2a	B

*10.1.2 **References***

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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). 340 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. CR 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***

Conclusions	**LE**
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.	3
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.	3

Recommendation	**GR**
Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches since they are more effective than radiotherapy alone.	B

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10.3 Chemotherapy

Chemotherapy alone rarely produces durable complete responses. 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***

Conclusion	**LE**
With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported.	2b

Recommendation	**GR**
Chemotherapy alone is not recommended as primary therapy for localised bladder cancer.	A

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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 TURBT + radiochemotherapy (n=331) with TURBT + 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 TURBT and chemoradiotherapy (5). Initial pCR rate was relatively low (39%) in the absence of a radical initial TURBT. 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
Delay in surgical therapy can compromise survival rates.	2b

Recommendations	**GR**
Transurethral resection of bladder tumour (TURB) alone cannot be offered as a standard curative treatment option in most patients.	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.	B

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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

Conclusion	LE
Adjuvant chemotherapy is under debate. Neither randomised trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy.	1a

Recommendation	GR
Adjuvant chemotherapy is advised within clinical trials, but not as a routine therapeutic option.	A

11.2 References

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12. METASTATIC DISEASE

Approximately 30% of patients with urothelial cancer present with muscle-invasive disease; about half will relapse after radical cystectomy depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for about 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 exceeded the median survival of 3-6 months (2).

12.1 Prognostic factors and treatment decisions

Bladder cancer is a chemosensitive tumour. Response rates differ with respect to patient-related factors and pre-treatment disease. Prognostic factors for response and survival have been established. In a multivariate analysis, Karnofsky PS of 80% or less and the presence of visceral metastases were independently prognostic of poor survival after treatment with MVAC (methotrexate, vinblastine, adriamycine and cisplatin). These so-called 'Bajorin' prognostic factors (3) have also been validated for newer combination chemotherapies (4,5) and are crucial for assessing phase II study results and stratifying phase III trials (6,7). Additional data on the prognostic value of elevated alkaline phosphatase and the number of disease sites (more or less than three) were generated prospectively (8). A retrospective analysis showed that, in elderly patients, an ECOG (Eastern Cooperative Oncology Group) PS 2-3 and a haemoglobin level of < 10 mg/dL were independent predictors of poor survival (9). Age itself has no impact on response or toxic events (9).

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

*12.1.1 **Comorbidity in metastatic disease***

Comorbidity is defined as „the presence of one or more diseases in addition to an index disease". Patients with a history of cancer have an average of three co-morbid conditions and co-morbidity is the rule, rather than the exception. Incidence and prevalence of co-morbidity increase with age. However, despite the importance of co-morbidity in clinical practice, it has not gained a considerable role in clinical trials, medical statistics and clinical practice (11). Co-morbidities are an important predictor of clinical outcome (12).

In multiple publications, co-mobidities proved predictive in 1-5 year mortality rates, which was true only in part for age and sex.

Source	N	Comorbidity	Predictive capacity
Charlson[13]	218	+	5-year mortality
Inouye[14]	318	+	2-year mortality
Lee[15]	8009	+	4-year mortality
Walter[16]	1427	+	1-year mortality

Comorbidity increases with age. However, chronologic age does not necessarily correlate with functional impairment. Physiologic impairment varies substantially between individuals. A number of definitions exist trying to establish how to select patients better as potentially "fit" or "unfit" candidates for chemotherapy. Age itself is not among them.

The EORTC conducted the first randomized phase II/III trial for „unfit" urothelial carcinoma patients (17). Their definition of „fit" and „unfit" for cisplatin is:

- „fit": GFR ≥ 60 ml/min and PS 0-1
- „unfit": GFR < 60 ml/min and /or PS 2

Furthermore and based on an expert survey; eligibility criteria for clinical trials enrolling patients with metastastatic UC "unfit" for cisplatin-based chemotherapy are: grade ≥ 2 audiometric loss and peripheral neuropathy and NYHA class III heart failure (18).

For urothelial cancer, more than 50% of patients are not eligible for cisplatin based chemotherapy (19-22).

Patient selection for systemic chemotherapy is key. There are a number of tools, which, so far, have not been able to solve this dilemma. Performance status is not accurate enough, particular in patients > 75 years of age. For measuring functional status, the comprehensive geriatric assessment (CGA) has proven to be more sensitive than the mere estimate of the physician (23). The CGA would most likely be helpful but, as yet,

has not been validated for urothelial cancer patients.
As for comorbidity, the Charlson score is not used as a standard. Renal function assessment is of utmost importance in the urothelial cancer population. Calculated creatinine clearance (crcl) with current formulas tends to under-estimate crcl in pts > 65 years compared to measured crcl (19,24).

The CGA includes: functional status, co-morbidities, socio- economic circumstances, cognition, emotional perception, co-medication, nutrition and geriatric syndrome (25).

Notwithstanding the clear advantages of this tool (description of physiologic aging, detection of reversible problems and issues, cognitive function assessment) the drawbacks preventing its widespread use in clinical practice is the fact that it is a resource intensive activity (both for time and staff involvement). This tool could potentially be the basis of a more user-friendly, accurate, questionnaire. However, validation in studies will be needed before standard use can be recommended.

12.2 Single-agent chemotherapy

Varying response rates of single-agent first-line chemotherapy have been reported with only 12% for cisplatin compared to MVAC (7), 12% for carboplatin (26), 42% for paclitaxel (27), 31% for docetaxel (28), 29% for methotrexate, 19% for adriamycin, 15% for epirubicin, 13% for mitomycin C, 35% for 5-FU, 14% for vinblastine, 29% for ifosfamide and 8% for cyclophosphamide (29,30). The most robust single-agent data is a response rate of about 25% for gemcitabine for first- and second-line use in several, larger-sized, phase II trials (31-38).

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 about 6-9 months. Patients with PS WHO 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 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 adriamycine) (7,39) and, more recently, to cisplatin/docetaxel (40). MVAC and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months, respectively (41-43). The lower toxicity of GC (43), however, has resulted in GC increasingly becoming a new standard regimen (44).

Neither of the two combinations was proven to be superior over the other, but equivalence was not tested, with response rates of 46% and 49% for MVAC and GC, respectively. The long-term survival results confirmed the anticipated equivalence of the two regimens (8). The major difference between the above-mentioned combinations was toxicity, with GC being less toxic (43). MVAC is better tolerated with the use of GCSF (40,44).

High-dose intensity MVAC (HD-MVAC) with GCSF 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 (45,46).

All disease sites have been shown to respond to cisplatin-based combination chemotherapy, but 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 versus 29% and 33% at extranodal sites (45). The sites of disease 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 (8).

Further intensification of treatment using new triplets, dose-dense schedules or adding targeted therapies is still being investigated. These approaches should be reserved for clinical trials and are not suitable for routine use (47,48).

12.4 Carboplatin-containing chemotherapy in 'fit' patients

Carboplatin-containing chemotherapy is not proven to be equivalent to cisplatin combinations. However, it is probably inferior and therefore should not be considered interchangeable or standard. The only randomised phase III study of carboplatin-containing chemotherapy had a disappointing response rate of only 28.2% in the investigational arm (paclitaxel/carboplatin) compared to MVAC and had to be closed down early because of a low accrual rate. There is therefore no evidence that this doublet might have adequate efficacy for first-line use (49).

Various carboplatin versus cisplatin combination chemotherapies in randomised phase II trials have produced lower complete response rates and a shorter overall survival for the carboplatin arms (50-52).

12.5 Non-platinum combination chemotherapy

Gemcitabine and paclitaxel combinations in different schedules have been studied as both first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination has been well tolerated and produced response rates between 38% and 60% in both lines. As there has not been a randomised comparison to standard cisplatin chemotherapy, non-platinum combination-chemotherapy is not recommended for first-line use in patients who are fit enough (38,53-59).

12.6 Chemotherapy in patients 'unfit' for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy, either because of a poor PS and/or impaired renal function, or because of co-morbidity preventing high-volume hydration (60,61). The first randomised phase II/III trial in this setting was conducted by the European Organisation for Research and Treatment of Cancer and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (Carbo/Gem) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients given Carbo/Gem versus 23% on M-CAVI, while the overall response rate was 42% on Carbo/Gem and 30% on M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provides limited benefit (62). The overall response rate and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group (62). Recent phase III data has confirmed these results (63).

12.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors are unclear in this setting. Suggested prognostic factors include the choice of first-line chemotherapy (peri-operative/metastatic), prior chemosensitivity, duration of response to first-line treatment, presence of visceral metastases, PS and the 'Bajorin'-prognostic factors. Until recently, there was no defined chemotherapy standard in this setting. A reasonable strategy may be to offer selected patients who initially responded to platinum-containing regimens, another course 12 months, or more, after the initial treatment.

Second-line response rates of paclitaxel (weekly), docetaxel, oxaliplatin, ifosfamide, topotecan, lapatinib, gefitinib and bortezomib range between 0% and 13% in small phase II trials (64-72). Although gemcitabine has also shown excellent response rates in second-line use (31,35-38), most patients already receive this drug as part of their front-line treatment.

In a phase II trial, pemetrexed 500 mg/m^2, given every 3 weeks, showed a promising response rate of 28% and manageable toxicity with the addition of vitamin B12 and folinic acid supplementation and dexamethasone prophylaxis (73). The excellent response rate could not be confirmed by a second, smaller sized trial (74).

Paclitaxel/gemcitabine showed response rates of 38-60%, depending on pre-treatment response and indication of prior chemotherapy. Unfortunately, no adequate randomised phase III trial has been conducted to assess the true value of this second-line combination (2,54,58).

Vinflunine, a novel third-generation vinca alkaloid, has shown objective response rates of 18% and disease control in 67% (75). A phase III trial of vinflunine plus best supportive care (BSC) randomised against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease was published recently (763). The results showed modest activity (overall response rate, 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 in 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 metastases only, good PS and an adequate renal function, including a high degree of complete responses, with up to 20% of patients achieving long-term disease-free survival (8,46,77,78). Stage migration may play a role in this positive prognostic development. A retrospective study of post-chemotherapy surgery after a partial or complete response indicated that post-chemotherapy surgery may contribute to long-term disease-free survival in selected patients (79-81).

12.9 Treatment of bone metastases

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer has been reported to be 30-40% (82). Skeletal complications due to MBD have a detrimental effect on pain and quality of life and are also associated with increased mortality (83). Bisphosphonates reduce and delay skeletal-related events (SRE) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with bladder cancer, SRE of bone metastases could be delayed (84). Denosumab is a fully human monoclonal antibody that binds to, and neutralizes, the receptor activator of nuclear factor kappa-B ligand (RANKL), thereby inhibiting osteoclast function and preventing generalized bone resorption and local bone destruction. Denosumab was noninferior to zoledronic acid (ZA) in preventing or delaying first on-study SRE in patients with advanced cancer metastatic to bone, including also a few urothelial carcinoma patients (85). Denosumab has been recently approved by the European Medicines Agency (EMA) for the treatment of patients with bone metastases of solid tumors. Patients with MBD, irrespective of the cancer type, should be considered for bone targeted treatment (83).

Patients treated with either zoledronic acid or denosumab should be informed about possible side effects and prophylactic management of osteonecrosis of the jaw and hypocalcemia, which is more common in denosumab treated patients. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow respective regulatory recommendations and should be adjusted according to pre-existing medical conditions (86). With the use of denosumab, no follow up of renal function is required because the agent has no potential nephrotoxicity and no dose adjustments are required.

12.10 Conclusions and recommendations for metastatic disease

Conclusion	LE
Performance status and the presence or absence of visceral metastases are independent prognostic factors for survival. These factors are at least as important as the type of chemotherapy administered.	3
Cisplatin-containing combination chemotherapy is able to achieve a median survival of up to 14 months, with long-term disease-free survival reported in about 15% of patients with nodal disease and good performance status.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin-combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy has produced substantial responses in first- and second-line use, but has not been tested against standard chemotherapy in fit patients or in a purely unfit patient group.	2a
To date, there is no defined standard chemotherapy for 'unfit' patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reached the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival.	3
Zoledronic acid and denusomab have been studied and approved for all cancer types including urothelial cancer, as they have been shown to reduce and delay skeletal-related events in metastatic bone disease.	1

Recommendations	GR
The selection of treatment should be guided by prognostic factors.	B
First-line treatment for "fit" patients:	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with GCSF, or HD-MVAC with GCSF.	A
Carboplatin and non-platinum combination chemotherapy are not recommended.	B
First-line treatment in patients ineligible ('unfit") for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C

For cisplatin-ineligible patients ('unfit') with either PS 2 or impaired renal function, or with 0-1 poor Bajorin prognostic factors, first-line treatment is carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin.	A
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.	A*
Zoledronic acid or denosumab, are recommended for the 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

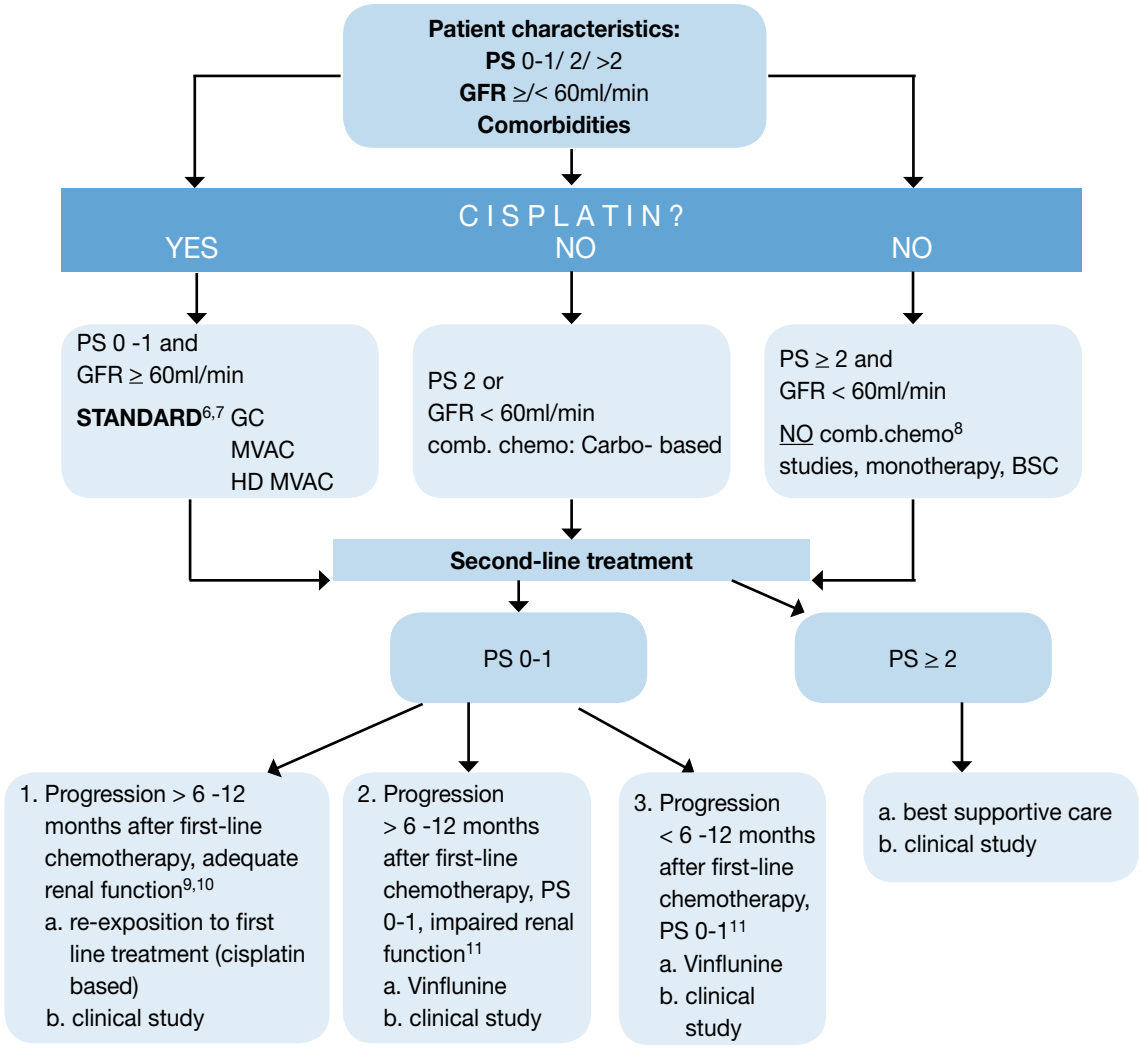
12.11 Biomarkers

Statistically relatively modest, disease control rates, but sporadically, remarkable responses in some patients with urothelial bladder cancer have led to the investigation of biomarkers for the assessment of prognosis after surgery and the potential value of perioperative chemotherapy, and as a predictor for response to chemotherapy or for its monitoring. Most of the biomarkers were associated with tumour angiogenesis. To date, 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), the detection of circulating tumour cells (92,93) and multi-drug resistance gene expression (94). Although a few biomarkers have shown potential, none has sufficient evidence to support their clinical routine use (LE: 3).

Recommendation on the use of biomarkers	**GR**
Currently, no biomarkers can be recommended in daily clinical practice since they have no impact on predicting outcome, treatment decisions or monitoring therapy in muscle-invasive bladder cancer.	A*

**Upgraded following panel consensus.*

Figure 2: Flowchart for the management of metastatic urothelial cancer



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

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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 and night-time incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have only 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 recent study has shown 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 neo-bladders (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 score 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 muscle-invasive bladder cancer, 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 health-related quality-of-life (HRQoL)

Conclusions	LE
No randomised, prospective HRQoL study has evaluated the different forms of definitive treatment for muscle-invasive bladder cancer.	
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.	2b
Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.	

Recommendations	GR
The use of validated questionnaires is recommended to assess HRQoL in patients with muscle-invasive bladder cancer	B
Unless a patient's co-morbidities, tumour variables and coping abilities present clear contra-indications, a continent urinary diversion should be offered.	C
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	C
Patient 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.	C

13.5 References

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14. FOLLOW-UP

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

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

Local pelvic recurrences after urothelial bladder cancer occur in 7-12%. For male and female patients, in contemporary series with bladder substitution, secondary and primary urethral tumours are found in 4-6% and 1,4-4%, respectively. Upper tract recurrences vary between 2,4-17% (5-8). Most recurrences manifest during the first 24 months, often within 6-18 months after surgery. However, late recurrences have also occurred up to 5 years after cystectomy. Pelvic recurrence can be predicted by pathological stage of the primary tumour (pTN) and pathological nodal status (pN).

Patients have a poor prognosis after pelvic recurrence. Even with treatment, median survival ranges from 4-8

months following diagnosis. Definitive therapy can sometimes provide prolonged survival, but in most cases provides only palliation of symptoms. Treatment options include 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 (9). Again, pT and pN were risk factors (10).

The most likely sites for distant recurrences are the lungs, liver and bones (11). Upper urinary tract recurrence is rarely seen (2-7%). However, when it develops, it usually does so within 22-40 months after cystectomy (1,11-13). Surveillance regimens often fail to detect tumours before symptoms develop. Radical nephro-ureterectomy can provide prolonged survival (12).

The relationship between follow-up, recurrences and outcome in neobladder patients was recently addressed by retrospective studies in two high volume centres (14,15), but their results were inconclusive with respect to the impact of follow-up on patient outcomes or survival. The first reported on 479 patients after neobladder surgery, who were prospectively followed up for a median of 4.3 years. Of 174 patients with a recurrence, 87 were found on routine follow-up (median time to recurrence 1 year), compared to 87 patients found with symptoms (median time to recurrence of 0.7 years) (14). Most patients (> 70%) had distant recurrences. Secondary urothelial tumours were in the UUT (14 patients, 8%) or urethra (24 patients, 13.8%, of which 21 were detected with cytology). Patients with asymptomatic recurrences had higher OS and CSS, suggesting some benefit of surveillance.

The second study reported on 1,207 patients after cystectomy, who were followed up for 59 months (15). Of 444 patients with a tumour recurrence, 154 were found after routine follow-up (mean time to recurrence 20 months), whilst 290 had symptomatic recurrence (mean time to recurrence 17.5 months). Only 12 (2.7%) had a urethral recurrence. One of the most important findings was that no difference in survival was demonstrated between symptomatic and asymptomatic recurrences.

14.1.2 ***Secondary urethral tumours***

The incidence of secondary urethral tumours is 5-17%, and they are most likely to occur 1-3 years after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients. In men, the most important risk factor for development of urethral recurrence is prostatic stromal invasion (21-64%) (16-18).

In women, the main risk factor is disease at the bladder neck (19). Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4%) (16,20-22) is significantly lower than after non-orthotopic diversion (6.4-11.1%) (16,21).

Recently, Boorjan et al. specifically addressed urethral recurrences after cystectomy (23). This retrospective study included 1,506 patients with a follow-up of 13.5 years. A neobladder was only constructed after negative urethral frozen section. Only 5.6% of patients experienced a recurrence, of which 55% were symptomatic and 45% asymptomatic. The majority of asymptomatic recurrences were detected with cytology. The 5 year CSS of symptomatic patients (41%) was much lower than in asymptomatic patients (80%). Risk variables for urethral recurrence were prostatic urethral involvement (HR 4.89), bladder tumour focality (HR 2.34) and orthotopic neobladder construction (HR 0.34).

Little data or agreement exist about urethral follow-up, with some recommending routine surveillance to include urethral wash cytology and urine cytology (18), and others doubting the need for routine urethral surveillance at all (20, 24-26). Urethral washes and urine cytology do not appear to have any effect on survival (24,27,28).

Treatment is influenced by the local stage and grade of a urethral recurrence:

- In CIS of the urethra, BCG instillations have shown success rates of 83% (20).
- In invasive disease, urethrectomy should be performed if the urethra is the only site of disease.
- In distant disease, systemic chemotherapy is indicated (11).

Table 5: Suggestions for general follow-up based on the stage of initial tumour after cystectomy

Procedure	Months after cystectomy								
<pT1	3	6	12	18	24	30	36	48	60
Ultrasound kidneys	x								
CT/MRI thor/abd plus UUT*			x		x		x	x	x
Lab,** sed, culture and cytology	x	x	x		x		x	x	x
pT2									
Ultrasound kidneys	x								
CT/MRI thor/abd, plus UUT*		X***	x	X***	x		x	x	x
Lab, sed, culture and cytology	x	x	x		x		x	x	x
>PT3 of N+									
Ultrasound kidneys	x								
CT/MRI thor/abd, plus UUT*	x	x	x	x	x	x	x	x	x
Lab, sed, culture and cytology	x	x	x		x	x	x	x	x

CT = computed tomography scan; MRI = magnetic resonance imaging; thor = thoracic; abd = abdominal; lab = laboratory investigations; sed = urine sediment analysis; UUT = upper urinary tract.
** If UUT is abnormal at CT or there is positive cytology, recurrent primary sampling should be performed.*
*** Blood chemistry, including serum creatinine, or renal function and blood gas analysis.*
****T2a,N0M0 tumours and/or Karnofsky <100%.*

14.1.3 Conclusions and recommendations for specific recurrence sites

Site of recurrence	Conclusion	LE	Recommendation	GR
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour	3	Local conservative treatment is possible for non-invasive tumour.	C
			In isolated invasive disease, urethrectomy should be performed.	B
			Urethral washes and cytology are not recommended.	A
Pelvic recurrence	Poor prognosis Treatment should be individualised depending on the local extent of tumour	2b	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination.	C
Upper urinary tract			Specific upper urinary tract imaging is only indicated in case of clinical symptoms.	
			Radical nephrectomy can provide prolonged survival.	

Imaging for urothelial carcinoma with, or without, cystectomy*

Radiological procedure	Rating scale[1]	Comments	Relative radiation level*
X-ray chest	4		Minimum
CT urography	8		High
X-ray abdomen loopogram	5	In patients with an ileal loop postcystectomy	Medium
X-ray intravenous urography	5	Utilisation of intravenous urography has continued to decline with the increasingly widespread use of CT urography	Medium
MR imaging abdomen and pelvis without and with contrast	7	See ESUR guidelines on contrast media version 7.0 (29)	None
CT abdomen and pelvis with contrast	1	Appropriate if CT urography is not available. Visceral/nodal status evaluated during CT urography	High
CT chest with contrast	5	Performed if chest X-ray is equivocal	Medium
US pelvis (bladder)	3		None
FDG-PET whole body indicated for suspected or nodal metastasis	2	Indicated for suspected nodal or distant metastasis	High
After 5 years of follow-up, oncological surveillance can be stopped and surveillance continued with functional surveillance			

[1]1 is least appropriate; 9 is most appropriate

** Adapted 2011 from: American College of Radiology. Follow-up Imaging of Bladder Carcinoma. Date of origin: 1996; Last review date: 2009 (30).*

CT = computed tomography; FDG-PET = fluorodeoxyglucose positron emission tomography; MR = magnetic resonance; US = ultrasound

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15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ARCO	accelerated radiotherapy with carbogen
ARCON	accelerated radiotherapy with carbogen nicotinamide
ASCO	American Society of Clinical Oncology
5-ALA	5-aminolaevulinic acid
4-ABP	4-aminobiphenyl
BC	bladder cancer
BT	brachytherapy
BCG	Bacille Calmette-Guérin
CGA	comprehensive geriatric assessment
CI	confidence interval
CIS	carcinoma *in situ*
CISCA	cisplatin, cyclophosphamide plus adriamycin
CM	cisplatin, methotrexate
CMV	cisplatin, methotrexate plus vinblastine
CT	multidetector computed tomography
EAU	European Association of Urology
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
FDG-PET	fluorodeoxyglucose positron emission tomography
5-FU	5-Fluorouracil
GC	gemcitabine plus cisplatin
GFR	glomerular filtration rate
GCSF	granulocyte colony stimulating factor
HAL	hexaminolaevulinate
HD-MVAC	high-dose methotrexate, vinblastine, adriamycin plus cisplatin
HIRU	Health Information Research Unit
HRQL	health-related quality of life
IARC	International Agency for Research on Cancer
IPD	independent patient data
ISUP	International Society of Urological Pathology
IVU	Intravenous urography
MCV	methrotrexate, cisplatin and vinblastine
MDCT	multidetector computed tomography
MiM-BC	Muscle-invasive and metastatic bladder cancer
MRC	Medical Research Council (UK)
MR(I)	magnetic resonance (imaging)
MVAC	methotrexate, vinblastine, adriamycin plus cisplatin
MVA(E)C	methotrexate, vinblastine, adriamycine or epirubicine, and cisplatin
NAT	N-acetyltransferase
NMIBC	non-muscle-invasive bladder cancer
NSF	nephrogenic systemic fibrosis
OS	overall survival
PAHs	polycyclic aromatic hydrocarbons
pCR	pathological complete remission
PDD	photodynamic diagnosis
PET	positron emission tomography
PS	performance status
PUNLMP	papillary urothelial neoplasms of low malignant potential
RALC	robotic-assisted laparoscopic cystectomy
R-biopsies	random biopsies
RCT	randomised controlled trial
SEER	Surveillance Epidemiology and End Results
SES	socio-economic status
SF-36	Short Form-36
SIGN	Scottish Intercollegiate Guidelines Network

SWOG	Southwest Oncology Group
TCC	transitional cell carcinoma
TNM	Tumour, Node, Metastasis
TUR	transurethral resection
TURB	transurethral resection of bladder tumour
UICC	Union International Contre le Cancer
UC	urethrocystoscopy
US	ultrasonography
UUTT	upper urinary tract tumours
UUT-UCC	upper urinary tract-urothelial cell carcinoma (UUT-UCC)
WHO	World Health Organization

Conflict of interest
All members of the Muscle-Invasive and Metastatic Bladder Cancer guidelines working group have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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
Prostate Cancer

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European
Association
of Urology

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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*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	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: Grade of recommendation*

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

**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 a considerable number of sections of the PCa guidelines were revised. This 2012 publication includes updated chapters and sections as detailed below. The literature for all chapters has been revisited and, where available, new literature has been included.

The 2012 PCa guidelines publication underwent a blinded peer-review process before publication.

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 6 “Diagnosis”:

- All literature has been revisited, new data has been added;
- Most notably in sections 6.2.3 (PCA3 marker), 6.4.8 (Antibiotics prior to biopsy), 6.4.11 (Complications), 6.5 (Pathology of prostate needle biopsies) and 6.6.2.3 (Definition of extraprostatic extension).
- In section 6.4.8 (Antibiotics prior to biopsy), the quinolones resistance related to infectious complications after biopsy.

Chapter 8 “Watchful waiting/active surveillance”:

- Additional data on the impact of radical prostatectomy compared to watchful waiting (WW) has been added.
- Data have been added supporting that comorbidity status is the leading cause of death at ten years, especially for Charlson score ≥ 2, irrespective of age, even for those with an aggressive tumour.
- Active surveillance as appropriate for highly selected, low risk patients only. Early re-biopsy plays as an increasingly important role in the patient’s selection process.
- In general, repeat biopsies are a major tool for patient follow-up.

Chapter 9 “Treatment: Radical prostatectomy”;

- Additional data have been included in section 9.1 (Introduction) on robot-assisted laparoscopic prostatectomy (RALP)
- Added emphasis is given to the need for a multidisciplinary approach in the treatment of high-risk localised disease Section 9.4 (High-risk localised PCa).

Chapter 10 “Treatment: Definitive radiation therapy”;

- Additional data has been added on the various hormonal therapy options, section 10.8 (Locally advanced PCa: T3-4, N0M0).

Chapter 11 “Experimental local treatment of prostate cancer”;

- Additional data has been added on oncological outcomes and treatment-associated complications (Section 11.3 -HIFU of the prostate).
- Additional data on salvage radical prostatectomy versus CSAP has been included (Section 16.6.2 - Salvage cryosurgical ablation of the prostate for radiation failures).
- A new section has been added on salvage high-intensity focused ultrasound (HIFU).

Chapter 12 “Hormonal treatment”;

- Data from the largest randomised controlled trial on PCa patients relapsing after radiotherapy has been incorporated, showing that intermittent androgen-deprivation therapy (ADT) proved to be as effective as continuous ADT.

- Additional data regarding bone protection and the potential role of denosumab in delaying secondary bone metastases. However, denosumab does not impact overall survival or cancer-specific survival.
- Further data on androgen deprivation therapy (ADT) was included. ADT is associated with increased cardiac morbidity, not an increase in cardiac mortality. The presence of a congestive heart failure or myocardial infarction increases the mortality risk

Chapter 15 “Follow up after hormonal treatment”;

- The literature has been revisited. The importance of bone- and testosterone monitoring is reinforced.

Chapter 16 “Treatment of biochemical failure after treatment with curative intent”

- In section 16.4 (Evaluation of PSA progression), additional data has been added on the role of choline PET/CT in the diagnosis of men with rising PSA following radical prostatectomy.

Chapter 17 “Castration resistant prostate cancer”;

- For section 17.4 (Recommendations for assessing therapeutic response), new literature has been incorporated and recommendations have changed;
- 17.8.5.2 (Abiraterone acetate), new information has been added;
- 17.9.10 (Specific bone targets), information from the ENTHUSE study has been included.

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/.

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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 undeveloped 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).

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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*

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour not palpable or visible by imaging	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
T2	Tumour confined within the prostate[1]	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule[2]	
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum,levator muscles, and/or pelvic wall	
N - Regional lymph nodes[3]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant metastasis[4]		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)

	M1c	Other site(s)

1 *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified asT1c.*

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

Group I	T1a-c	N0	M0 PSA < 10	Gleason ≤ 6
	T2a	N0	M0 PSA < 10	Gleason ≤ 6
Group IIA	T1a-c	N0	M0 PSA < 20	Gleason 7
	T1a-c	N0	M0 PSA ≥ 10 < 20	Gleason ≤ 6
	T2a, b	N0	M0 PSA < 20	Gleason ≤ 7
Group IIb	T2c	N0	M0 Any PSA	Any Gleason
	T1-2	N0	M0 PSA ≥ 20	Any Gleason
	T1-2	N0	M0 Any PSA	Gleason ≥ 8
Group III	T3a, b	N0	M0 Any PSA	Any Gleason
Group IV	T4	N0	M0 Any PSA	Any Gleason
	Any T	N1	M0 Any PSA	Any Gleason
	Any T	Any N	M1 Any PSA	Any Gleason

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

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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 (3). Patients with hereditary PCa usually have an onset 6-7 years prior to spontaneous cases, but do not differ in other ways (4).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (5). 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 (6). 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 (7) (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 (8) and occupational exposure have all been discussed as being aetiologically important (9). Prostate cancer is 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]) (8). 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-oestrogens (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 (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).

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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* Section 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).

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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

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

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

** Acknowledgment: Section 6.4 is partly based on the Guidelines of the AUO Study Group Urologic Oncology of the AustrianSociety of Urologists and Andrologists (W. Höltl, W. Loidl, M. Rauchenwald, M. Müller, M. Klimpfinger, A. Schratter-Sehn,C. Brössner).*

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.

*6.2.2 **PSA velocity (PSAV), PSA doubling time (PSADT)***

There are two methods of measuring PSA over time: (1) PSAV, which is defined as an absolute annual increase in serum PSA (ng/mL/year) (12) (LE: 1b); and (2) 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 normalized 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: (1) rising and/or persistently elevated PSA; (2) suspicious DRE (30); (3) atypical small acinar proliferation (ASAP); and (4) 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, 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 hospitalizations 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*

Complications	% 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 hospitalization	0.3

** Adapted from NCCN Guidelines Prostate Cancer Early Detection. V.s.2010 (42).*

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*

Benign/negative for malignancy. If appropriate, include a description (e.g. atrophy).
Active inflammation, negative for malignancy
Atypical adenomatous hyperplasia/adenosis, no evidence of malignancy
Granulomatous inflammation, negative for malignancy
High-grade PIN, negative for adenocarcinoma
High-grade PIN with atypical glands suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation suspicious for cancer
Adenocarcinoma

**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 ≥ 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

Total embedding of a prostatectomy specimen is preferred, either by conventional (quadrant sectioning) or by whole-mount sectioning.
The entire surface of RP specimens should be inked before cutting to evaluate the surgical margin status.
The apex should be separately examined using the cone method with sagittal or radial sectioning.

*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

Histological type
Type of carcinoma, e.g. conventional acinar, ductal, etc.
Histological grade
Primary (predominant) grade
Secondary grade
Tertiary grade (if applicable)
Total/global Gleason score
Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional)
Percentage of prostatic gland involved
Tumour size of dominant nodule (if identified), greatest dimension in mm
Pathological staging (pTNM)
Presence of extraprostatic extension (indicate focal or extensive) • If present, specify site(s) • Presence of seminal vesicle invasion
If applicable, regional lymph nodes • Location • Number of lymph nodes retrieved
• Number of lymph nodes involved
Surgical margins
Presence of carcinoma at margin • If present, specify sites and extra- or intraprostatic involvement
Other
If identified, presence of angioinvasion
Location (site, zone) of dominant tumour (optional)
Perineural invasion (optional) • If present, specify extra- or intraprostatic location

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 1) it does not correlate with clinical T2 substage and 2) 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 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

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7. CLINICAL STAGING

The primary extension assessment of prostate cancer (PCa) is usually made by digital rectal examination (DRE), prostate-specific antigen (PSA) measurement, and bone scan, supplemented with computed tomography (CT) or magnetic resonance imaging (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 transrectal ultrasound (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 bioptic Gleason score with the final pathological stage: about 70% of patients have localized 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 tumor 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).

E-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 localization 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 ^{11}C-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, stagesT2b-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 (< 10%, *see reference number 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 or less 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 in the short axis 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 ^{18}F-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}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}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}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 (up to 7: 3+4) differentiated 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

Diagnosis of PCa - Conclusions
An abnormal digital rectal examination (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 < 2-3 ng/mL are often used for younger men.
The diagnosis of PCa depends on histopathological (or cytological) confirmation.
Staging of PCa - Conclusions
Despite its high specificity in the evaluation of extraprostatic extension (EPE) and seminal vesicle invasion (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 computed tomography (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).
Currently only sentinel lymph node dissection or extended PLND allow for histological detection of lymph node metastases with high sensitivity.

Diagnosis of PCa - Recommendations		**GR**
Biopsy and further staging investigations are only indicated if they affect the management of the patient.		C
	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.	B
	Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates.	C
	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).	B
	Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	C
Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies.		A
Staging of PCa - Recommendations		
Local staging (T-staging) of PCa should be based on magnetic resonance (MR) imaging. Further information is provided by the number and sites of positive prostate biopsies, the tumour grade and the level of serum PSA.		C
For local staging TRUS should not be used since it has low sensitivity and a tendency to understage PCa.		
	Lymph node status (N-staging) need only be assessed when potentially curative treatment is planned. Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score ≤ 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation.	B
	In clinically localized 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 (< 5 mm),	
Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is < 20 ng/mL in the presence of well or moderately differentiated tumours.		B
In equivocal cases, ^{11}C-choline-, ^{18}F-flouride-PET/CT or whole body MRI are an option.		C

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.

7.5 References

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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 (WW)*

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 $\leq$ 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

Grade	5 years (%)	10 years (%)
Disease-specific survival		
Grade 1	98 (96-99)	87 (81-91)
Grade 2	97 (93-98)	87 (80-92)
Grade 3	67 (51-79)	34 (19-50)
Metastasis-free survival		
Grade 1	93 (90-95)	81 (75-86)
Grade 2	84 (79-89)	58 (49-66)
Grade 3	51 (36-64)	26 (13-41)

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)

Gleason score	Risk of cancer death* (%)	Cancer-specific mortality† (%)
2-4	4-7	8
5	6-11	14
6	18-30	44
7	42-70	76
8-10	60-87	93

** 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 not yet been published (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 (348) or radical prostatectomy (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)

	RP (N = 347) % (n)	WW (N = 348) % (n)	Relative risk (95% CI)	p value
Disease-specific mortality	14.6	20.7	0.62	0.01
Overall mortality	46.1	57.2	0.75 (0.61-0.92)	0.007
Metastatic progression	21.7	33.4	0.59 (0.45-0.79)	< 0.001
Local progression	21.5	49.3	0.34 (0.26-0.45)	

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) is an ongoing, controlled, multicentre, randomised clinical

trial comparing radical prostatectomy with WW in patients with clinical stage T1-T2 disease. Between 1994 and 2002, 731 patients with a median age of 67 years were enrolled. The median PSA was 7.8 ng/mL (mean 10.2 ng/mL). Three-quarters of the men had clinical stage T1c disease. Using previously developed tumour risk categorizations based on PSA levels, Gleason histological grade and tumour stage, approximately 43% of men had low-risk PCa, 36% had medium-risk PCa, and 20% had high-risk PCa. Follow-up is planned for 15 years, and the primary endpoint is the overall mortality. Men enrolled in PIVOT are more representative of men diagnosed and treated in everyday clinical practice than those enrolled in SPCG-4. Preliminary unpublished results have been presented at the latest AUA meeting (21). The results suggested that overall there was a lack of survival benefit. However, there appeared to be an overall survival benefit in men with an intermediate- and high-risk PCa, as well as a cancer specific survival benefit in men with high-risk PCa or with a PSA above 10 ng/mL. Full results are urgently awaited.

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	**LE**
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.	1b
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.	3
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).	2a
The comparison of immediate hormonal treatment to WW in localised PCa remain controversial and may be associated with an increased mortality with bicalutamide.	2a

It appears that many small localised well-differentiated PCas 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 (31) (LE: 3). 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 ≤ 10 ng/mL were enrolled with an overall Gleason score ≤ 6 (PSA ≤ 15), with patients > 70 years having a Gleason score ≤ 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

	N	Median age	Criteria
Dall'Era (35)	376	62	Gleason ≤ 3+3, PSAd ≤ 0,15 ng/dL, T ≤ T2, ≤ 33% biopsies+, ≤ 50% cores
Van den Berg (36)	616	66	Gleason ≤ 3+3, PSA ≤ 10 ng/mL, PSAd ≤ 0,2 ng/dL, T≤T2, ≤ 2 biopsies +
Van As (37)	326	67	Gleason ≤ 3+4, PSA ≤ 15 ng/mL, T ≤ T2a, ≤ 50% biopsies +
Soloway (38)	230	64	Gleason ≤ 6, PSA ≤ 10 ng/dL, T ≤ T2, ≤ 2 biopsies+, ≤ 20% cores +
Klotz (34)	453	70	Gleason ≤ 6, PSA ≤ 10 ng/dL, (up to 1999: Gleason ≤ 3+4, PSA ≤ 15 ng/mL) < 3 biopsies +, < 50% each core
Tosoain (39)	633	66	Gleason ≤ 3+3, PSAd ≤ 0,15 ng/dL, T1, ≤ 2 biopsies+, ≤ 50% cores
Adamy (40)	238	64	Gleason ≤ 3+3, PSA ≤ 10 ng/mL, T ≤ T2a, ≤ 3 biopsies+, ≤ 50% length

Table 13: Clinical trials of AS for organ-confined PCa: main results

		Progression			Survival (%)		
	Median follow-up (months)	Biopsy (%)	PSA / PSA DT	Patient's request	OS	CSS	PFS
Dall'Era	47	35	5	8	97	100	54
Van den Berg	52	-	13	18	91	100	68
Van As	22	13	18	2	98	100	73
Soloway	32	10	-	-	100	100	86
Klotz	82	9	14	3	68	97	70
Tosoain	32	14	-	9	98	100	54
Adamy	22	13	14	11	-	-	-

OS = overall survival: CSS = cancer-specific survival; PFS =progression-free survival.

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 orchiectomy compared with delayed treatment (48,49).

In a recent 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 ≤ to 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***	**LE**
In presumed localised PCa (Nx-N0, M0):	
Stage T1a: 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.	2a
Stage T1b-T2b: well and moderately differentiated tumours. In asymptomatic patients with a life expectancy of < 10 years.	2a
Active surveillance	2a
In patients with the lowest risk of cancer progression: cT1-2a, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 (at least 10 cores), ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	
Active surveillance selection is based on confirmatory biopsies.	
Follow-up is based on DRE, PSA and repeated biopsies. The optimal timing for follow-up is still unclear (yearly or every 2 years).	
The trigger for patients being moved off active treatment is based mainly on grade progression on repeated biopsies or at the patient's request.	
PSA progression is controversial.	
8.5.2 ***Options***	
In presumed localised PCa (Nx-N0, M0):	
Stage T1b-T2b 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.	3
In locally advanced disease (stage T3-T4):	
Asymptomatic patients with well or moderately differentiated cancer, PCa and a short life expectancy.	3
PSA < 50 ng/mL and PSA doubling time > 12 months.	1
In metastatic disease (M1):	
A very rare patient without any symptoms and the possibility of close follow-up.	4

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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).

RP was first applied at the beginning of the 20th century by Young (5) using a perineal approach, while Memmelaar and Millin were the first to perform retropubic RP (6). In 1982, Walsh and Donker described the anatomy of the dorsal venous complex and the neurovascular bundles (NVBs). This resulted in a significant reduction in blood loss and improved continence and potency rates (7). Currently, RP is the only treatment for localised PCa to show a benefit for cancer-specific survival (CSS), compared with conservative management, as shown in a prospective randomised trial (8). Surgical expertise has decreased the complication rates of RP and improved cancer cure (9-12).

Total surgical removal is an excellent treatment option in well-selected patients with localised PCa. 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 (13,14).

Radical retropubic prostactectomy (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 prostate cancer 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 relative superiority to more-established treatment modalities. Recent in-depth systematic reviews of the literature have compared the results of RRP versus LRP/RALP. It has been concluded that LRP and RALP are followed by significantly lower blood loss and transfusion rate, but the available data are not sufficient and of insufficient quality to prove the superiority of any surgical approach in terms of functional and oncological outcomes (15-17).

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 the randomised trial comparing retropubic RP versus watchful waiting (WW) in localised PCa (8). In this study, the survival benefit was similar before and after 9 years of follow-up, was observed also among men with low-risk PCa, 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.

*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 adenomectomy]. 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 before 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 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. RP 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 grade (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 the randomised trial comparing RRP versus WW in localised PCa (8). In this 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.

RP 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 randomised trial comparing RP and WW that included mostly T2 PCa patients, with a significant reduction in disease-specific mortality in favour of RP (8).

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

Reference	No. of patients	Year of RP	Median follow-up (mo)	10-year PSA-free survival (%)	10-year cancer-specific survival (%)	15-year cancer-specific survival (%)	25-year cancer-specific survival (%)
Isbarn *et al*. (2009) (37)	436	1992-97	122	60	94		
Roehl *et al*. (2004) (38)	3478	1983-2003	65	68	97		
Han *et al*. (2001) (39)	2404	1982-99	75	74	96	90	
Hull *et al*. (2002) (40)	1000	1983-98	53	75	98		
Porter *et al*. (2006) (41)	752	1954-94	137	71	96	91	82
Bill-Axelson *et al*. (2011) (8)	347	1989-99	153			85	
Stephenson et al. (42)	6398	1987-2005	48			88	

The first externally validated nomogram predicting PCa-specific mortality after RP for patients treated in the PSA era was published recently. 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 prostate cancer: cT3a or Gleason score 8-10 or prostate-specific antigen > 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 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 androgen-deprivation therapy (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 (49-54).

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

progression-free survival (PFS) (53,54). In 33.5-66% of patients, positive section margins are present, and 7.9-49% have positive lymph nodes (55). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or HT (53,54). Nevertheless, excellent 5-, 10- and 15-year overall survival (OS) and cancer-specific survival (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 (27,55). In addition, nodal imaging with computed tomography (CT), and seminal vesicle imaging with magnetic resonance imaging (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 (56). RP 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 (53,57). It has been shown that continence can be preserved in most cases, and in selected cases, potency can also be preserved (58).

Table 15: OS and CSS rates for PCa.

Reference	no. of patients	Median and/or mean follow-up	BPFS (%)			CSS (%)		
			5 years	10 years	15 years	5 years	10 years	15 years
Yamada *et al*. (1994) (49)	57	Median, 5.4 years	45.5 (PSA > 0.4)	-	-	-	-	-
Gerber *et al*. (1997) (50)	242	Mean, 39 months Median, 26 months	-	-	-	85	57	-
Van den Oudene*t al*. (1998) (51)	83	Median, 52 months	29 (PSA > 0.1)	-	-	85	72	-
Martinez de la Riva *et al*. (2004) (52)	83	Mean, 68.7 months (cT3a only)	- (PSA > 0.3)	59.8	-	100	-	-
Ward *et al*. (2005) (53)	841	Median, 10.3 years	58 (PSA > 0.4)	43	38	95	90	79
Hsu *et al*. (2007) (54)	200	Mean, 70.6 months (cT3a only)	59.5 (PSA > 0.2)	51.1	-	99	92	-

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 (59).

*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 (60). Spahn et al. published the largest multicentre clinical series of its kind, comprising 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively (61). 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 (62).

eLND 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 (63). 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. OS 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 (64).

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. 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 N+ PCa has been shown to achieve a 10-year CSS rate of 80% (65,66). Most urologists are reluctant to perform RP for clinical N+ disease, or cancel surgery if a frozen section shows lymph node invasion. However, a recent study has shown a dramatic improvement in CSS and OS in favour of completed RP versus 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 (67). These findings have been corroborated in a contemporary series (68). RP 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.

It should also be noted that definitive pathological examination after RP could show microscopic lymph node invasion. The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only (69,70). 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 HT in patients with increased 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 (71).

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% (72). Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (73,74). Clearly, the removal of a greater number of nodes results in improved staging. In the largest study of its kind, a cut-off ≤ 2 versus > 2 affected nodes was shown to be an independent predictor of CSS (69).

9.6.1 ***Conclusions***

Extended LND is not necessary in low-risk, localised PCa, because the risk for positive lymph nodes does not exceed 5% (31).

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% (31). Limited LND should no longer be performed, because it misses at least half the nodes involved.

9.6.2 ***Extent of extended lymph node dissection***

Extended LND includes removal of the nodes overlying 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 ileac 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 (75). For eLND to be representative, a mean of 20 lymph nodes should be removed (76). 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.

9.6.3 ***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 (77-79). In some series, the number of nodes removed during lymphadenectomy has correlated significantly with time to progression (80). 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 (81). Further studies should confirm these results.

9.6.4 ***Morbidity***

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended versus limited LND, threefold higher complication rates have been reported by some authors (82). Complications consist of lymphocoeles, lymphoedema, deep venous thrombosis, and pulmonary embolism. Other authors, however, have reported more acceptable complication rates (83,84).

9.6.5 ***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 individual cases.

9.7 Summary of radical prostatectomy 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.

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 (85). In a recent review and meta-analysis, the role of NHT and prostatectomy has been studied (86). 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 (87). 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 fistulas are seen in 1.2-4% of patients (88); and urinary incontinence persists after 1 year in 7.7% (89). 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 (90-92).

Erectile dysfunction used to occur in nearly all patients, but this can be avoided by using nerve-sparing techniques in early-stage disease (93). 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

Complication	Incidence (%)
Perioperative death	0.0-2.1
Major bleeding	1.0-11.5
Rectal injury	0.0-5.4
Deep venous thrombosis	0.0-8.3
Pulmonary embolism	0.8-7.7
Lymphocoele	1.0-3.0
Urine leak, fistula	0.3-15.4
Slight stress incontinence	4.0-50.0
Severe stress incontinence	0.0-15.4
Impotence	29.0-100.0
Bladder neck obstruction	0.5-14.6
Ureteral obstruction	0.0-0.7
Urethral stricture	2.0-9.0

9.10 Summary of indications for nerve-sparing surgery* (100-104)

Reference name	Sofer (94)	Walsh (95)	Alsikafi (96)	Graefen (97)	Bianco (98)
Preoperative selection criteria					
Stage > T2	+	+	+	+	+
PSA > 10	+				
Biopsy Gleason score 7			+		
Biopsy Gleason score 8-10	+			+	
Partin tables		+			+
Side with > 50% tumour in biopsy			+		
Side with perineural invasion		+/-	+		
Intra-operative selection criteria					
Side of palpable tumour			+		
Side of positive biopsy				+	
Induration of lateral pelvic fascia		+			+
Adherence to neurovascular bundles		+			+
Positive section margins	**24%**	**5%**	**11%**	**15.9%**	**5%**

**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 (99,100). 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 (101).

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 (102,103). Finally, the early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. A recent placebo-controlled prospective study has shown no benefit from daily early administration of vardenafil versus on-demand vardenafil in the postoperative period (104), whereas another placebo-controlled prospective study has shown that sildenafil has a significant impact on return of normal spontaneous erections (105).

9.11 Conclusions and recommendations for radical prostatectomy

Indications	**LE**
In patients with low and intermediate risk localised PCa (cT1a-T2b and Gleason score 2-7 and PSA ≤ 20 ng/mL) and life expectancy > 10 years.	1b
Optional	
Patients with stage T1a disease and a life expectancy >15 years or Gleason score 7.	3
Selected patients with low-volume, high-risk, localised PCa (cT3a or Gleason score 8-10 or PSA > 20 ng/mL).	3
Highly selected patients with very-high-risk, localised PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.	3
Recommendations	
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.	1a
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables/nomograms).	3
Unilateral nerve-sparing procedures are an option in stage T2a-T3a disease.	4

*9.12 **References***

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10. TREATMENT: DEFINITIVE RADIATION THERAPY

10.1 Introduction

There are no randomised studies comparing radical prostatectomy (RP) with either external beam radiation therapy (EBRT) or brachytherapy for localised PCa. However, the National Institutes of Health (NIH) consensus set up in 1988 (1) remains available: external irradiation offers the same long-term survival results as surgery; moreover, EBRT provides a QoL at least as good as that provided by surgery (2).

Intensity modulated radiotherapy (IMRT) +/- image guided (IGRT) is the gold standard and all centres unable to offer this should have a plan to introduce it as a routine for the definitive treatment of prostate cancer (PCa).

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 radiation therapy scientific societies, such as the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC), have established the indications for the combination of external irradiation and androgen deprivation treatment (ADT).

Whatever the technique used, the choice of treatment - after the appropriate assessment of tumour

extension - must be based on a multidisciplinary approach and should consider the following:

- 2009 TNM classification;
- Gleason score defined on a sufficient number of core biopsies (at least 12);
- baseline PSA;
- age of the patient;
- patient's co-morbidity, life expectancy and QoL;
  IPSS score and uroflowmetry recordings;
- National Comprehensive Cancer Network (NCCN) and prognostic class D'Amico's prognostic factor classification (2b).

It is essential to obtain a patient's informed consent after providing full information to him, regarding diagnosis, therapeutic modalities and morbidity. Additional information on the various aspects of radiotherapy in the treatment of PCa is available in a newly published extensive overview (3).

10.2 Technical aspects: three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated external beam radiotherapy (IMRT)

Anatomical data, acquired by scanning the patient in a treatment position, are transferred to the 3D treatment planning system, which visualises the clinical target volume and then adds a (surrounding) safety margin. At the time of irradiation, a multi-leaf collimator automatically and, in the case of IMRT, continuously, adapts to the contours of the target volume seen by each beam. Real-time verification of the irradiation field by means of portal imaging allows for 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 increasing the risk of morbidity.

The use of IMRT is possible with linear accelerators equipped with the latest multileaf collimators and specific software. Movement of the leaves during the course of the irradiation 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.

Whatever the techniques and their 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 non-metastatic prostate cancer

Several randomized and non-randomised studies have shown that dose escalation (range, 76-80 Gy) has a significant impact on 5-year survival without biochemical relapse (5-7,10-12,15).
Two randomised trials focused on clinical stages T1-3 N0 M0 have paved the way for dose escalation:

- The MD 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 and, with a median follow-up of 8.7 years, showed a significant increase in freedom from biochemical and/or clinical failure for low-risk patients ($p = 0.04$) (5).
- The PROG 95-09 study evaluated 393 T1b-T2b patients, of whom 75% had a Gleason score ≤ 6 and a PSA < 15 ng/mL. Patients were randomised 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 of 5.5 years, there was a significant increase in 5-year freedom from biochemical failure ($p < 0.001$) in favour of low-risk patients given a higher dose (79.2 Gy) versus those given a conventional dose (70.2 Gy) (6).

In daily practice, a minimum dose of ≥ 74 Gy is recommended for EBRT + hormone therapy (expert opinion) (7).

The following phase III trials argue for the combination of ADT and RT, or for dose-escalated RT:

- A Dutch randomised phase III trial comparing 68 Gy with 78 Gy showed a significant increase in 5-year freedom from clinical or biochemical failure for patients in an intermediate-risk group (10).
- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy 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 of 59 months, a high dose should provide a better 5-year biological outcome in intermediate-risk patients, especially if the initial PSA > 15 ng/mL (11).
- The RTOG 94-08 trial in 1979 patients with T1b-T2b, PSA < 20 ng/mL has shown that the addition of complete androgen blockade for 2 months before, and 2 months during conventional, lower-dose RT (66 Gy) significantly improved 10-year overall survival (62% vs 57%, $p = 0,03$) (12).
- Patients who are reluctant to accept short-term hormonal treatment (13) can receive definitive

radiotherapy alone, provided that a dose escalation up to 78-80 Gy is proposed.

- The MRC RT01 study, comparing a dose of 64 Gy with 74 Gy, both with neoadjuvant hormonal therapy, showed an 11% difference in 5-year BDFS (14).
- The PROG 95-09 study showed a significant increase in 5-year freedom from biochemical failure ($p < 0.02$) in favour of high-risk patients given a higher dose (79.2 Gy) versus those given a conventional dose (70.2 Gy) (10).
- An MD Anderson study showed a significant improvement in mestatases-free survival for high-risk patients ($p = 0.004$) (5).
- The EORTC trial 22991, comparing 3D-CRT +/- IMRT with a choice of three levels of dose (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; its results are awaited (15).

A combination of external irradiation with short-term ADT improves overall survival, based on the results of a phase III randomised trial which included 206 patients with a PSA level of at least 10 ng/mL (maximum 40 ng/mL), a Gleason score of at least 7 (range 5-10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with 6 months of ADT. After a median follow-up of 7.6 years, intermediate- or high-risk patients without moderate or severe co-morbidity, who had been randomised to receive 3D-CRT + ADT, showed a 13% improvement in overall survival rate ($p < 0.001$) (13). In contrast, data from the EORTC-22961 randomised phase III trial, comparing 36 months of hormonal treatment + radiotherapy with 6 months of hormonal treatment + radiotherapy, showed that increased hormonal treatment improved overall survival in patients with high-risk PCa at 5 years (14).

*10.3.1 **Prophylactic irradiation of pelvic lymph nodes in high-risk localised PCa***

Invasion of the pelvic lymph nodes is a poor prognostic factor and mandates systemic medical treatment because radiotherapy alone is insufficient (15). Prophylactic whole-pelvis irradiation has been abandoned since randomised trials failed to show that patients benefited from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77 06 study with 484 T1b-T2 patients (16), the Standford study with only 91 patients (17), and the GETUG-01 trial, which included 444 T1b-T3 N0 pNx M0 patients (18). Pelvic lymphadenectomy may be needed to improve the selection of patients who might benefit from pelvic lymph node irradiation and to supplement the use of Partin's tables (19) and/or the Roach formula (20). The results of pelvic lymphadenectomy, particularly for young patients, will enable radiation oncologists to tailor both the planning target volume and the duration of ADT: specifically, no pelvic irradiation for pN0 patients, but pelvic irradiation for pN1 patients with long-term ADT. The benefits of pelvic nodal irradiation merit further investigation in a clinical trail (one trial using high-dose IMRT is currently being designed).

10.4 Innovative techniques

*10.4.1 **Intensity modulated radiotherapy***

Intensity modulated radiotherapy enables radiation oncologists to increase radiation doses homogeneously, up to as much as 86 Gy within the target volume, while respecting the tolerance doses in organs at risk. Certainly, IMRT is the only safe means of treatment delivery for dose escalation beyond 75 Gy, using conventional 2 Gy fraction sizes, or for dose escalation using hypofractionated radiotherapy, in which there has been renewed interest. However, both treatment scenarios should be performed only within the confines of a properly designed clinical trial.

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 image-guided radiotherapy (IGRT), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear (21).

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 computed tomography (CT) scanning. Preliminary data suggest that this technique is feasible in PCa treatment (22).

*10.4.2 **Proton beam and carbon ion beam therapy***

In theory, proton beams are an attractive alternative to photon beam radiotherapy for PCa because they deposit almost all 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. Additionally, there is 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) radiation therapy using protons or carbon ions offers inherent biological advantages over photons, having more 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 mentioned above compared standard-dose conformal radiotherapy with dose-escalated radiotherapy using protons for the boost dose (6). 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 for dose escalation. A randomised trial comparing equivalent doses of proton beam therapy with IMRT is needed to compare the efficacy of protons versus photons; such a study 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 (23); the other study suggested a clearer advantage to protons (24). 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 compared with IMRT, because of the lower integral dose of radiation, but there are no data in patients treated for PCa to support this.

Carbon ions offer similar theoretical advantages as 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 in a dose equivalent to 66 Gy in 20 fractions over 5 weeks (25). Treatment appeared to be well tolerated, with no RTOG grade 3 or 4 bowel or genitourinary toxicity, and an overall four-year BDFR of 88% (24). 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 consensus on the following eligibility criteria:

- stage cT1b- T2a N0, M0;
- a Gleason score ≤ 6 assessed on a sufficient number of random biopsies;
- an initial PSA level of ≤ 10 ng/mL;
- $\leq 50\%$ of biopsy cores involved with cancer;
- a prostate volume of < 50 cm^3;
- an International Prostatic Symptom Score ≤ 12 (IPSS) (26).

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 (27).

In 1983, Holm et al. described the transperineal method with endorectal sonography in which the patient is positioned in a dorsal decubitus gynaecological position (28). Implantation is undertaken 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 are no randomised trials comparing brachytherapy with other curative treatment modalities, and outcomes are based on non-randomised case series. Results of permanent implants have been reported from different institutions, with a median follow-up ranging between 36 and 120 months (29). Recurrence-free survival after 5 and 10 years was reported to range from 71% to 93% and from 65% to 85%, respectively (30-37).

A significant correlation has been shown between the implanted dose and recurrence rates (38). Patients receiving a D90 of > 140 Gy demonstrated a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at 4 years than patients receiving less than 140 Gy (92% vs 68%). There is no benefit from adding neoadjuvant or adjuvant ADT to LDR brachytherapy (29).

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implant transurethral resection of the prostate (TURP) (up to 8.7%), and incontinence (0-19%) (39b). A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity (39). 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 symptoms prior to brachytherapy. Previous TURP for benign prostatic hyperplasia increases the risk of post-implant incontinence and urinary morbidity.

The incidence of grade III toxicity is less than 5%. Erectile dysfunction develops in about 40%

of patients after 3-5 years. In a recent retrospective analysis of 5,621 men who had undergone LDR brachytherapy (40), 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 cases of permanent implants, iodine-125 in granular form is the radio-element of reference, while palladium-103 may be used for less differentiated tumours with a high doubling time. The dose delivered to the planning target volume is 144 Gy for iodine-125, and 125 Gy for palladium-103. A Gleason score of 7 remains a 'grey area', but patients with a Gleason score of 4 + 3 showed no difference in outcome (41).

A small randomised trial has suggested that the use of stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice (42).

In cases of intermediate- or high-risk localised PCa, brachytherapy in combination with supplemental external irradiation (43) or neoadjuvant hormonal treatment (44) may be considered.

The optimum dose of supplemental EBRT is unclear. A randomised trial comparing 44 Gy with 20 Gy of EBRT + palladium-103 brachytherapy closed early, showing no difference in biochemical outcomes (45).

Non-permanent 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 (46). 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 (47).

Recent data suggest an equivalent outcome in terms of BDFS compared with high-dose EBRT (HD EBRT) (48). In a retrospective analysis of modern series (49,50), BDFS rates of 85.8%, 80.3% and 67.8% in men with low-, intermediate- and high-risk PCa, respectively, are reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar between high-dose EBRT and high-dose rate (HDR) brachytherapy in terms of diarrhoea and insomnia (51). However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs 34%). A single randomised trial of EBRT versus EBRT + HDR brachytherapy has been reported (52). A total of 220 patients with organ-confined PCa 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. Compared to EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in biochemical relapse-free survival ($p = 0.03$). There were no differences in the rates of late toxicity. Patients randomised to EBRT + 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 (52). There is still a need to compare dose-escalated EBRT + hormone therapy, with the same followed by a brachytherapy boost, in intermediate- 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 RP, according to a study of 2991 patients diagnosed with T1-2 consecutive localised PCa treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Center with a minimum of 1-year follow-up (48).

10.6 Late toxicity

Patients must be informed about the potential late genitourinary or gastrointestinal toxicity that may occur, as well as the impact of irradiation on erectile function. Late toxicity was analysed using a dose of 70 Gy in the prospective EORTC randomised trial 22863 (1987-1995) (53), in which 90% of patients were diagnosed as 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 (22.8%) patients had grade ≥ 2 urinary or intestinal complications or leg oedema, of which 72 had grade 2 (moderate) toxicity, 10 had grade 3 (severe) toxicity, and four died due to grade 4 (fatal) toxicity. Although four (1%) late treatment-related deaths occurred, long-term toxicity was limited, with fewer than 5% grade 3 or 4 late complications being reported (Table 17). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT or IMRT.

Table 17: Incidence of late toxicity by RTOG grade (from EORTC trial 22863)

Toxicity	Grade 2		Grade 3		Grade 4		Any significant toxicity (≥ grade 2)	
	No.	%	No.	%	No.	%	No.	%
Cystitis	18	4.7	2	0.5	0	0	20	5.3
Haematuria	18	4.7	0	0	0	0	18	4.7
Urinary stricture	18	4.7	5	1.3	4	1	27	7.1
Urinary incontinence	18	4.7	2	0.5	0	0	20	5.3
Overall GU toxicity	**47**	**12.4**	**9**	**2.3**	**4†**	**1†**	**60**	**15.9**
Proctitis	31	8.2	0	0	0	0	31	8.2
Chronic diarrhoea	14	3.7	0	0	0	0	14	3.7
Small bowel obstruction	1	0.2	1	0.2	0	0	2	0.5
Overall GI toxicity	**36**	**9.5**	**1**	**0.2**	**0**	**0**	**37**	**9.8**
Leg oedema	**6**	**1.5**	**0**	**0**	**0**	**0**	**6**	**1.5**
Overall toxicity*	**72**	**19.0**	**10**	**2.7**	**4**	**1**	**86**	**22.8**

GU = genitourinary; GI = gastrointestinal.

** 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 rate of probability for maintaining erectile function was 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 (54).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (55,56). 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 (55). Another analysis (56) showed that the relative risk of developing bladder cancer increased by 2.34-fold compared with a healthy control population. On the other hand, a re-analysis of SEER data with 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 (57).

Corresponding data on late toxicity has also been reported by the Memorial Sloan-Kettering Cancer Center group, from its experience in 1,571 patients with T1-T3 disease treated with either 3D-CRT or IMRT in doses of between 66 Gy and 81 Gy, with a median follow-up of 10 years (57). Both acute GI and GU toxicity appeared to predict for corresponding late toxicity. The overall rates of NCIC-CTC grade 2 or more GI toxicity was 5% with IMRT, compared with 13% with 3D-CRT. The incidence of grade 2 or more late GU toxicity was 20% in patients treated with 81 Gy, compared with 12% in patients treated with lower doses. The overall incidence of grade 3 GI toxicity was 1%, and grade 3 GU toxicity was 3%. These data suggest that IMRT can successfully protect against late GI toxicity, but, interestingly, with dose escalation, GU toxicity may become the dominant morbidity (58).

10.7 Immediate and delayed post-operative external irradiation after radical prostatectomy

Extracapsular invasion (pT3) is associated with a risk of local recurrence, which can be as high as 30% (59). In a multifactorial analysis, the predictors of biochemical relapse are:

- PSA level ($p = 0.005$);
- Gleason score of the surgical specimen ($p = 0.002$);
- positive surgical margins ($p < 0.001$) (60).

Three prospective randomised trials have assessed the role of immediate post-operative radiotherapy (adjuvant radiotherapy, ART). The EORTC study 22911, with a target sample size of 1,005 patients, compared

immediate post-operative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after retropubic RP. Immediate post-operative radiotherapy proved to be well tolerated, with a risk of grade 3-4 urinary toxicity of less than 3.5%, without significantly worsening the rate of incontinence and/or stricture of the anastomosis. The study concludes that immediate post-operative radiotherapy after surgery significantly improved 5-year clinical or biological survival: 72.2% versus 51.8% ($p < 0.0001$) (61). After re-evaluation by central pathological review, the highest impact (30%) was seen in patients with positive margins (R1), but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors (62,63).

The most suitable candidates for immediate radiation therapy might be those with multifocal positive surgical margins and a Gleason score > 7. The conclusions of the ARO trial 96-02 (n = 385) appear to support those of the EORTC study. After a median follow-up of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical progression-free survival of 72% versus 54%, respectively ($p = 0.0015$). However, of major interest and in contrast to other studies, patients were randomised after achieving an undetectable PSA 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 (63). Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomised 425 pT3 patients, showed that adjuvant radiation significantly improved metastasis-free survival, with a 10-year metastasis-free survival of 71% versus 61% (median prolongation of 1.8 years, $p = 0.016$) and a 10-year overall survival of 74% versus 66% (median: 1.9 years prolongation, $p = 0.023$) (65).

Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, two options can be offered within the framework of an informed consent:

- *either* immediate radiotherapy (ART) to the surgical bed (61,63,65,66) upon recovery of urinary function;
- *or* clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL (67,68).

Early salvage radiotherapy provides the possibility of cure to patients with an increasing or persisting PSA after RP. More than 60% of patients who are treated before the PSA level rises to more than 0.5 ng/mL will achieve an undetectable PSA level again (67,68), so providing patients with the chance of about 80% being progression-free 5 years later (68). A retrospective analysis based on 635 patients undergoing RP from 1982-2004, followed up through to December 2007, who experienced biochemical and/or local recurrence and received no salvage treatment (397) or salvage radiotherapy alone (160) within 2 years of biochemical recurrence, has shown that SRT was associated with a threefold increase in PCa-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage radiotherapy has also been effective in patients who have had a rapid PSA-doubling time (69). So far, the optimal SRT-dose has not been well defined. It should be at least 66 Gy. However, newer data suggest that higher total doses can achieve higher rates of biochemical control at 3 to 5 years (70,71).

The role of an additional ADT in combination with SRT remains controversial. The RTOG 9601 randomised, multi-centre phase III trial was designed to compare anti-androgen therapy (bicalutamide monotherapy 150 mg/dL) plus SRT (n = 387) to a placebo plus SRT alone (n = 383) in men with pT3 (n = 518)/ pT2 R1 (n = 252) N0 M0 prostate cancer with an elevated PSA after surgery. The median follow-up in surviving patients was 7.1 years. The addition of 24 months of peripheral and androgen blockade during and after RT significantly improved freedom from PSA progression (FFP) 57% versus 40% ($p < 0.0001$) and reduced the incidence of metastatic PCa (7.4% versus 12.6%, $p < 0.04$), without adding significantly to radiation toxicity. Longer follow-up is required to assess the significance of benefit in overall survival and to provide analysis of risk-stratified subsets (72).

These two approaches, together with the efficacy of neoadjuvant hormone therapy, are currently being compared in the UK MRC RADICALS randomised trial. The role of short-term hormone therapy in combination with radiotherapy is being investigated in the EORTC 22043 randomised trial.

10.8 Locally advanced PCa: T3-4 N0, M0

The incidence of locally advanced PCa has declined as a result of individual or mass screening. Pelvic lymph node irradiation is optional for N0 patients, but the results of radiotherapy alone are very poor (73). Because of the hormonal dependence of PCa (74), ADT has been combined with external irradiation with the aim of:

- reducing the risk of distant metastases by potentially sterilising micrometastases already present at the moment of diagnosis;
- decreasing the risk of non-sterilisation and/or local recurrence as a source of secondary metastases (73) through the effect of radiation-induced apoptosis (75,76). Numerous randomised trials have confirmed the value of long-term administration.

10.8.1 ***Neo-adjuvant and concomitant short-term androgen deprivation therapy***

The Trans-Tasman Radiation Oncology Group 96.01 trial included 818 men randomly assigned to RT alone (66 Gy/33 fractions) (77), 3 months of ADT with goserelin and flutamide starting 2 months before radiotherapy, or 6 months of ADT with the same regimen starting 5 months before RT. After a median follow-up of 10.6 years, those assigned to 3 months of ADT had a decreased cumulative incidence of PSA progression ($p = 0.003$), local progression ($p = 0.0005$), and event-free survival ($p = 0.0001$), compared with patients assigned to RT alone. Six months of ADT reduced PSA progression ($p < 0.0001$) and local progression ($p = 0.0001$) and led to a greater improvement in event-free survival ($p < 0.0001$). Furthermore, 6 months of ADT decreased distant progression ($p = 0.001$), cancer-specific mortality ($p = 0.0008$), and all-cause mortality ($p = 0.0008$) compared with RT alone (77).

10.8.2 ***Neo-adjuvant and concomitant hormonal therapy***

The 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 per cent of patients were diagnosed as T2, 70% as T3-4, and 91% as N0. The hormone treatment consisted of oral eulexine, 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 overall survival estimates were 43% for ADT + irradiation versus 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 biochemical failure (65% vs 80%; $p < 0.0001$), with the addition of ADT having no statistical impact on the risk of fatal cardiac events (78).

10.8.3 ***Concomitant and long-term adjuvant hormonal therapy***

The EORTC study 22863 recruited 415 patients diagnosed with T1-2 grade 3 WHO (World Health Organization) or T3-4 N0 M0 and any histological grade, and compared radiotherapy + adjuvant ADT with radiotherapy alone. The use of ADT was allowed in cases of relapse. A total of 82% of patients was 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 of 66 months, combination therapy compared with radiotherapy alone yielded significantly better survival (78% vs 62%, $p = 0.001$) (79). At a median follow-up of 9.1 years, the 10-year overall survival remained significantly higher at 58.1% vs 39.8% ($p < 0.0001$), as did clinical progression-free survival at 47.7% vs 22.7% ($p < 0.0001$). The 10-year cumulative incidence of PCa mortality was 11.1% versus 31% ($p < 0.0001$), and the 10-year cumulative incidence of cardiovascular mortality was 11.1% versus 8.2% ($p = 0.75$) (80).

10.8.4 ***Long-term adjuvant hormonal therapy***

The 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 bed 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 overall survival was significantly greater for the adjuvant arm, at 49% versus 39% ($p = 0.002$) (81).

The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study included 1205 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 randomised to lifelong ADT (bilateral orchidectomy or LHRH agonist), with or without RT (65-70 Gy to prostate +/- 45 Gy to pelvic lymph nodes). With a median follow-up of 6 years, the addition of RT to ADT reduced the risk of death from any cause by 23% ($p = 0.03$) and the risk of death due to PCa by 46% ($p = 0.0001$) (82,83).

The GETUG trial included 273 patients with locally advanced PCa T3-4 or pT3 N0 M0, who were randomly assigned to lifelong ADT using an LHRH agonist (leuproreline), with or without RT (70 Gy to the prostate plus 48+/- 2Gy to pelvic lymph nodes). With a median follow-up of 67 months, there was a significant improvement in 5-year disease free survival ($p < 0.001$), metastases disease-free survival ($p < 0.018$) and loco-regional progression-free survival ($p < 0.0002$), but the effect on overall survival was not reported (84).

The SPCG-7/SFUO-3 randomised study (85) compared hormonal treatment alone (i.e. 3 months of continuous androgen blockade followed by continuous flutamide treatment (n = 439) with the same treatment

combined with radiotherapy (n = 436). After a median follow-up of 7.6 years, the 10-year cumulative incidence for prostate cancer-specific mortality was, respectively, 23.9% and 11.9% (95% CI: 4.9-19.1), and the 10-year cumulative incidence for overall mortality was 39.4% in the hormonal treatment-only group, and 29.6% in the hormonal + RT group (95% CI: 0.8-18%).

10.8.5 ***Neo-adjuvant, concomitant and long-term adjuvant hormonal therapy***

The RTOG 9202 trial closed in 1995 after accruing 1554 patients. Statistically significant improvements were observed in actuarial biochemical freedom from disease control, distant metastatic failure, local control, and disease-free survival in patients receiving long-term ADT (before, during, and 2 years after radiotherapy), compared with short-term ADT (2 months before and during radiotherapy). With a median follow-up of 11.27 years of all survival patients, the long-term ADT arm showed significant improvement over the short-term ADT arm in all efficacy endpoints, except 10-year overall survival, which was 51.6% versus 53.9% (p = 0.36), respectively. In a subset of patients that was not part of the original study design, with Gleason score 8-10 tumours, the long-term ADT arm showed significantly better overall survival after 10 years than the short-term ADT arm, with 45% versus 32% (p = 0.006) (86).

10.8.6 ***Short-term or long-term adjuvant hormonal treatment***

Following the EORTC trial 22863, the EORTC equivalence trial 22961 was set up to test whether similar survival could be achieved in patients who underwent irradiation (to 70 Gy) and 6 months of combined ADT without further ADT, i.e. short-term ADT arm, compared with patients with 2.5 years of further treatment with luteinising hormone-releasing hormone analogue, i.e. long-term ADT arm. Eligible patients had T1c-2b N1-2 or pN1-2, or T2c-4 N0-2 (UICC 1992) M0 PCa with PSA < 150 ng/mL.

Non-inferior survival was defined as a mortality hazard ratio (HR) = 1.35 for short-term ADT versus long-term ADT. A total of 970 patients were randomised. With a 5.2-year median follow-up, the 5-year overall survival rate was 85.3% on long-term ADT, and 80.6% on short-term ADT (HR = 1.43; 96.4% CI; 1.04-1.98), and failed to prove non-inferiority (87).

10.8.7 ***Dose escalation with hormonal therapy***

Zelefsky et al. (88) reported a retrospective analysis of 2251 patients with T1-3 N0-X M0 PCa comprised 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 (3D-CRT) or IMRT were given to the prostate and seminal vesicles only. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered within the last 10 years by employing image-guided IMRT. Androgen deprivation therapy by complete androgen blockade with a luteinizing hormone releasing hormone (LHRH) agonist plus oral anti-androgen was given at the discretion of the treating physician to 1,249 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 prior to RT and continued during RT. The end-points were 10-year biochemical disease-free survival and distant metastases-free survival. With an 8-year median follow-up, the 10-year biochemical disease-free survival of each risk group was significantly improved by dose escalation: 84% (> 75.6 Gy) versus 70% for low-risk patients (p = 0.04), 76% (> 81 Gy) vs 57% for intermediate- risk patients (p = 0.0001), and 55% (> 81 Gy) versus 41% for high-risk patients (p = 0.0001). The 6-month ADT also influenced the biochemical disease-free survival of intermediate-risk and high-risk patients, with 55% versus 36% for high-risk patients (p < 0.0001). In multivariate analysis, a dose greater than 81 Gy (p = 0.027) and ADT (p = 0.052) were significant predictors for distant metastases-free survival, but none of these parameters influenced PCa mortality or overall survival. There were very low rates of grade 3-4 acute or late toxicity (89).

10.9 Very high-risk PCa: c or pN1, M0

Patients with a pelvic lymph node involvement lower than the iliac regional nodes, younger than 80 years old, with a WHO performance status 0-1, and no severe co-morbidity may be candidates for EBRT plus immediate long-term hormonal manipulation. The RTOG 85-31 randomised phase III trial has shown, with a median follow-up of 6.5 years, that 95 patients out of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better 5-year (54%) and 9-year (10%) progression-free survival (PSA < 1.5 ng/mL) versus 33% and 4%, respectively, with radiation alone and hormonal manipulation instituted at the time of relapse (p < 0.0001). Multivariate analysis showed that this combination had a statistically significant impact on overall survival, disease-specific failure, metastatic failure and biochemical control (90). The GETUG 12 trial has addressed the impact of neoadjuvant chemotherapy with docetaxel on progression-free survival in a cohort of 413 high-risk patients, defined as having one or more of the following criteria: T3-4, Gleason score ≥ 8, PSA ≥ 20 ng/mL, pN+. Patients were randomly assigned to either goserelin, 10.8 mg every 3 months for 3 years, plus 4 cycles of docetaxel, 70 mg/m^2 every 3 weeks plus estramustine 10 mg/kg/dL on days 1 to 5 (arm 1), or

goserelin alone (arm 2). Local therapy was administered at 3 months and consisted of RT in 358 patients (87%). Toxicity included grade 3-4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death and no secondary leukaemia. With a median follow-up of 4.6 years, the 4-year progression-free survival was 85% in arm 1 versus 81% in arm 2 (p = 0.26), but the data need to mature (91).

10.10 Guidelines summary for definitive radiation therapy

	LE
In localised prostate cancer T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended, even for young patients who refuse surgical intervention.	2
For high-risk patients, long-term ADT prior to and during radiotherapy is recommended because it results in increased overall survival.	2a
In patients with cT1-T2a, Gleason score < 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.	2b
In patients with pathological tumour stage T3 N0 M0, immediate post-operative external irradiation after RP may improve overall survival and biochemical and clinical disease-free survival with the highest impact in cases of positive margins.	1
In patients with pathological tumour stage T2-3N0M0, salvage irradiation is indicated in case of persisting PSA or biochemical failure, but before the PSA level rises above 0.5 ng/mL.	3
In 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 because it improves overall survival.	1
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 because it may favourably influence overall survival.	1b
In very high-risk prostate cancer, c-pN1 M0 with no severe co-morbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended because it will improve overall survival, disease-specific failure, metastatic failure and biochemical control.	2b

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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 consecutive ischaemia;
- apoptosis (1-4).

Freezing of the prostate is ensured by placement of 12-15 17G-cryoneedles under transrectal ultrasound (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. Prostate-specific antigen (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 recent 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 recent review mentioned above (12), HIFU showed PFS (based on PSA ± biopsy data) of 63-87% (projected 3- to 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% (27.2-57.89%) 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	**GR**
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.	**C**
Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	**C**

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12. HORMONAL THERAPY

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 advanced PCa management. 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. These two methods of androgen deprivation (surgical or medical castration and the use of anti-androgens) 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 (5). This has led to a revisiting of the current definition of castration, with some authors suggesting < 20 ng/dL as a more appropriate level.

12.2.2 ***Bilateral orchiectomy***

Bilateral orchiectomy, either total or by means of a subcapsular technique (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. The use of bilateral orchiectomy has declined in recent years, probably because of stage migration towards earlier disease and the introduction of equally effective pharmacological modalities of castration.

12.2.3 ***LHRH agonists***

Long-acting LHRH agonists (busereline, gosereline, leuproreline, triptoreline) 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-, or 6-monthly basis. Initially, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release. This then elevates testosterone production (known as the 'testosterone surge' or 'flare-up' phenomenon), which begins about 2-3 days after the first injection and lasts for about the first week of therapy.

12.2.3.1 Achievement of castration levels

Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors. This then suppresses pituitary LH and FSH secretion and testosterone production, so that testosterone levels decrease to castration levels usually within 2-4 weeks (7). However, about 10% of patients treated with LHRH agonists fail to achieve castration levels (8). 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 showed that LHRH agonists have comparable efficacy to orchiectomy and DES (9) (LE: 1a). This finding raises a 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 (9) (LE: 3).

12.2.3.2 Flare-up phenomenon

Today, LHRH agonists have become the 'standard of care' in hormonal therapy because they avoid the physical and psychological discomfort associated with orchiectomy and lack the potential cardiotoxicity associated with DES. However, the main concerns associated with the administration of LHRH agonists 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 review (10) 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. The review also identified that patients at risk of clinical flare are usually patients with high-volume, symptomatic, bony disease, which account for only 4-10% of M1 patients.

Anti-androgen treatment

Concomitant therapy with an anti-androgen decreases the incidence of clinical relapse (i.e. clinical flare), but does not completely remove the possibility of its occurrence. Anti-androgens should be started on the same day as the depot LHRH injection and should be continued for a 2-week period. However, other strategies for immediately ablating testosterone levels, such as bilateral orchiectomy or LHRH-antagonists, must be used in patients with impending spinal cord compression. Except in this patient group, the clinical impact of the flare-up observation is unknown.

Long-term use of LHRH agonists

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 that a mini-flare is associated with a negative impact on overall survival (*see* Section 17.4).

12.2.4 ***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 seemingly more desirable mechanism of action has made LHRH antagonists very attractive. 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.

12.2.4.1 Abarelix

Two published phase III randomised multicentre trials compared the LHRH antagonist, abarelix, with the LHRH agonist, leuprorelin acetate (11), and with CAB (12), 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. The biochemical 'flare up' phenomenon was not reported in the abarelix arm and the overall incidence of severe adverse events (including allergic reactions) was similar across all treatment groups. Data on survival end-points and long-term safety are not yet available.

The US Food and Drug Administration has recently licensed the clinical use of abarelix, but only in metastatic and symptomatic PCa, for which no other treatment option is available. However, based on prolonged analysis, the FDA have issued a warning about allergic reactions with the long-term use of abarelix, which has resulted in suspension of its further development.

12.2.4.2 Degarelix

Degarelix is another LHRH antagonist that has shown promising preliminary results in a monthly subcutaneous formulation. Following phase II trials, a large, randomised, non-inferiority, dose-finding study (n = 610) compared two degarelix dosages with 7.5 mg monthly leuprorelin injections (13). The study showed that 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 with degarelix, which was associated with a quicker decline in PSA as quickly as day 14. No allergic reaction was observed. The main criterion (suppression of testosterone $\leq$ 0.5 ng/mL at all monthly measurements) was similar in the three treatment groups at 1 year. 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 leuprorelin (14).

12.2.4.3 Conclusions

Overall, this new family of agents seems appealing, but their advantages over LHRH agonists are far from proven. Further trials are needed to confirm the preliminary observed increased efficacy compared to leuprorelin. The use of LHRH antagonists is limited by a monthly formulation, compared with 3-month and 6-month depot formulations for the available LHRH analogues. Suppression of the initial flare-up with monotherapy is only clinically relevant in a few symptomatic metastatic patients.

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) (15).

12.3.1 ***Diethylstilboesterol (DES)***

Diesthylstilboesterol (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, as it was the dosage used in CAB. 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. Because of these concerns and the introduction of LHRH agonists and anti-androgens, the use of DES was greatly reduced. There has been renewed interest in using oestrogens (9).

12.3.2 ***Renewed interest in oestrogens***

There are three main reasons for a renewed interest in using oestrogens to treat PCa:

1. LHRH agonists have a number of deleterious side-effects and their long-term widespread use is costly, while oestrogens suppress testosterone levels and do not seem to lead to bone loss and cognitive decline (16) (LE: 3).
2. In phase II trials with patients diagnosed with hormone-refractory PCa (HRPC), 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 (15).

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 set up a prospective randomised trial of more than 900 men with metastatic PCa, which compared a parenteral oestrogen (polyoestradiol phosphate) with CAB (orchiectomy, or an LHRH agonist + flutamide). The trial found no significant difference in disease-specific survival and OS between the treatment groups, and no significant increase in cardiovascular mortality in the oestrogen-treated group. However, in the oestrogen-treated group, there was a significantly higher incidence of non-fatal adverse cardiovascular events, particularly ischaemic and heart decompensation events (17).

In addition, thromboembolic complications have been observed in recent (though small) phase II trials of patients with advanced PCa or CRPC. The trials evaluated 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 (18,19).

12.3.4 ***Conclusions***

Diethylstilboesterol is one of the classic forms of hormonal therapy. Its efficacy was demonstrated many years ago and was recently re-confirmed in a meta-analysis as comparable to that of bilateral orchiectomy (9) (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 Anti-androgens

Anti-androgens compete with testosterone and DHT at the receptor level in the prostate cell nucleus, thus promoting apoptosis and inhibiting PCa growth (20).

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 due to central inhibition of the pituitary gland. As a consequence, non-steroidal antiandrogens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

12.4.1 ***Steroidal anti-androgens***

These compounds are synthetic derivatives of hydroxyprogesterone. In addition to peripherally blocking androgen receptors, they have progestational properties and inhibit the release of gonadotrophins (LH and FSH) and suppress adrenal activity. At high doses, megestrol acetate is cytotoxic. 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.

12.4.1.1 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, with many questions about its use unanswered, e.g. the optimal dose, or unclear, e.g. comparison with standard forms of castration, surgical or with an agonist.

Comparison of CPA with medical castration

There has been only one randomised trial (21) comparing CPA with standard hormonal therapy, i.e. medical castration. Patients in arm A (no contraindications to DES) were randomly assigned to CPA, goserelin or DES, while patients in arm B (contraindications to DES) were assigned to CPA or goserelin. In arm A, treatment with CPA was associated with a significantly poorer median OS than goserelin only; adjusting for baseline characteristics did not account for this difference. 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.

Dosage regimen of CPA
Because there have been no dose-finding studies of CPA monotherapy, the most effective dose 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 (22).

Comparative study of CPA with flutamide
The only comparative study on anti-androgens as monotherapy was recently published by the European Organisation for Research and Treatment of Cancer (EORTC). The final analysis of Protocol 30892 (a randomised trial of 310 patients comparing CPA with flutamide in metastatic PCa) showed no difference in cancer-specific survival and OS at a median follow-up of 8.6 years, although the study was underpowered (23) (LE: 1b).

12.4.1.2 Megestrol acetate and medroxyprogesterone acetate
Very limited information is available on these two compounds. Early studies with megestrol acetate demonstrated a symptomatic and partially beneficial clinical response, both in previously untreated metastatic PCa (24,25) and less so in CRPC (26). No apparent dose-response correlation was found (27). The overall poor efficacy has prevented megestrol acetate and medroxyprogesterone acetate from being recommended for either primary- or second-line hormonal therapy.

The only prospective randomised trial evaluating medroxyprogesterone acetate as primary therapy in advanced (M0-1) PCa is the EORTC 30761 study (28), in which 236 patients were given CPA, DES or medroxyprogesterone acetate. There was no difference in cancer-specific survival and OS between CPA and DES. However, medroxyprogesterone acetate resulted in a less favourable course, with a shorter survival time and time to progression than CPA or DES.

12.4.2 ***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 (29). 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 (30). All three agents share a common liver toxicity and liver enzymes must be monitored regularly.

12.4.2.1 Nilutamide
There are no comparative trials of nilutamide monotherapy with castration or with other anti-androgens.

A large randomised controlled trial in 457 patients with M1 PCa showed a significant benefit for cancer-specific survival and OS with orchiectomy + nilutamide, 300 mg/day, versus orchiectomy + placebo (31). Nilutamide has recently shown encouraging results as a second-line hormonal therapy in HRPC (32,33).

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.

12.4.2.2 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 to maintain therapeutic serum levels. The recommended daily dosage is 750 mg (22).

Early phase II trials demonstrated the efficacy of flutamide in advanced PCa, even though the reported response rates cannot be correlated with currently recommended end-points. The main advantage shown in these small single-arm studies was the preservation of sexual function, which was maintained in up to 80% of patients with no pre-treatment erectile dysfunction. This rate has not been confirmed in the above-mentioned EORTC trial 30892 (23), in which as few as 20% of men treated with flutamide maintained sexual activity for up to 7 years.

Although several phase III studies have been conducted, the results are often difficult to evaluate because of several drawbacks, such as the use of non-standard combinations, short-term follow-up and underpowering. Of these studies, survival data for advanced PCa has been reported in only one published phase III randomised trial comparing flutamide monotherapy with CAB (34).

No significant difference in OS for flutamide or castration in patients with a PSA < 100 ng/mL (34). At a higher PSA, flutamide was inferior. However, both trials were underpowered. Results are eagerly awaited from an ongoing Swedish study, which randomised 700 patients with M1 PCa to flutamide, 250 mg three times daily, or CAB (29). The non-pharmacological side-effects of flutamide are diarrhoea and hepatotoxicity (occasionally fatal).

12.4.2.3 Bicalutamide

Dose-finding studies of bicalutamide

Early studies with bicalutamide monotherapy used the 50 mg/day dosage licensed for use in CAB. Although this dosage provided clinical benefits, it resulted in a poorer OS than with castration (median difference 97 days) (35). Subsequent dose-finding studies established that bicalutamide, 150 mg once daily, achieved a similar PSA response to castration, while maintaining a good tolerability profile (36). Accordingly, the 150 mg dosage was chosen for further evaluation as both primary and adjuvant monotherapy.

Primary monotherapy with bicalutamide

Bicalutamide, 150 mg/day, as first-line monotherapy has been compared to medical or surgical castration in two large prospective randomised trials with identical study designs, including a total of 1,435 patients with locally advanced M0 or M1 PCa (37). A pooled analysis showed:

- In M1 patients, an improvement in OS with castration, although the difference in median survival between the groups was only 6 weeks (37);
- In M0 patients (n = 480), no significant difference was noted in OS (38) 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 randomised trials, high-dose bicalutamide was compared with CAB. In the first trial (251 patients with predominantly M1 stage), there was no apparent difference in OS (39). In the second trial (220 patients with M0 and M1 stage), there was no difference in OS for well-differentiated tumours or tumours that were only moderately well-differentiated (40) (LE: 1b). However, both studies were underpowered, and the first one has not yet been fully published.

Adjuvant therapy with bicalutamide

In the adjuvant setting, the ongoing Early Prostate Cancer Programme (EPCP) is a study comprising three different clinical trials (known as Trials 23, 24 and 25) of similar design. The programme included 8,113 patients worldwide and evaluated the efficacy and tolerability of high-dose (150 mg/day) bicalutamide versus placebo, given in addition to standard primary care (i.e. radical prostatectomy, radiotherapy or watchful waiting) in either localised PCa (T1-2, N0-X) or locally advanced PCa (T3-4, any N, or any T N+). The first combined analysis of the programme showed that, after a median follow-up of 3 years, adjuvant bicalutamide reduced the risk of objective disease progression by 42% compared with standard care alone (41).

After a median follow-up of 5.4 years, the positive effects of bicalutamide were obvious in patients with locally advanced disease (stage M0). Bicalutamide significantly improved PFS, irrespective of standard care. However, survival appeared to be reduced in patients with localised disease treated with bicalutamide versus those given placebo (42). After a median follow-up of 7.4 years, there appeared to be no benefit to PFS from the addition of bicalutamide to standard care in localised PCa, with a trend towards decreased survival in patients otherwise undergoing watchful waiting (WW) (hazard ratio [HR], 1.16; 95% CI: 0.99-1.37; p = 0.07).

The same overall results were observed in the most recent analysis of the bicalutamide treatment arm of the EPCP 24 trial (43). Bicalutamide significantly improved OS in patients receiving radiotherapy (HR, 0.65; 95% CI: 0.44-0.95; p = 0.03), mainly due to a lower risk of PCa-related deaths. Bicalutamide produced a trend towards improved OS in patients with locally advanced disease otherwise undergoing WW (HR, 0.81; 95% CI:0.66-1.01; p = 0.06). No survival difference was evident in the subgroup undergoing radical prostatectomy (42).

Even though the EPCP is a combination of three trials and among the largest conducted in PCa patients, it is difficult to draw clear conclusions because of the following problems with the protocols:

- The three trials grouped for analysis were different in terms of patients; 80% of patients underwent prostatectomy in Trial 23 versus 13% in Trial 25. In addition, treatment duration was 2 years in Trial 23, but treatment was prolonged until progression in Trials 24 and 25.
- The OS benefit claimed with radiotherapy is mainly driven by a respiratory or cardiovascular improvement, and not by a cancer-specific survival benefit, which is different to other trials with LHRH agonists.
- Furthermore, the EPCP trials are underpowered for locally advanced patients, compared with oriented trials such as the Bolla (44) or Pilepich (45) trials.

- Direct protocol analysis revealed quite different results, such as those from EPCP Trial 23 (80% prostatectomy, 19% radiotherapy) (46). At a median 7.7 years of follow-up, no PFS benefit was observed (HR, 1.00; 95% CI: 0.84-1.19; p = 0.991). Likewise, OS did not differ. Even after stratifying for disease stage, no PFS benefit was apparent.
- The OS benefit must be balanced by the very prolonged (mainly permanent) use of bicalutamide combined with radiotherapy in contrast to the more limited use of agonists (6 months to 3 years).
- Although a QoL benefit has been claimed, in fact a QoL benefit cannot be demonstrated because none of the EPCP trials used a systematic, validated QoL questionnaire. The only available data were derived from a specific questionnaire and a limited population. The observed benefit was only significant for physical capacity and sexual interest (not function!). For all other QoL items (emotional well-being, vitality, social function, pain, activity limitation and bed disability), there was no difference compared with castration (38). The breast problems related to bicalutamide are also important, as they can lead to a 16.4% treatment cessation (47).

The lack of data means that many questions are still debatable with bicalutamide, such as the practical management after progression under bicalutamide. Furthermore, the clear trend (even if not statistically significant) towards a decreased OS in localised disease otherwise treated with WW is a clear argument against the use of bicalutamide in such situations (42). The mechanisms involved remain unclear.

Conclusions for the use of bicalutamide in primary and adjuvant therapy

High-dose bicalutamide has emerged as an alternative to castration for patients with locally advanced (M0) if PFS is the target, and in highly selected, well-informed cases of M1 PCa with a low PSA.
Bicalutamide monotherapy should be avoided in patients with localised PCa.
The expected benefit of bicalutamide for QoL compared with castration is far from being proven.
The survival benefit observed with adjuvant use after radiotherapy in locally advanced PCa must be considered with caution, as the EPCP trials do not have the clear power of trials conducted with LHRH agonists. The lack of any direct comparison between both bicalutamide and LHRH agonists in combination with radiotherapy leads to a major limitation of any guidelines, which should therefore be based on unquestionable trials, which are mainly those with analogues

Side-effects of bicalutamide

Non-pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens (49-51), prophylactic radiotherapy (52), or treatment with surgical mastectomy or radiotherapy (53). However, bicalutamide clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists (54,55).

12.5 Combination therapies

*12.5.1 **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 these adrenal androgens can be blocked by the addition of 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 (castration through LHRH analogues) have produced contrasting results (56). 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 (57-60) (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 antiandrogens (62) 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 orchiectomy alone.

*12.5.2 **Minimal androgen blockade (or peripheral androgen blockade)***

Minimal androgen blockade is produced by combining finasteride with a non-steroidal anti-androgen. Finasteride reduces intraprostatic levels of DHT by inhibiting 5-α-reductase, while the anti-androgen competes with the binding of the residual DHT to its receptor. This enables testosterone levels to be maintained within normal ranges to ensure acceptable sexual function and a reasonable QoL.

Several phase II trials (63-67) have evaluated the association of finasteride and flutamide, either given together or sequentially, using the PSA response rate in patients with advanced or biochemically recurrent PCa. Notwithstanding the small sample and short follow-up, nearly all patients experienced a substantial decline in PSA (by up to 96% compared with the baseline level at entry). In a long-term follow-up of one study, stronger end-points were reported, including castration-free survival (median: 37 months), androgen independent PCa-free survival (median: 48.6 months) and OS (65% at 5 years). These results indicated that combination therapy was able to induce an overall period of hormone-responsive disease exceeding 4 years (68). In all these trials, sexual function was preserved in 55-86% of men studied.

The preliminary data make minimal androgen blockade a very attractive option in the management of patients for whom QoL is the main concern. However, while awaiting the results of follow-up and larger controlled trials, this treatment should be considered investigational.

12.5.3 ***Intermittent versus continuous ADT***

For reasons beginning to be clarified, 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, characterised by an 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 (69). 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 Shionoggi model), which may be significantly different from 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.

Phase II results

A detailed systematic review was recently published (70), with no other trials published since this review. According to the review, several phase II trials demonstrated the feasibility of IAB in metastatic or biochemically recurrent disease (70). Both PSA response rates and symptom improvement were similar to those seen with CAB. However, these trials included very heterogeneous patients and used different PSA thresholds for decisions regarding castration. This should be borne in mind when considering the main findings.

- Most patients were treated with an LHRH agonist, with or without an anti-androgen.
- The cycle lengths were quite stable regarding the off-treatment periods.
- Testosterone recovery, when tested, was frequent during the first cycle, but tended to decrease during subsequent cycles.
- Early occurrence of early refractory status was quite uncommon.
- Overall tolerability was acceptable, and sometimes there was a QoL benefit, especially for sexual function.

These findings suggest a potential benefit for IAD. However, randomised trials are required to clarify the potential survival benefit suggested by animal models.

Randomised controlled trials

Overall, eight randomised trials are underway, only some of which have published findings. Most of the trials included a mixed patient population of both locally advanced and metastatic disease. Only three trials included only metastatic patients, and two trials only relapsing patients. The two largest trials each contained more than 1,300 patients, with one trial focused only on metastatic patients (SWOG 9346) and the other on relapsing patients after radiotherapy (SWOG PR7). Few fully published trials are available, some are pending. But, all available results are similar so far, allowing the inclusion of abstract-only references. A short summary of the most important published findings from these trials follows.

- The South West Oncology Group (SWOG) trial 9346 randomised 1,134 men with stage D2 PCa to intermittent and continuous ADT after 7 months' induction ADT with PSA reduction < 4 ng/mL. A very preliminary analysis has identified no significant differences with regard to survival between treatment groups (71). A PSA reduction to < 0.2 ng/mL, < 4 ng/mL and > 4 ng/mL was identified as a significant prognostic factor with regard to survival, achieving 13 months, 44 months and 75 months, respectively. In a similar patient population and using a quite similar protocol, no difference was observed in OS or in PFS between IAD and CAB in 173 randomised patients (72), with a mean follow-up of 47 months. No QoL benefit was observed in any treatment arm. The same lack of difference in OS was seen with CPA in another randomized study of 366 patients (73), after a mean follow-up of 66 months.

- The largest trial available so far (still unpublished) has been presented at several meetings (74). A total of 1,386 patients relapsing after radiotherapy, given as either primary treatment or for relapsing patients after surgery, were randomized to continuous ADT or intermittent ADT. Continuous treatment was for a fixed 8-month period. Intermittent ADT was stopped when PSA < 4 ng/mL and resumed when above 10 ng/mL. After a median 7 years of follow-up, the median OS was 9.1 years in the continuous arm and 8.8 years in the intermittent arm (HR: 1.02:; 95% CI= 0.86-1.21).
- In other studies (75,76) of mixed populations of locally advanced and metastatic PCa, there has also been no evidence found of decreased survival using IAD. The larger study (76) included 478 patients with either M1 disease (40%) or N+ (N1-3) disease. In this study, 335 patients were randomised to IAD after 6 months of CAB if the PSA decreased to < 4 ng/mL or a decrease of > 90% was observed. The mean initial level of PSA was 158 ng/mL in the IAD-treated group and 139 ng/mL in the CAB-treated group. In the IAD group, treatment was resumed if the PSA rose > 10 ng/mL and stopped when it decreased < 4 ng/mL. However, after a median follow-up of 50.5 months, no significant difference was observed in the median PFS (16.6 months in the IAD group vs 11.5 months in the CAB group, p = 0.17) in either the total study population or in the N+ or M1 subgroup populations. In the IAD arm, 88% of patients were off-treatment for more than 50% of the time and normalised their testosterone in a mean of 70 days after stopping treatment.
- To date, the largest fully published trial (n = 766) has been carried out by the South European Uro-Oncological Group (SEUG) (77). Patients followed an induction regimen of 3 months, in which CPA was given for 2 weeks followed by monthly LHRH + CPA. Patients with a PSA < 4 ng/mL or a PSA decrease > 80% were randomised to IAD or CAB. In the IAD-treated group, treatment was resumed, if the PSA level rose to ≥ 10 ng/mL for symptomatic patients. For patients whose PSA level dropped to < 80% of the initial value, therapy was restarted when the PSA level rose to ≥ 20% above the nadir. 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). Metastatic status and PSA at randomisation 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 (28% sexually active vs 10% at 15 months after randomisation, respectively). After follow-up for a median of 7 years, it should be highlighted that both the IAD treatment arm and the continuous treatment arm showed similar non-significant specific death increases. This finding suggests that, even if continuous treatment provides a specific survival difference compared to IAD, the survival difference is completely counterbalanced by the increased specific toxicity of continuous ADT, which therefore results in a lack of difference in OS survival, the increasing of which remains the main objective.

Alternative IAD regimen

Recently, a published randomised trial (n = 129) suggested an alternative IAD regimen, which alternated fixed 6-month periods of CAB treatment and surveillance (78). The PSA response was not used to guide treatment in the heterogeneous study population. After a mean follow-up of 44.8 months, no difference was observed in OS, cancer-specific survival or PFS. The QoL also showed no difference between the two groups, except that painkillers were required more often in the IAD arm, and the ability to get and maintain an erection was better in the IAD arm.

Other benefits of IAD

Intermittent androgen deprivation has not been shown to be associated with prolonged hormone-sensitive status or OS increase. This modality is well accepted by patients, urologists and oncologists. Although the QoL benefit is less than expected or absent, except in two studies (73,74), IAD is better tolerated and sometimes benefits sexual functioning (76,77). Other possible long-term benefits, which are not clearly proven, include bone protection (79,80) and/or a protective effect against metabolic syndrome. Testosterone recovery is seen in most studies (70), leading to an intermittent castration (not just an intermittent treatment delivery).

Optimal threshold for stopping or resuming ADT

The optimal thresholds at which ADT must be stopped or resumed are empirical (70). The best candidates for IAD have still not been completely defined (70,80), but are probably patients with locally advanced or relapsing disease, provided a perfect response is obtained (*see below*). Nevertheless, several points are clear (70,81):

- 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 randomised trials.

- 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 is the follow-up). The PSA level should be measured by the same laboratory to ensure standardization of testing.
- Treatment is resumed when the patient reaches either a clinical progression, or a PSA value above a predetermined, empirically fixed threshold. This is usually 4-10 ng/mL in non-metastatic situations or 10-15 ng/mL in metastatic patients (80).
- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same rules until the first sign is seen of hormone-refractory status.

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).

Increased duration of off-treatment periods in IAD

There have recent attempts to increase the duration of off-treatment periods in IAD. Although hormonal manipulation using finasteride (82) has been suggested, finasteride has never been tested in randomised trials and its use in PCa has been recently questioned (83). However, there have been trials of non-hormonal compounds, including a COX-2 inhibitor (84) and anti-angiogenic drugs (85). In a study of the anti-angiogenic drug, thalidomide, 159 patients, who had relapsed after local treatment, were randomized to an LHRH antagonist for 6 months, followed by placebo or thalidomide, 200 mg daily. When PSA progression occurred, a crossover was done using the same regimen. A non-significant difference was observed in the time-to-PSA progression during the first treatment round (15 vs 9.6 months). However, after crossover, the time-to-PSA progression showed a highly significant difference (17.1 vs 6.6 months, p = 0.0002) in favour of the thalidomide treatment arm. This finding was not linked to any hormonal effect. This observation provides proof of principle and warrants further larger studies, particularly because thalidomide required dose reduction in 47% of patients due to intolerability.

12.5.4 ***Immediate versus deferred ADT***

There is still controversy over the most appropriate time to introduce hormonal therapy in patients with advanced PCa. Should ADT be given immediately upon diagnosis in locally advanced and asymptomatic metastatic disease or deferred until there are signs and symptoms of clinical progression? (This has already been partly discussed in Section 8.3.)

The controversy over whether only immediate treatment with ADT has a positive effect on survival and QoL has arisen because of the lack of properly conducted randomised controlled trials. Many trials are methodologically flawed because of small size and underpowering, heterogeneity of patient enrolment with advanced PCa (i.e. locally advanced, nodal and metastatic stages of disease), and variation in the hormonal treatments given and in the follow-up schedules and modalities used.

Bearing these limitations in mind, the evidence for immediate versus deferred ADT is provided by four systematic reviews of the literature (including a meta-analysis). A report by the Agency for Health Care Policy and Research (AHCPR) indicated a possible survival advantage for early ADT in single studies where hormonal treatment was the primary therapy (86). Furthermore, androgen suppression was shown to be the most cost-effective therapy if initiated after patients had experienced symptoms from metastatic disease (87).

The Cochrane Library review extracted four, good-quality, randomised, controlled trials, i.e. namely VACURG I and II studies, the MRC trial and the Eastern Cooperative Oncology Group (ECOG) 7887 study, which were all conducted in the pre-PSA era. The studies included patients with advanced PCa, who received early versus deferred ADT, either as primary therapy or adjuvant to radical prostatectomy (but not to radiotherapy). Early androgen suppression significantly reduced disease progression and complication rates due to progression itself. However, it did not improve cancer-specific survival and provided a relatively small benefit in OS, with an absolute risk reduction of 5.5% after 10 years (88). Finally, a systematic review was published last year, highlighting again the benefit of immediate versus deferred ADT in term of overall survival (+ 10%) and specific survival (+ 20%) (89). In the PSA era, the EORTC 30891 study (90) has produced the same results, namely a small benefit in OS, but no cancer-specific survival benefit. 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 on when to start hormonal therapy in advanced asymptomatic PCa, until data becomes available from studies using modern diagnostic and biochemical tests and standardised follow-up schedules (48).

Based on meta-analyses published, treatment appears to be most cost-effective when started after the onset of symptoms. Based on exploratory analysis, treatment with anti-androgen monotherapy does not lead to a survival benefit in men with localised PCa managed with non-definitive therapy, and the impact is still questionable after external beam therapy. This was explored in detail above with regard to the EPCP trials (*see Section* 12.4.2.3).

For asymptomatic patients with locally or regionally advanced PCa who undergo radiotherapy, several randomised controlled trials have produced good evidence to show that concomitant and/or adjuvant hormonal therapy provides longer time-to-disease progression and/or longer OS than radiotherapy alone followed by androgen suppression at progression (*see Section* 12.8) (LE: 1b).

The detailed discussion on immediate or deferred ADT combined with surgery or radiation therapy is discussed in Section 8.3.

12.6 Indications for hormonal therapy

Table 18 lists the indications for hormonal therapy.

Table 18: Indications for hormonal therapy

Hormonal therapy Indications for castration	**Benefits**	**LE**
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	1b
	Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence.	1
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b
	An active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective.	3
N+	Immediate castration to prolong PFS and even OS.	1b
	Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy.	3
Locally advanced M0	Immediate castration to improve cancer-free survival.	1b
- Locally advanced disease treated with radiotherapy	High-risk d'Amico: combined and prolonged ADT.	1a
	Intermediate-risk d'Amico: - If low dose (< 75 Gy) radiotherapy: 6 months of ADT; - If high dose (> 75 Gy) radiotherapy: ADT questionable.	1b 2a
- Locally advanced disease treated with radical prostatectomy	No benefit in term of survival either as neoadjuvant or adjuvant treatment.	3
- Locally advanced asymptomatic unfit for local definitive treatment	Limited OS improvement not related to a CSS benefit (90).	1a
	CAB compared compared to castration monotherapy: survival benefit (<5% after 5 years of follow-up).	1a
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).	1b

Non-steroidal anti-androgen monotherapy	Primary monotherapy as an alternative to castration in patients with locally advanced PCa (T3-4, any N, or any T).	2a
	No place in localised disease as a single-treatment modality.	
	Combined with radiotherapy: no clear recommendation is possible at the present time.	
	Combined with radical prostatectomy: no place so far in an adjuvant setting.	

12.7 Contraindications for various therapies

Table 19 lists the contraindications for various therapies.

Table 19: Contraindications for various therapies.

Therapy	Contraindications
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration.
Oestrogens	Known cardiovascular disease.
LHRH agonists alone	Patients with metastatic disease at high risk for clinical 'flare up' phenomenon.
Anti-androgens	Localised PCa as primary therapy.

12.8 Outcome

Outcome depends on the stage and grade of disease at diagnosis.

In M1 cases, the median OS ranges between 28 and 53 months (9). Only 7% of patients with metastatic cancer treated with hormonal therapy have been reported alive at 10 years or longer (93). Survival is likely to depend on the PSA level at diagnosis, the Gleason score, the volume of metastatic disease, and the presence of bony symptoms.

In locally advanced M0 patients, the median OS is frequently reported to exceed 10 years (57).

12.9 Side-effects, QoL, and cost of hormonal therapy

The many deleterious side-effects of long-term ADT have been well known for years. Some can have a detrimental effect on QoL, especially in young men, while others may contribute to an increased risk of serious health concerns associated with ageing.

Many patients with PCa for whom long-term ADT is indicated are still young and physically and sexually active. Quality of life is an issue of paramount importance when considering the various hormonal treatment options. Thus, in selected patients, monotherapy with a non-steroidal anti-androgen (e.g. bicalutamide) is becoming more popular because it maintains normal (or even higher) serum testosterone levels and has a good tolerability profile.

*12.9.1 **Sexual function***

Loss of libido and erectile dysfunction are well-known side-effects of hormonal therapy. The management of erectile dysfunction is not specific.

*12.9.2 **Hot flashes***

Hot flashes are probably the most common side-effect of ADT. They appear 3 months after starting ADT, persist long term in most patients and can have a significant impact on QoL in some patients. Treatments include hormonal therapy and antidepressants.

12.9.2.1 Hormonal therapy

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flashes. Both treatments carry a risk of cardiovascular complications (94). Soya phytoestrogens have shown efficacy for hot flashes in breast cancer patients (95), but have not been evaluated in men. Progesterone-based treatments, such as megestrol acetate, medroxyprogesterone acetate and CPA, have also demonstrated efficacy, with 80% of patients showing an improvement with CPA (96) or chlormadinone (97).

12.9.2.2 Antidepressants

Antidepressants may have some efficacy against hot flashes, including venlafaxine (a non-specific selective noradrenaline and serotonin reuptake inhibitor), which has shown efficacy in breast cancer patients, and the

selective serotonin reuptake inhibitor, sertraline, which appears to be effective in men with PCa.

Recently, a randomised trial (n = 919) compared three drugs: venlafaxine, 75 mg daily, medroxyprogesterone, 20 mg daily, or CPA, 100 mg daily (98). After 6 months of LHRH, only 311 men had significant hot flushes and were randomized. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

12.9.2.3 Other options

Other treatments have also been tested, including clonidine and veralipride, and even acupuncture (99). With a placebo effect influencing up to 30% of patients (100), few treatments are approved for the control of hot flashes in men with PCa. There is a lack of large, prospective, randomised controlled trials in this area.

12.9.3 ***Other systemic side-effects of ADT***

More recently, other systemic side-effects have been described and require increased attention, including bone problems, obesity and sarcopenia, lipid alterations and insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease (101).

12.9.3.1 Non-metastatic bone fractures

Androgen deprivation therapy increases the risk of non-metastatic bone fracture due to increased bone turnover and decreased BMD in a time-dependent manner, and there is an increased risk of fracture of up to 45% relative risk with long-term ADT (102). This is an important side-effect, as hip fractures in men are associated with a significant risk of death (103). Increased exercise, calcium and vitamin D supplementation are protective. Bicalutamide monotherapy could also be a bone-protective method based on a small, prospective, randomised trial, including 103 patients comparing bicalutamide, 150 mg/day, or medical castration (104) (LE: 1b).

Bisphosphonates

Recently, bisphosphonates, such as pamidronate, alendronate or zoledronic acid, have been shown to increase BMD in the hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid is unclear. One study recommends treatment every 3 weeks (105), while another trial has produced similar results with an annual injection (106). The optimal regimen is very important because of the risk of jaw necrosis, which may be both dose- and time-related (107). The initial BMD could be used to guide the choice of regimen (108). Thus, a 3-month injection might be given in osteoporotic patients for whom a yearly injection is likely to provide insufficient protection.

As previously observed in breast cancer, a significant benefit in OS has recently been demonstrated for biphosphonates in PCa, particularly oral first-generation clodronate versus placebo. After at least 10 years of follow-up, an absolute 8% increase in OS was observed at 8 years in a clodronate-treated group of PCa patients, who had an overall survival of 22% versus 14% in the placebo group (109). The benefit for OS applied only to M1 patients, but not to M0 patients. Although this is a post-hoc analysis and the results are surprising because clodronate has no bone protective effect in PCa, this study again highlights the potential impact of bone-targeted drugs and the need for continuous trials, e.g. the Zeus trial, which uses a more recent biphosphonate.

Denosumab

In 2009, a major advance in bone protection was made with the introduction of denosumab, a fully human monoclonal antibody against RANKL, which is a key mediator for osteoclast function, activation and survival. A total of 1,468 men with non-metastatic PCa receiving ADT were randomised to denosumab, 60 mg subcutaneous every 6 months, or placebo (110). The primary end-point was the percentage change in lumbar spine BMD at 2 years. Denosumab was associated with 5.6% increase in the lumbar BMD versus 1% decrease in the placebo arm. There were also significant BMD increases at the total hip, femoral neck and distal third of the radius. The vertebral fracture rate was less in the denosumab-treated group versus the placebo-treated group (1.5% vs 3.9%, p = 0.006). This benefit was similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, as the rates of adverse events were the same in both groups, without any jaw osteonecrosis or delayed healing in vertebral fractures. Denosumab may therefore represent a major advance in bone protection.

In addition, this drug has been shown to postpone bone metastases in non-metastatic patients in a large RCT of 1,432 patients (111). Denosumab, 120 mg every 4 weeks, increased the time to bone metastasis-free survival by 4.2 months compared to placebo, but was accompanied by the side effects of jaw necrosis in 5% of treated patients versus 0% in the placebo arm and hypocalcaemia in 2% of treated patients versus less than 1% in the placebo arm. However, the increase in bone metastasis-free survival had no impact on overall

survival, which was 43.9 months in the denosumab group compared to 44.8 months in the placebo group. These results highlight the potential importance of targeting the bone microenvironment. However, the daily use of denosumab remains questionable because of related side effects and cost.

Lifestyle changes before starting long-term ADT
Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption and normalisation of their body mass index (BMI). A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry before starting long-term ADT. An initial low BMD (T-score > 2.5, or > 1 if other risk factors are present) indicates a high risk of subsequent non-metastatic fracture, suggesting the need for early preventive bisphosphonate therapy.

Obesity and sarcopenia
Obesity and sarcopenia are common and often occur early, during the first year of ADT. There is an expected increase in body fat mass by up to 10%, and a decrease in lean tissue mass by up to 3% (112). Both changes are linked to an increased risk of fracture.

12.9.3.2 Lipid levels
Lipid alterations are common and may occur as early as the first 3 months of treatment (112). Androgen deprivation therapy also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. Once again, exercise must be recommended as a protective tool.

12.9.3.3 Metabolic syndrome
Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The risk factors include:

- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure > 130/80 mmHg;
- HDL cholesterol < 1 mmol/L;
- glycaemia > 6.1 mmol/L.

The prevalence of metabolic syndrome is higher during ADT compared with untreated men (113).

12.9.3.4 Cardiovascular disease
Androgen deprivation therapy has been associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction in several studies (114).

Analysis of the RTOG 92-02 data has confirmed an increase in cardiovascular risk, which is unrelated to the duration of ADT. No increase in cardiovascular mortality was found (115). Similar findings were observed in the RTOG 94-08 trial (116). These observations have been much discussed because no increase in cardiovascular mortality has been reported in trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863. However, an increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis (117).

In summary, since 6 or less months of ADT may already be associated with increased cardiovascular morbidity the FDA issued a warning and a consensus paper from the American Heart, Cancer Society and Urological Associations was published (118). However, to date, the data on cardiovascular mortality remain inconsistent. Preventive advice is associated with non-specific measures, such as loss of weight, increased exercise, improved nutrition and the cessation of smoking.

12.10 Quality of life (QoL)

There is little data on QoL during hormone treatment. The only large, prospective, randomised study is a double-blind, placebo-controlled trial including 739 patients with M1 PCa, which compared orchiectomy + flutamide versus orchiectomy + placebo. The QoL was assessed in the first 6 months of treatment. Combined therapy resulted in a lower QoL, with statistically significant differences in two QoL parameters, namely more frequent diarrhoea and worse emotional functioning, compared with castration alone (119).

A prospective, non-randomised, observational study, which included 144 patients with locally advanced PCa or PSA failure after definitive local treatment, found that patients who received immediate ADT (by means of bilateral orchiectomy, LHRH agonist or CAB) reported a lower overall QoL (increased fatigue, emotional distress, and decreased physical functioning) than patients in the deferred hormone treatment arm (120) (LE: 2a).

A retrospective, non-randomised study included 431 patients with stage PCa who received orchiectomy or LHRH agonists as their primary therapy within 12 months of initial diagnosis. The study

assessed health-related quality of life (HRQoL) outcomes at 12-months' follow-up. Men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than were orchiectomised patients. The stage at diagnosis had no significant independent effect on health outcome. However, the study was underpowered (121) (LE: 2b).

A recent, small, randomised, controlled trial evaluated the HRQoL of patients with non-localised PCa allocated to leuprorelin, goserelin, CPA or no treatment at 1-year follow-up. Both sexual and cognitive function significantly declined in men on all forms of androgen suppression, while emotional distress significantly increased in those assigned to CPA or no treatment (122) (LE: 1b).

Intermittent androgen deprivation may be associated with an improved overall QoL based on the normal testosterone levels during off-treatment periods. Until recently, the results were inconclusive, showing either no benefit, or only a marginal one, in QoL. However, recent results from the JPR7 trial have shown a clear benefit for QoL (74).

As for LHRH agonists, QoL has been evaluated in the previously mentioned studies of bicalutamide monotherapy using a specific non-validated questionnaire. At 12 months, bicalutamide showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) (38) (LE: 1b).

A further post-hoc analysis, including only patients with sexual interest at study entry, found that significantly more patients receiving bicalutamide, 150 mg/day, maintained their interest in sex and felt that they were still sexually attractive (123,124), or had a preserved libido and erectile function compared to castration (125).

The most common side-effects during non-steroidal anti-androgen monotherapy are gynaecomastia and breast pain, which are caused by an imbalance in the androgen-to-oestrogen ratio within breast tissue. In bicalutamide studies, these events were reported by up to 66% and 73% of patients, respectively, and may have led to treatment cessation in 16.4% of patients.

12.11 Cost-effectiveness of hormonal therapy options

A recent formal meta-analysis and literature review evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa (e.g. bilateral orchiectomy, DES, LHRH-agonist, non-steroidal anti-androgen monotherapy, and CAB using non-steroidal anti-androgens).

For the analysis, a sophisticated statistical model was generated, assuming the base case at entry to be a 65-year-old man with clinically evident local recurrence of PCa and no distant metastases, followed for a 20-year time horizon. The study concluded that, for men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits for a high relative cost. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred (87) (LE: 1a).

Finally, once ADT is started, if a clear response is obtained (*see Section* 12.3.3), then IAD might be a useful way to lower treatment costs.

12.12 Conclusions and guidelines for hormonal therapy in prostate cancer	LE
In advanced PCa, androgen deprivation therapy (ADT) delays progression, prevents potentially catastrophic complications, and palliates symptoms effectively, but does not prolong survival.	1b
In advanced PCa, all forms of castration used as monotherapy (e.g. orchiectomy, LHRH and DES) have equivalent efficacy.	1b
Non-steroidal anti-androgen monotherapy (e.g. bicalutamide) is an alternative to castration in patients with locally advanced disease.	2a
In metastatic PCa, the addition of a non-steroidal anti-androgen to castration (CAB) results in a small advantage in OS over castration alone, but is associated with increased adverse events, reduced QoL, and high costs.	1a
In metastatic PCa, ADT should only be offered to carefully selected patients.	2a
In advanced PCa, immediate ADT (given at diagnosis) significantly reduces disease progression, as well as the complication rate due to progression itself, compared with deferred ADT (delivered at symptomatic progression). However, the survival benefit is at best marginal and not related to cancer-specific survival.	1b
Bilateral orchiectomy might be the most cost-effective form of ADT, especially if initiated after the occurrence of symptoms from metastatic disease.	3

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13. MANAGEMENT OF PROSTATE CANCER IN OLDER MEN

13.1 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 adult 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.

13.2 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). External Beam Radiotherapy (EBRT) has similar outcomes in terms of cancer control and treatment related comorbidities in both older and younger patients, assuming a dose of $\geq$ 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 biphosphonates 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/m^2 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.

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14. QUALITY OF LIFE OF PATIENTS WITH LOCALISED PROSTATE CANCER

14.1 Introduction

The increase in life expectancy of patients with localised PCa has made the quality of life 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-centered 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 generic issues of well-being, including physical, social, emotional, and cognitive functioning, vitality/fatigue, pain, general health status, global quality of life 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.

14.2 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).

14.3 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 (13-16).

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 (17). Sexual function and interest are the two prostate-specific domains that decline most after surgery and remain most affected after 1 year (18). The recovery of sexual dysfunction and urinary incontinence occurs over 2 to 3 years (19-21). Sanda and colleagues (14) 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 (14,22) and can also help to improve urinary function (21,22). Both RALP and open RP have demonstrated comparable functional outcomes and should therefore theoretically have similar HRQoL scores (24). Recently, Hu et al. (25) compared minimally invasive RP (all laparoscopic techniques) with traditional open RP using a dataset of nearly 2000 Medicare patients. The incontinence and erectile dysfunction rate were higher in the minimally invasive group compared with the open RP group (LE: 3). In a prospective, longitudinal study, Thornton et al. assessed changes in the cognitive, emotional, and interpersonal components of PCa-related QoL in 71 men who underwent RALP. Although some components of QoL returned to baseline by 1 year after surgery, there were enduring decreases in sexual intimacy, sexual confidence, and masculine self-esteem (26). More motivated patients

seemed to experience greater distress and were less satisfied (27). 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 (19,21,28).

A new methodology for reporting outcomes after RP was proposed recently: the so-called trifecta (29) and pentafecta (30). 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.

14.4 External-beam radiation therapy (EBRT) and low-dose rate (LDR) brachytherapy

Patients undergoing EBRT and I^{125} LDR brachytherapy may have urinary, sexual and bowel dysfunction after treatment (31). 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 (32). Roeloffzen et al. (32,33) 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 (14). 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 (14) (LE: 3).

It has been shown that both EBRT and LDR brachytherapy had a significant impact on the bowel and rectal HRQoL domains (14,34). Bowel/rectal problems appeared to have an overall impact close to that of the urinary v domain (35,36). The onset of symptoms occurred during or early after treatment, and sometimes persisted longer into follow-up. Sanda et al. reported rectal urgency, frequency, pain, fecal incontinence, or hematochezia-caused distress related to bowel function in 9% of patients at 1 year after EBRT or LDR brachytherapy (14). In a retrospective observational study of fecal incontinence in 143 men, who had received LDR brachytherapy for localised PCa, 13.2% (20) of patients at 2 years reported that fecal incontinence was impacting their ability to participate in daily activities (37). A multivariable analysis suggested that bowel and rectal symptoms were less profound after LDR brachytherapy than after EBRT (7) (LE: 2a).

Roeloffzen et al. (33) reported a statistically significant deterioration in HRQoL in patients treated with I125 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 were seen for 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 (38). 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.

Recently, Sanda et al. showed that adjuvant androgen suppression exacerbated the adverse effects of external radiotherapy or brachytherapy on sexuality and vitality (14). The negative effects of adjuvant hormonal therapy have been shown in some other studies (31,39).

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 have 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).

14.5 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 quality of life may change with time. There are very few

trials investigating a direct comparison of different treatment modalities.

Most early studies addressing general HRQL 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 more recent 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 (28,40). 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 (17). 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 (35). 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, tenesmus and rectal urgency will change little, and episodes of rectal bleeding will become more prevalent (7) (LE: 2a).

A recent, 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 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).

The quality of life 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 (14), patients in the LDR brachytherapy group reported long-lasting urinary irritation, bowel and sexual symptoms and transient problems with vitality or hormonal function. The adverse effects of RP on sexual function were mitigated by nerve-sparing procedures. 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 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 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 (34) is most acceptable to them when making a decision about treatment.

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15. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF PCA

Stage	Treatment	Comment	GR
T1a	Watchful waiting	Standard treatment for Gleason score ≤ 6 and 7 adenocarcinomas and < 10-year life expectancy.	B
	Active surveillance	In patients with > 10-year life expectancy, re-staging with TRUS and biopsy is recommended.	B
	Radical prostatectomy	Optional in younger patients with a long life expectancy, especially for Gleason score ≥ 7 adenocarcinomas	B
	Radiotherapy	Optional in younger patients with a long life expectancy, in particular in poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.	B
	Hormonal	Not an option.	A
	Combination	Not an option.	C
T1b-T2b	Active surveillance	Treatment option in patients with cT1c-cT2a, PSA < 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 biopsies positive, ≤ 50% cancer involvement of each biopsy.	B
		Patients with a life expectancy < 10 years.	
		Patients with a life expectancy > 10 years once they are informed about the lack of survival data beyond 10 years.	
		Patients who do not accept treatment-related complications.	

T1a-T2c	Radical prostatectomy	Optional in patients with pT1a PCa. Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.	A
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications.	B
		Patients with contraindications for surgery.	
		Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below).	
	Brachytherapy	Low-dose rate brachytherapy can be considered for low risk PCa patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.	B
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.	C
		Anti-androgens are associated with a poorer outcome compared to 'active surveillance' and are not recommended.	A
	Combination	For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately-differentiated tumours, and a life expectancy < 10 years who are unfit for local treatment.	C
	Radical prostatectomy	Optional for selected patients with T3a, PSA < 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy > 10 years.	C
		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.	
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation of > 74 Gy seems to be of benefit. A combination with hormonal therapy can be recommended.	A
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSA-Doubling Time (DT) < 1 year.	A
		Patient-driven, unfit patients.	
		Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.	
	Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation.	A
		NHT plus radical prostatectomy: no indication.	B
N+, M0	Watchful waiting	Asymptomatic patients. Patient-driven (PSA < 20-50 ng/mL), PSA DT > 12 months. Requires very close follow-up.	B
	Radical prostatectomy	Optional for selected patients with a life expectancy of > 10 years as part of a multimodal treatment approach.	C
	Radiotherapy	Optional in selected patients with a life expectancy of > 10 years, combination therapy with adjuvant androgen deprivation for 3 years is mandatory.	C
	Hormonal	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.	A
	Combination	No standard option. Patient-driven.	B

M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.	B
	Radical prostatectomy	Not a standard option.	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.	C
	Hormonal	Standard option. Mandatory in symptomatic patients.	A

DT = doubling time; NHT = neoadjuvant hormonal treatment; IPSS = International Prostatic Symptom Score; PSA = prostatespecific antigen; TRUS = transrectal ultrasound; TURP =transurethral resection of the prostate

16. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

16.1 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.

16.2 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.

16.3 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.

*16.3.1 **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.

*16.3.2 **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.

16.3.3 ***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.

16.3.4 ***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).

16.3.5 ***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).

16.3.6 ***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).

*16.3.7 **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).

*16.3.8 **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).

16.4 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.

16.5 Guidelines for follow-up after treatment with curative intent

Recommendations	GR
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.	B
After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.	B
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.	B
Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.	B
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.	B
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.	C
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.	B

16.6 References

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17. FOLLOW-UP AFTER HORMONAL TREATMENT

17.1 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.

17.2 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.

17.3 Methods of follow-up

17.3.1 ***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.

17.3.2 ***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.

17.3.3 ***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).

17.4 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.

17.5 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 flushes, 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 biphosphonates 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).

17.6 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.

17.6.1 ***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.

17.6.2 ***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.

17.6.3 ***Castration-refractory PCa***

Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualised follow-up scheme.

17.7 Guidelines for follow-up after hormonal treatment

Recommendation	GR
Patients should be evaluated at 3 and 6 months after the initiation of treatment.	
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.	B
If patients undergo intermittent androgen deprivation, PSA and testosterone should be monitored in 3-month intervals during the treatment pause.	C
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.	C
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.	C
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.	C
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
When disease progression occurs, or if the patient does not respond to the treatment given, the follow-up needs to be individualised.	C
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 < 50 ng/dL).	
Routine imaging of stable patients is not recommended.	B

17.8 References

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18. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENT WITH CURATIVE INTENT

18.1 Background

Primary curative procedures, such as RP and radiotherapy, are well-established therapeutic options in the management of localised PCa. Technical advances in surgery and radiation therapy have improved therapeutic efficacy and decreased treatment-associated morbidity and toxicity, respectively. However, despite these improvements, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or radiation therapy develop local or distant recurrences within 10 years of initial therapy and 16-35% of patients receive second-line treatment within five years of initial therapy (1-5,6).

18.2 Definitions

*18.2.1 **Definition of treatment failure***

Treatment failure was previously defined as recurrence on DRE or the development of metastatic disease. Currently, treatment failure is defined as a rising PSA level based on a study of Pound et al. (7), which showed that no patient followed for more than five years developed any recurrence without a concomitant rise in PSA.

The level of PSA that defines treatment failure differs between men who have undergone RP and men treated with radiotherapy. Following radical retropubic prostatectomy (RRP), there is an international consensus that recurrent cancer may be defined by two consecutive values of PSA > 0.2 ng/mL (6,8). However, the most appropriate definition of biochemical progression after RP remains uncertain. A retrospective analysis of 2782 men who had undergone RP for clinically localised PCa (9) was used to determine the best PSA cut-off point

for defining biochemical recurrence. Another study found that 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 ng/mL, 0.3 ng/mL, 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 can therefore be managed initially by surveillance.

Similar data have been presented by Stephenson et al. (10). The study identified a PSA value of > 0.4 ng/mL as the best cut-off level to explain the development of distant metastasis among 10 candidates. This level was estimated using definitions developed from a retrospective review of 75 patients, who had developed distant metastases following RP. A cut-off of 0.4 ng/mL is therefore appropriate to define progression with clinical relevance, i.e. necessitating salvage treatment.

Following radiotherapy, three consecutive increases in PSA are considered to provide a reasonable definition of biochemical relapse, according to ASTRO (11). This new definition indicates a relapse if the PSA increase is > 2 ng/mL higher than the PSA nadir value, independent of the serum concentration of the nadir (12).

18.2.2 ***Definitions of recurrence***

A recurrence of CaP can be defined as:

- Following RP, PSA values > 0.2 ng/mL confirmed by two consecutive measures.
- Following radiotherapy, a PSA value of 2 ng/mL above the nadir after radiotherapy.

18.3 Local or systemic relapse

Once a PSA relapse has been diagnosed, it is of major importance to determine whether the recurrence has developed at local or distant sites. About 50% of patients who have undergone radical retropubic prostatectomy will have local disease, while the remainder will have either distantdisease alone, or distant and local disease (11).

Several important parameters help to differentiate between local or distant relapse:

- timing of the PSA increase after surgery;
- PSA velocity;
- PSA doubling time (PSA DT);
- pathohistological stage;
- Gleason score of the prostatectomy specimen.

PSA elevations 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 might be associated with distant relapse, whereas a median PSA DT of 11.7 months predicts local failure (13). According to a recent study (14), a PSA velocity of < 0.75 ng/mL/y was observed in 94% of patients with local recurrence, whereas 56% of patients with distant metastases demonstrated a PSA velocity of > 0.75 ng/mL/y. There is no indication to perform ultrasound-guided biopsies of the vesicourethral anastomosis to diagnose local relapse as this method has low sensitivity and low predictive accuracy in men with rising PSA levels < 1.0 ng/mL.

With radiotherapy, any continuously rising PSA following a nadir after radiation is an indicator for local recurrence, systemic metastatic spread or a combination of both (11,14-16). However, due to the well- known PSA bounce phenomenon, biochemical recurrence is defined by a PSA rise of 2 ng/mL above the PSA nadir according to ASTRO guidelines. After radiotherapy, a late and slowly rising PSA is a sign of local failure only.

Local recurrence of PCa is defined by:

- a prostatic biopsy demonstrating malignant cells at 18 months or longer after initial radiotherapy;

plus

- an associated rise in PSA, although prostate biopsy is only indicated if the patient is a candidate for a secondary local salvage therapy with curative intent;

plus

- no evidence of metastatic spread documented by CT or MR imaging and bone scintigraphy.

18.3.1 ***Definition of local and systemic failure***

The definitions of local and systemic failure are as follows:

- Local failure following RP is predicted with an 80% probability by a PSA increase at 3 years after RP, a PSA DT ≥ 11 months, a Gleason score ≤ 6, and stage ≤ pT3a pN0, pTx R1.
- Systemic failure following RP is predicted with > 80% accuracy by a PSA increase.
- At less than 1 year after RP, there is a PSA DT of 4-6 months, a Gleason score of 8-10, and stage pT3b, pTxpN1.

- Local failure after radiotherapy is documented by a positive prostatic biopsy and negative imaging studies.
- Prostatic biopsy after radiotherapy is necessary only if local procedures, such as salvage prostatectomy, are indicated in an individual patient.

18.4 Evaluation of PSA progression

Prior to an extensive diagnostic work-up in patients with PSA relapse following local treatment, men must be stratified into those who are candidates for salvage therapy and those who are not. Men must also be stratified into those who are candidates for local salvage treatment and those who might need systemic therapy. All 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 underwent physical and sonographic examinations, as well as radiology or biopsies of the prostatic fossa and the vesicourethral anastomosis to confirm the recurrence identified by serological studies. For patients with asymptomatic PSA-only progression, the yield is very low. Lange et al. (14) have shown that biochemical failure precedes clinical disease by 6-48 months.

In general, DRE is not useful in men with undetectable or very low PSA levels. In a recent study by Öbek et al. (17), it was shown that only 4/72 patients (5.5%) with a PSA recurrence following RP had an abnormal DRE.

Imaging studies are used to differentiate local from systemic relapse to help select the most appropriate treatment modality. However, it must be remembered that most imaging studies are probably not sensitive enough to identify the anatomical location of relapsing PCA at PSA levels < 0.5-1.0 ng/mL.

*18.4.1 **Diagnostic procedures for PSA relapse following RP***

Traditionally, bone scans and abdominal CT scans have been used to evaluate PSA elevations following primary treatment. However, both imaging studies have low sensitivity and specificity and can be safely omitted in the routine work-up of relapsing patients. A recent study (18) looked at bone scans in 144 patients, 122 of whom had undergone RP without hormone treatment, while 22 had received either neoadjuvant or adjuvant androgen-deprivation therapy (ADT). Bone scans in 93 patients with PSA recurrence identified metastatic disease in only 4.1% of men who had undergone RP and 27% of men who had been treated with ADT. The lowest PSA associated with positive findings was 46 ng/mL in the absence of adjuvant ADT, whereas the lowest PSA value was 15.47 ng/mL in patients who had received hormonal therapy.

The probability of a positive bone scan remains < 5% until the serum PSA reaches at least 40 ng/mL. Similar data have been achieved by other groups, which have demonstrated that patients with a true positive bone scan had an average PSA level of > 60 ng/mL and a PSA velocity of 22 ng/mL/year (19,20). Logistic regression analysis showed that PSA and PSA velocity were good predictors of bone scan results and PSA velocity for CT scan results. Of 132 patients with biochemical recurrence, 9.4% had a positive bone scan and 14% had a positive CT scan. However, there may be a slight difference between patients after radical retropubic prostatectomy and patients after radiation therapy, as shown by Johnstone et al. (21), who found that 5% and 30%, respectively, of bone scans, were positive.

In summary, bone scintigraphy and CT scans are of no additional diagnostic value, unless the PSA serum levels are higher than 20 ng/mL or the PSA velocity is more than 20 ng/mL/year.

Endorectal coil imaging is a useful technique to detect local recurrences after RP (22). In a series of 48 patients, local recurrence was correctly identified in 81%, with the mean PSA being 2 ng/mL at diagnosis.

The diagnostic accuracy of endorectal MRI (eMRI) was investigated in a series of 72 men with PSA relapse following RP (23). The mean total PSA was1.23 +/- 1.3 ng/mL, with men undergoing eMRI using a 1.5-Tesla system. The data were compared to standard references for local recurrence, including prostatectomy bed biopsy results, choline positron emission tomography results, PSA reduction or increase after pelvic radiotherapy, and PSA modification during active surveillance. Sensitivity, specificity, predictive positive value, negative predictive value and accuracy were 61.4%, 82.1%, 84.4%, 57.5% and 69.4% for unenhanced eMRI, and 84.1%, 89.3%, 92.5%, 78.1% and 86.1% for enhanced eMRI. The two evaluations showed a statistically significant difference in accuracy (chi(2) = 5.33, p = 0.02) and sensitivity (chi(2) = 9.00m, p = 0.0027).

Although eMRI appears to be very sensitive and predictive in identifying local recurrences following RP, it is currently not a routine imaging modality to be performed in every case, as local versus systemic relapse

must be differentiated at PSA levels < 0.5 ng/mL (see Section 18.6). At this PSA level, eMRI is not sufficiently sensitive or accurate.

Positron emission tomography (PET) has been successfully applied in many human cancers for early identification of local or systemic recurrences. In PCa, there are few, but promising, published data on the clinical efficacy of PET in detecting local recurrences after RP (23-25). However, it must be kept in mind that the uptake of ^{11}C-choline is not specific for PCa and may also be due to inflammatory intraprostatic lesions.

In a series of 31 patients with biochemical progression after RP, ^{11}C-acetate-PET demonstrated a high sensitivity and specificity for the detection of local recurrences when the PSA serum level was > 1 ng/mL (24). In another recent series of 43 patients with newly diagnosed CaP, there was a significant correlation between ^{11}C-choline uptake and the intraprostatic location of PCa in RP specimens (26). Similar results have been reported for the detection of locally recurrent PCa after radiation therapy (27). However, ^{11}C-PET was significantly less sensitive at detecting extraprostatic extension compared with MRI.

The most recent series evaluating the role of ^{11}C-choline PET/CT in men with biochemical recurrence after RP have shown that metastases were more likely to be identified at higher PSA levels. ^{11}C-choline PET/CT was able to locate metastases in 20-36% of men with PSA levels < 1 ng/mL, increasing to 63-83% of men with PSA levels > 3 ng/mL (28-31).

In 190 patients with PSA relapse following RP, Castelucci et al. (32) investigated how the ^{11}C-choline PET/CT detection rate was affected by:

- trigger PSA level (i.e. total PSA level at the time of the scan);
- PSA velocity (PSA VEL);
- PSA doubling time (PSA DT) (Table 20).

The study found that the mean PSA relapse was 4.2 ng/mL (median 2.1, range 0.2-25.4). Disease relapse was detected by ^{11}C-choline PET/CT in 74/190 patients (38.9%). The study also found that trigger PSA values were statistically different between PET-positive patients (median PSA 4.0 ng/mL) and PET-negative patients (median PSA 1.4 ng/mL) (p = 0.0001), with the optimal cutoff point for trigger PSA being 2.43 ng/mL. In 106 patients, PSA DT and PSA level values were statistically different between patients with PET-positive (p = 0.04) and PET-negative scans (p = 0.03).

Table 20: Relationship between different measurements of PSA and ^{11}C-choline PET/CT detection rate

PSA measurement	n	^{11}C-choline PET/CT detection rate (%)
Trigger PSA		
< 1 ng/mL	51	19
1 < PSA < 2 ng/mL	39	25
2 < PSA < 5 ng/mL	51	41
PSA > 5 ng/mL	49	67
PSA velocity		
< 1 ng/mL/y	33	12
1 < PSA VEL < 2 ng/mL/y	26	34
2 < PSA VEL < 5 ng/mL/y	19	42
PSA VEL > 5 ng/mL/y	28	70
PSA doubling time		
PSA DT > 6 mo	45	20
4 < PSA DT < 6 mo	20	40
2 < PSA DT < 4 mo	31	48
PSA DT < 1 mo	10	60

A recent publication from Giovacchini et al. (32) comprising 109 patients with rising PSA level and negative conventional imaging studies concluded that ^{11}C-choline PET/CT might be helpful in restaging PCA but it

should not be used to guide therapy. The authors found that only 12 of 109 patients (11%) had positive PET/CT findings. Scans were positive in 5%, 15%, and 28% of patients with PSA < 1ng/mL, between 1 and 2 ng/mL, and > 2ng/mL, respectively ($p < 0.05$). The use of ^{11}C-choline PET/CT in all men with a rising PSA level > 1 ng/mL would result in 85% incidence of unnecessary examinations, significant increase of medical costs, and no benefit for the individual patient.

Another retrospective study of 37 patients scheduled for salvage radiation therapy after RP (34) reported that about 13% of the patients demonstrated ^{11}C-choline PET/CT-positive lymph nodes outside the prostatic fossa, implicating an extension of the target volume. However, none of the lesions was verified histologically, and the mean PSA of choline-positive patients (1.1 ng/mL, range 0.5-1.8 ng/mL) was significantly higher than in ^{11}C-choline PET/CT-negative patients (0.4 ng/mL, range: 0.3-0.7 ng/mL).

The most recent review published by Picchio et al. (35) has concluded that the routine use of ^{11}C-choline PET/CT cannot be recommended for PSA values < 1 ng/mL. Its accuracy is correlated to PSA value, PSA DT, and other pathological features. The authors propose that ^{11}C-choline PET/CT may be proposed as a guide for individualised treatment of recurrence. A similar conclusion can be made from another recent study by Castellucci et al (32).

However, the indication to perform ^{11}C-choline PET/CT must be placed in the context of the above-mentioned clinical parameters. It therefore remains doubtful whether a patient with elevated PSA, rapid PSA DT and a prostatectomy Gleason score > 8 will receive therapy other than ADT based on the findings of ^{11}C-choline PET/CT.

In summary, the role and the diagnostic accuracy of ^{11}C-choline PET/CT in men with rising PSA following RP is dependent on the absolute PSA, PSA DT, and PS AV. The higher the PSA level and the faster PSA DT, the better 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. There is therefore an urgent need for well-conducted and histologically controlled trials to explore the potential role of ^{11}C-choline PET/CT.

The role of choline PET/CT to detect local or systemic recurrences in men with PSA relapse following radiotherapy is unclear and based on very few studies (36,37). Thus, no final recommendations can be made. Its sensitivity and specificity with regard to the detection of lymph node metastases are less reliable, and the routine use of ^{11}C-PET cannot therefore be recommended, especially not for PSA values < 1 ng/mL.

It has been common practice to perform transrectal ultrasound (TRUS)-guided biopsies of the prostatic fossa, the anastomosis or the prostate gland to exclude local recurrence after radical retropubic prostatectomy or radiotherapy. However, according to available studies, routine biopsy of the vesicourethral anastomosis appears not to be justified based on a verification rate of only 54% (38-40). Only in the presence of a palpable lesion or a hypoechoic lesion on TRUS can the diagnostic yield of the biopsy be improved to approximately 80%. Furthermore, there is a strong correlation between the positive biopsy rate and PSA serum concentrations (38-40); 28% and 70% of the biopsies were positive if the PSA level was, respectively, below 0.5 ng/mL or greater than 2.0 ng/mL.
Thus, it is now commonsense that routine anastomotic biopsy is not indicated, and the use of PSA and PSA DT is sufficient for clinical practice. In addition, PSA-free survival in biopsy-proven recurrences does not differ significantly compared with PSA-only recurrences.

*18.4.2 **Diagnostic studies for PSA relapse following radiation therapy***

With regard to PSA relapses following radiation therapy, routine prostate biopsy should no longer be performed for the evaluation of PSA-only recurrences, according to an ASTRO consensus recommendation (15). However, prostate biopsy documenting local recurrence represents the main cornerstone in the decision-making process for salvage RP in patients with rising PSA levels following a nadir after radiation therapy (41). It is a general recommendation to wait about 18 months and three months following radiation therapy or seeds, and cryotherapy or high-intensity focused ultrasound (HIFU), respectively. Patients with rising PSA and viable cancer on biopsy 2 years after radiation therapy have true locally recurrent disease and might be candidates for salvage RP.

Recent studies have evaluated the role of eMRI, MRI spectroscopy and dynamic-contrast enhanced MRI in the identification of locally recurrent PCA following radiation therapy (42-44). These studies have demonstrated that locally recurrent PCA can be differentiated from benign nodules due to the low T2-weighted signal intensity. Endorectal MRI and MR spectroscopy were more sensitive than TRUS or TRUS-guided prostate biopsies

to detect viable PCa. Endorectal MRI has also contributed important information about the presence of extraprostatic extension and seminal vesicle invasion with a sensitivity of 86% and a specificity of 96%.

Endorectal MRI is therefore strongly recommended in the diagnostic work-up of men with PSA relapse after radiation therapy, who might be candidates for secondary local salvage therapy with curative intent.

*18.4.3 **Diagnostic procedures in patients with PSA relapse***

Following RP, CT scans of the pelvis and abdomen are of low sensitivity and specificity in patients with PSA levels < 20 ng/mL or a PSA velocity of < 2 ng/mL/y. Endorectal MRI or PET scans may help to detect local recurrences if PSA is > 1.0 ng/mL, but is not routine clinical practice for the early detection of local relapses.

Following radiation therapy, local recurrence is documented by a positive biopsy > 18 months after the procedure. Endorectal MRI is of valuable importance for men who are candidates for radical salvage prostatectomy.

18.5 Treatment of PSA-only recurrences

The timing and mode of treatment of PSA-only recurrence after RP or radiation therapy remains controversial. After RRP observation, the therapeutic options are:

- radiation therapy to the prostatic bed;
- (complete) androgen blockade (CAB);
- intermittent androgen deprivation (IAD);
- combination of antiandrogens with 5-α-reductase inhibitors;
- early chemohormonal approaches.

These same therapeutic options may be applied to PSA recurrences following radiation therapy. In addition, salvage prostatectomy, cryotherapy or brachytherapy may be indicated in carefully selected patients.

*18.5.1 **Radiation therapy for PSA-only recurrence after RP***

Three large RCTs in adjuvant radiation have now been published (45-48). All three trials showed a benefit with adjuvant radiotherapy of at least 15% at 5 years in biochemical recurrence-free survival.

The largest trial (EORTC-22911, n = 1005) (46) and the smallest trial (ARO-96-02, n = 307) (47) trial were powered to detect a benefit in biochemical disease recurrence-free survival, while metastasis-free survival was the primary endpoint of the third trial, SWOG-S8794 (n = 431) (47). The three trials had similar inclusion criteria; however, the EORTC trial also included pT2R1 patients, while the other two trials allowed only pT3 cancers with or without a positive resection margin. In all three trials, quite a high proportion of patients (63-68%) had a positive surgical margin.

It should be noted that the post-operative PSA level of men before they were randomised to adjuvant radiotherapy was different between 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 patients in the EORTC and SWOG trials received ‘salvage‘ radiation therapy rather than adjuvant radiotherapy for a non-normalised PSA. It is therefore interesting that not all men in the non-adjuvant arms of the trials were treated with salvage radiotherapy by the time of a biochemical recurrence: delayed or salvage radiotherapy to the prostatic fossa was administered to 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 radiation was superior to salvage radiation as in the control arm, as at most only half of the men received radiation at the time of PSA recurrence.

Indeed, the authors of the EORTC trial suggested that salvage radiation may be equivalent to adjuvant therapy provided the PSA is lower than 1 ng/mL (46). However, only the SWOG trial was powered to address the effect of delayed radiation since it was the only trial with metastasis-free survival as the primary endpoint. In the SWOG trial, men in the control arm were less likely to receive salvage radiation (33%). However, it took a median follow-up of over 12 years before metastasis-free survival improve d in the adjuvant treatment arm suggesting that adjuvant therapy may not be helpful in men with a life expectancy < 10 years (45,47). Recently, it has been demonstrated that patients in the control group had a higher frequency of Gleason score 8-10 CaP and were more likely to not receive ADT at the time of PSA relapse.

There have been many studies on the use of radiation therapy for PSA-only recurrence following RRP. As a result there is a growing body of parameters predicting outcome that may help to differentiate between the

need for observation, radiation or hormonal therapy. As confirmed by various studies, the pre-radiation PSA level is critically important for optimal treatment results (41-44,49-53):

- Applying a pre-radiation cut-off of < 2.5 ng/mL, Wu et al. (49) and Schild et al. (50) reported disease-free survival rates of 53% and 76%, compared with 8% and 26%, respectively, for patients with PSA serum levels > 2.5 ng/mL.
- Forman et al. (51) demonstrated a disease-free survival rate of 83% versus 33% in patients with a PSA-only recurrence of < 2.0 ng/mL and greater than 2.0 ng/mL, respectively.
- Nudell et al. (52) even reported progression-free survival rates of 58% and 21% in patients having undergone radiation of the prostate bed if PSA serum levels were below 1.0 ng/mL or greater than 1.0 ng/mL, respectively.

Based on these data, ASTRO has published a consensus paper recommending a dose of at least 64 Gy when the PSA level is < 1.5 ng/mL after RRP (15). Furthermore, recent papers (53-58) have corroborated the data of early salvage radiation therapy demonstrating a significant difference in 5-year biochemical-free and overall survival rates in patients treated for PSA-recurrence only or for palpable local recurrence. In another study, Stephenson et al. (59) evaluated prognostic models to predict the outcome of salvage radiation therapy on a cohort of 1603 men with PSA progression after RP and operated on in 17 North American tertiary referral centres.

The authors identified a significant relationship between PSA serum concentration at the time of radiation therapy and therapeutic outcome: the 6-year biochemical-free survival was 48% in men with PSA < 0.5 ng/mL, but only 40%, 28%, and 18% in men with PSA levels of 0.51-1 ng/mL, 1.01-1.5 ng/mL and > 1.5 ng/mL, respectively.

For the SWOG and EORTC non-adjuvant radiotherapy arms, the median interval to salvage radiotherapy was 2 and 2.2 years, respectively. In the SWOG 8974 study, 23% of men had a PSA > 1.5 ng/mL prior to salvage radiation. In a subanalysis of the SWOG 8974 trial, Swanson et al. (60) showed that men in all categories of post-prostatectomy PSA level (< 0.2, 0.2-1.0, > 1.0 ng/mL) showed an improvement with salvage radiotherapy in metastasis-free survival. However, the therapeutic benefit was most evident in the presence of minimal PSA serum levels. These data suggest that, although less effective, salvage radiation treatment may help improve metastasis-free survival.

In a recent multi-institutional, matched-control analysis of adjuvant and salvage post-operative radiation for pT3-4N0 PCa, Trabulsi et al. (61) have demonstrated a biochemical recurrence-free survival advantage in favour of adjuvant radiotherapy versus salvage radiotherapy. Interestingly, in a multivariate Cox regression analysis, adjuvant versus salvage radiotherapy were not independent predictors in metastatic progression-free survival, when corrected for adverse clinical and pathological factors.

Recently, data on overall survival and salvage radiation have become available. In a group of men with a median follow-up of 9 years after prostatectomy, the benefit of salvage radiation for prostate cancer-specific mortality was seen particularly in men with a PSA DT of less than 6 months, who had been given salvage radiation to the prostate fossa within 2 years after a rise in PSA (62). This suggests that local disease control may prolong prostate cancer-specific survival in men formerly thought to be at risk for systemic disease progression and less likely to benefit from (salvage) radiation. It has been suggested that men with slowly progressing disease, even though still at risk of systemic progression, may not benefit from salvage radiotherapy because they have a low risk of development of lethal PCa. Certainly, longer follow-up is needed to answer this question.

However, more data are required from prospective randomised trials.

18.5.1.1 Dose, target volume, toxicity

The three randomised trials on adjuvant radiation therapy all used dosages less than 66 Gy, which is currently the most frequently used dose for adjuvant and salvage radiation. 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 (63,64). Dosages up to 70 Gy showed better biochemical recurrence-free rates at higher doses, with 66.8 Gy radiation found to be the dose required for 50% biochemical recurrence-free survival (TCD50). Even higher doses may be considered, particularly when using improved imaging techniques, such as fiducial markers (65). The finding that 9% of men develop a local recurrence after adjuvant radiation of 60 Gy provides support for an increase in dosage and target volume (60). Target volume delineation has been found to vary by up to 65% between different radiotherapists administering

adjuvant or salvage radiation to the prostatic fossa (66,67), despite the presence of guideline (68). It is therefore important not to overlook local toxicity. In the EORTC 22911 study, 3.1% of men had to interrupt adjuvant radiation because of local complaints, mainly diarrhoea. Although grade 3 or 4 toxicity is rare for either adjuvant or salvage radiation to the prostate 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 urethral stricture (relative risk [RR], 9) and incontinence (RR, 2.3).

*18.5.2 **Hormonal therapy***

Systemic failure following RP is predicted with > 80% accuracy by PSA relapse < 1 year, PSA DT of 4-6 months, Gleason score 8-10 and stage pT3b, pTxpN1. There is some evidence that early hormonal therapy may help to delay progression and possibly achieve a survival benefit (69,70).

18.5.2.1 Adjuvant hormonal therapy after RP

In the absence of randomised controlled trials for post-operative 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 non-metastatic disease. It is uncertain whether or not such data are relevant to men with rising post-operative PSA levels.

Two randomised studies have compared immediate hormonal therapy (after diagnosis) with deferred hormonal therapy (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 (T0-4N0M0) illustrate that, although immediate hormonal therapy after diagnosis can delay disease progression in men with PCa, it does not necessarily result in an improved cancer-specific survival (71,72).

The survival advantage for immediate (adjuvant) ADT after RP has only been proven in patients with positive-lymph-node PCa in a single randomised study (69,70). The updated results of this multicentre Eastern Cooperative Oncology Group study after a median follow-up of 11.9 years showed a significant improvement in overall survival, cancer-specific survival, and progression-free survival in lymph-node positive (N+) patients treated with immediate ADT (70).

Adjuvant bicalutamide, 150 mg, could decrease progression in men with locally advanced PCa, but did not result in an overall survival benefit (73). Several retrospective analyses from the Mayo Clinic showed that adjuvant hormonal therapy after RP had a positive effect on time to progression and cancer death in patients with pT3b and N+ PCa (74-76). However, a recent large series from the Mayo Clinic with a median follow-up of 10.3 years showed that adjuvant hormonal therapy in patients with surgically managed N+ PCa decreased the risk of biochemical recurrence and local recurrence, but did not significantly impact systemic progression or cancer-specific survival (77). A recent retrospective study with a median follow-up of 5.2 years showed that immediate and delayed hormonal therapy (at PSA recurrence) in patients with surgically managed N+ PCa provided similar outcomes (78).

An observational study showed that deferring immediate ADT in men with positive lymph nodes after RP may not significantly compromise survival. There was no statistically significant difference in survival with 90, 150, 180 and 365 days as the definition of adjuvant ADT. These results need to be validated in a prospective study (79).

18.5.2.2 Post-operative hormonal therapy for PSA-only recurrence

Androgen deprivation therapy

Although patients with post-operative PSA recurrence often undergo ADT before evidence of metastatic disease, the benefit of this approach is uncertain. A retrospective study including 1352 patients with post-operative PSA recurrence showed no significant difference in the time to clinical metastases with early ADT (after PSA recurrence, but before clinical metastases) versus delayed ADT (at the time of clinical metastases). However, upon risk stratification, early ADT could delay the time to clinical metastases in high-risk patients with a Gleason score > 7 and/or a PSA DT < 12 months. Androgen deprivation therapy had no overall impact on prostate cancer-specific mortality (80).

A recent retrospective study from the Mayo Clinic showed that adjuvant ADT (within 90 days of surgery) slightly improved the cancer-specific survival and systemic progression-free survival after RP in a large group of high-risk patients with PCa. However, the survival advantage was lost when ADT was delivered farther in the disease process, at the time of PSA recurrence or systemic progression. It should be emphasised that there was no overall survival advantage (83% for both groups) and that the difference in cancer-specific survival and systemic progression-free survival was only 3% and 5%, respectively (81). In a recent retrospective

study, including 422 patients with post-operative PSA recurrence, 123 developed distant metastasis, of whom 91 patients with complete data received deferred ADT at the time of documented metastasis after RP. The authors concluded that patients when closely followed after PSA recurrence may have an excellent response to deferred ADT and a long survival with a median failure time of 169 months from RP to death (82). However, these three studies are limited by their retrospective design and in assessing the side effects of long-term ADT. Evidence from well-designed, prospective, randomised studies is needed before the use of early hormonal therapy can be advocated in clinical practice.

Antiandrogens
Although gynaecomastia and breast tenderness were the most predominant side effects for the treatment of 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 CAB (83).

Antiandrogens may represent a viable alternative to other modes of androgen deprivation for the management of PSA-only recurrences, especially in young and otherwise healthy men. In a prospective, placebo-controlled, randomised trial of adjuvant bicalutamide, 150 mg, following RP in patients with locally advanced disease, the risk of objective progression of the disease was significantly reduced in patients receiving bicalutamide. However, overall survival did not differ between groups (84). Low-dose flutamide, 250 mg daily, is currently being investigated in men with PSA recurrence. Bicalutamide, 150 mg daily, has not yet been studied in this clinical setting (85).

Intermittent androgen deprivation
Intermittent androgen deprivation (IAD) has been examined as a potential alternative to CAD to:
- delay the time to androgen independence and hormone-refractory disease;
- minimise side-effects;
- reduce costs of prolonged therapy.

The Cochrane Collaboration revealed that there were no long-term data of large-scale randomised controlled trials that proved the superiority of IAD over CAD for survival. Limited information suggests that IAD may result in a slight reduction of adverse effects (86). 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. Summarising the series in which PSA-only recurrences were treated by IAD (87-91), PSA threshold levels at study-entry varied significantly, as did the PSA level at discontinuation of hormonal therapy. Only the study of 150 patients by Tunn et al. (91) had a sufficiently appropriate study design to allow the drawing of important clinical conclusions. Patients were started on IAD for 9 months when the post-prostatectomy PSA serum level was greater than 3.0 ng/ mL, and all patients reached a nadir of less than 0.5 ng/mL. Intermittent androgen deprivation was re-started when PSA increased to more than 3.0 ng/mL. After a mean follow-up of 48 months, and a mean duration of hormonal therapy of 26.6 months, none of the patients had progressed to hormone-refractory disease. In the meantime, IAD remains attractive to selected, closely monitored and well-informed patients with post-operative PSA recurrence.

Minimal androgen blockade
In some studies, finasteride and flutamide have been combined to manage PSA-only recurrences since both agents work additively by blocking the intraprostatic conversion of testosterone to dihydrotestosterone (DHT) and blocking the intracytoplasmic DHT receptor (92-94). In the latest report (93) including 73 patients, the application 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 of 15 months, none of the patients had progressed to traditional hormonal therapy. 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 hormonal therapy to salvage radiotherapy (n = 78) was not associated with any additional increase in cancer-specific survival (94). A recent phase II trial including 74 patients with post-operative PSA recurrence showed that combined treatment with salvage radiotherapy plus 2 years of maximum androgen blockade (castration + oral antiandrogen) had relatively minor long-term effects on quality of life (95). 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 radiotherapy + placebo versus the

combination of radiotherapy + bicalutamide, 150 mg daily, in the post-operative setting.

Radiotherapy and Androgen Deprivation in Combination after Local Surgery is a recently started, large, randomised, controlled study, sponsored by the Medical Research Council. The study addresses the timing of radiotherapy (adjuvant vs early salvage) and the duration of hormonal therapy (none vs short-term vs long-term) used together with post-operative radiotherapy. The primary outcome measure will be cancer-specific survival. Secondary outcome measures will include overall survival, ADT administered outside the protocol, and reported treatment toxicity. The study also aims to assess the long-term effect of radiotherapy after RP on sexual, urinary and bowel function, and the long-term effect of ADT on sexual function and overall quality of life. Patients will be asked to complete four short questionnaires. These assessments will be done at baseline, 5 years and 10 years (96).

Currently, 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 to initiate a cytotoxic regime remains controversial (97).

18.5.3 ***Observation***

Observation until the development of clinically evident metastatic disease might represent a viable option for patients with a Gleason score < 7, PSA recurrence longer than 2 years after surgery, and a PSA DT longer than 10 months. In these patients, the median actuarial time for the development of metastasis will be 8 years, and the median time from metastasis to death will be another 5 years (7).

18.5.4 ***Management of PSA relapse after RP***

Recommendations	GR
Local recurrences are best treated by salvage radiation therapy with 64-66 Gy at a PSA serum level < 0.5 ng/mL.	B
For patients with presumed local recurrence who are too unfit or unwilling to undergo radiation therapy, expectant management can be offered.	B
PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases.	B
Luteinising hormone releasing hormone (LHRH) analogues/antagonists/orchiectomy or bicalutamide, 150 mg/day, can both be used when there is an indication for hormonal therapy.	A

18.6 Management of PSA failures after radiation therapy

In a recent review of the data of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) comprising 2336 patients with PCa, Grossfeld et al. (98) demonstrated that 92% of patients initially irradiated received ADT for secondary treatment of PSA progression. In the absence of 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 radiation therapy (41,99-108). Salvage RRP has not, however, gained widespread acceptance because of its associated morbidity, namely incontinence, local recurrences and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

18.6.1 ***Salvage radical prostatectomy***

Previously, most series reporting on salvage RP 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 morbidities. Up to 60% of patients who underwent salvage RP 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 only 1.3 years.

Recent reports analysing patients who were operated on during the past decade, have described far more optimistic outcomes after salvage RP. In the series examined by Gheiler et al. (103), 40 patients with a mean PSA of 14 ng/mL underwent salvage RP. When stratified by PSA < 10 ng/mL, the 3-year disease-specific survival was 68% and 26%, respectively. In the series reported by Garzotto and Wajsman (104), 24 patients underwent radical cystoprostatectomy or RP with neoadjuvant ADT. Neoadjuvant ADT was associated with a lower rate of positive surgical margins (21%) compared with patients in whom androgen deprivation failed and

who exhibited a positive surgical margin rate of 80%. The authors demonstrated that disease-specific survival correlated strongly with the surgical margin status. At a mean follow-up of 5 years, the disease-specific survival rate was 95% and 44% for those with negative and positive surgical margins, respectively. Vaidya and Soloway (105) demonstrated a low rate of complications, good post-operative continence and only one biochemical recurrence at 36 months after salvage RP.

Similar data have been achieved by Stephenson et al. (106), who reported on 100 consecutive patients undergoing salvage RP associated with a very low rate of peri-operative complications. The 5-year progression-free rates have improved, with results similar to those of standard RP in cases of similar pathological stages. In contemporary series, the 10-year cancer-specific survival and overall survival rates are 70-75% and 60-66%, respectively. In most contemporary series, organ-confined disease, negative surgical margins and the absence of seminal vesicle and/or lymph node metastases are favourable prognostic indicators associated with a better disease-free survival of approximately 70-80%, compared with 40-60% in patients with locally advanced PCa (107).

Recently, Heidenreich et al. (108) reported on the oncological and functional outcome of 55 patients who underwent radical salvage therapy for locally recurrent PCA after various types of modern state-of-the-art radiation therapy, 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. On multivariate analysis, significant predictors of organ-confined PCa with negative surgical margins were:

- biopsy Gleason score prior to salvage RP ($p = 0.02$);
- < 50% positive biopsy cores ($p = 0.001$);
- PSA DT > 12 months ($p = 0.001$);
- low-dose brachytherapy ($p = 0.001$).

Urinary continence was achieved after a mean of 8 months in basically all men after low-dose-radiation brachytherapy, while incontinence persisted in about 20% of patients who underwent external beam radiation therapy or high-dose radiation brachytherapy. Salvage RP is a surgically challenging but effective secondary local treatment of radiorecurrent PCa with curative intent. The identified predictive parameters will help to select patients most suitable for salvage RP with long-term cure and good functional outcome.

18.6.1.1 Summary of salvage RP

In general, salvage RP should be considered only in patients with a low co-morbidity, a life expectancy of at least 10 years, an organ-confined PCa < T2, Gleason grade < 7, and pre-surgical PSA < 10 ng/mL. In all other patients, accurate pre-surgical staging is not easily defined after radiation therapy, increasing the risk not only for anterior and total extirpation procedures, but also for associated complications and decreased long-term disease-specific survival.

18.6.2 ***Salvage cryosurgical ablation of the prostate (CSAP) for radiation failures***

Salvage cryosurgery has been proposed as an alternative to salvage RP because it has the potential to have less morbidity but equal efficacy. However, there have only been a very few studies, with disappointing results. Pisters et al. (109) reported on 150 patients who had undergone CSAP for PSA recurrences following radiotherapy (n = 110) or other extensive pre-treatment (n = 40). After a mean follow-up of 13.5 months, 58% of patients exhibited biochemical failure, while only 31% demonstrated undetectable PSA serum levels. The complications associated with salvage CSAP were significant, and occurred in virtually all patients, with the main complications being urinary incontinence (73%), obstructive symptoms (67%), impotence (72%) and severe perineal pain (8%). After 1-year follow-up, incontinence resolved in most patients, with persistent significant incontinence in 22% of patients.

According to a recent study by Cespedes et al. (110), the risk for urinary incontinence and impotence at least 12 months after CSAP are as high as 28% and 90%, respectively. In addition, 8-40% of patients complained about persistent rectal pain, and an additional 4% of men had undergone surgical procedures for the management of treatment-associated complications.

With regard to oncological outcome, recent studies demonstrated that a durable PSA-response can be achieved in about 50% of patients with a pre-cryosurgery PSA of < 10 ng/mL (111). In a recent multicentre study, the contemporary results of CSAP in 279 patients treated at a large number of centres, participating in the Cryo On-Line Data Registry, were analysed (112). Pre-treatment PSA was 7.6 +/- 8.2 ng/mL and the Gleason score was 7.5 +/- 1.1 (median 7). Patients were followed for 21.6 +/- 24.9 months and 47 were

followed for longer than 5 years. The 5-year actuarial biochemical disease-free rate was 54.5% +/- 4.9% (Phoenix). As predicted, based on the preservation of some prostatic tissue, 83% +/- 3.5% of patients had a detectable PSA level > 0.2 ng/mL at 5 years. Positive biopsies were observed in 15 of the 46 patients (32.6%) who underwent prostate biopsy after salvage cryotherapy. The incontinence rate (requiring pad use) was 4.4%. The rectal fistula rate was 1.2% and 3.2% of patients underwent transurethral prostate resection to remove sloughed tissue.

Quite recently, a case-matched control study between RSP and CSAP was performed among men with radiorecurrent PCa. The authors compared the oncological outcome of both salvage treatment options after a mean follow-up of 7.8 and 5.5 years for the radical salvage prostatectomy group and the cryosurgery group, respectively. RSP resulted in a statistically significant biochemical disease-free survival at 5 years of 61% versus 21% for the cryosurgery procedure. Also, the 5-year overall survival was significantly superior for the RSP group (95% vs 85%, $p < 0.001$) (113).

*18.6.3 **Salvage brachytherapy for radiation failures***

The experience with salvage brachytherapy for radiation failures is very limited. There is only one study that includes a representative number of patients and a mean follow-up of 64 months (114). Grado et al. (114) treated 49 patients with transperineal TRUS-guided brachytherapy and reported 3- and 5-year disease-free survival rates of 48% and 43%, respectively. Beyer (115) reported a 5-year biochemical freedom from relapse in 34-53% of patients, with local cancer control achieved in 98% of patients. However, the complication rate was quite severe:

- 27% became incontinent;
- 14% needed palliative transurethral resection due to acute urinary retention;
- 4% developed rectal ulcers;
- 2% required permanent colostomy.

Burri et al. (116) reported on the long-term outcomes and toxicity after salvage brachytherapy with palladium-103 or iodine-125 for local failure after initial radiotherapy for PCa in 37. Median follow-up was 86 months (range, 2-156). The median dose to 90% of the prostate volume was 122 Gy (range, 67-166). The 10-year biochemical disease-free survival and cancer-specific survival were 54% and 96%, respectively. There were three grade 3 toxicities and one grade 4 toxicity (10.8%). In conclusion, careful patient selection for salvage brachytherapy may result in improved outcomes and reduced toxicity.

In a similar approach, Moman et al. (117) retrospectively evaluated the outcome and toxicity after salvage iodine-125 implantation in 31 patients with locally recurrent PCa after primary iodine-125 implantation and external beam radiotherapy. The mean follow-up was 9 years (SD +/-4). Freedom from biochemical failure after 1-year follow-up was 51% and after 5 years was 20%. Fourteen (45%) patients died of PCa after a mean (+/- SD) follow-up of 73 (+/-39) months. 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 biochemical failure after salvage iodine-125 implantation for locally recurrent PCa after radiotherapy is limited, and both genitourinary and gastrointestinal toxicity occur frequently.

*18.6.4 **Observation***

Patients with signs of local recurrence only (i.e. low-risk patients with late recurrence and a slow PSA rise), who are not opting for second-line curative options, are best managed by observation alone. A retrospective cohort analysis of hormonal therapy versus watchful waiting (WW) in 248 men with PSA failure after radiotherapy showed no advantage for hormonal therapy in the subgroup of men with a PSA DT of > 12 months after radiotherapy. The 5-year metastasis-free survival rate was 88% with hormonal therapy versus 92% with WW ($p = 0.74$) (118).

*18.6.5 **High-intensity focused ultrasound (HIFU)***

The experience of HIFU for the treatment of locally recurrent PCa after radiation therapy is limited to a few retrospective studies. Zacharakis et al. (119) investigated the oncological and functional outcome of HIFU in a cohort of 31 men with biopsy-proven locally recurrent PCa following EBRT. The mean (range) pre-operative PSA level was 7.73 (0.20-20) ng/mL. The patients were followed for a mean (range) of 7.4 (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 urinary incontinence in two (6%). Rectourethral fistula occurred in two men (7%). Overall, 71% had no evidence of disease following salvage HIFU.

Using a similar approach, Murat et al. (120) evaluated the safety and efficacy of salvage HIFU in 167 patients with local PCA recurrence after EBRT and to determine prognostic factors for optimal patient selection. Local cancer control was achieved with negative biopsy results in 122 (73%) patients. 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 required no hormonal therapy. The actuarial 5-year overall survival rate was 84%. The actuarial 3-year progression-free survival was significantly lower in three situations:

- worsening of the pre-EBRT stage with 53%, 42%, and 25% for low-, intermediate-, and high-risk patients, respectively;
- an increase in the pre-HIFU PSA;
- use of ADT during PCa management.

In multivariate analyses, the risk ratios for intermediate- and high-risk patients were 1.32 and 1.96, respectively. The risk ratio was 2.8 if patients had been treated with 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 fistula are the most significant complications of salvage HIFU therapy (119-121). About 30% of men develop some type of incontinence, with significant urinary incontinence treated with an artificial urinary sphincter in about 10% of patients. The oncological control rate after a short median follow-up of about 2 years is 30-40%.

18.6.5.1 Salvage HIFU therapy

Ahmed et al. (122) evaluated the outcome of whole-gland HIFU in 84 patients with radiorecurrent CaP following external beam radiation therapy. After a mean follow-up of 19.8 months, the 1- and 2-year progression-free survival rates were 59% and 43%, respectively. Four men developed rectourethral fistula and another 20% needed to undergo surgical treatment for subvesical outlet obstruction.

Berge et al. (123) evaluated the health-related quality of life using the Los Angeles Prostate Cancer Index questionnaire in 61 patients following HIFU for radiorecurrent, clinically organ-confined CaP. The mean time between treatment and quality of life evaluation was 17.5 months The treatment of localised radiorecurrent PCa by salvage HIFU is associated with clinically significant reductions in urinary and sexual function domains, but not in mental domains.

18.6.6 ***Guidelines for the management of PSA relapse after radiation therapy***

Recommendations	**GR**
Local recurrences may be treated by salvage RP in carefully selected patients, who presumably demonstrate organ-confined disease, i.e. PSA < 10 ng/mL, PSA DT > 12 months, low-dose-radiation brachytherapy, biopsy Gleason score < 7.	B
Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery.	B
High-intensity-focused ultrasound 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.	
In patients with presumed systemic relapse, ADT may be offered.	B

18.7 Guidelines for second-line therapy after treatment with curative intent

Recommendations	GR
Presumed local failure after radical prostatectomy	
Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably before PSA has risen above 0.5 ng/mL.	B
Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on.	
Presumed local failure after radiotherapy	
Selected patients may be candidates for salvage RP and patients should be informed about the higher risk of complications, e.g. incontinence and erectile dysfunction.	C
Salvage RP should only be performed in experienced centres.	
Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on.	
Presumed distant failure	
There is some evidence that early hormonal therapy may be of benefit in +/- local failure, delaying progression, and possibly achieving a survival benefit in comparison with delayed therapy. The results are not without controversy.	B
Local therapy is not recommended except for palliative reasons.	

18.9 References

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19. CASTRATION-RESISTANT PCA (CRPC)

19.1 Background

Cancer of the prostate is a heterogeneous disease. Our knowledge of the mechanisms involved in androgen independence, which is now known as castration-resistant prostate cancer (CRPC), remains incomplete (1-4), but is starting to become clearer (5,6). In the past, it was thought that androgen ablation provides a selective advantage androgen-independent cells that grow and eventually comprise most of the tumour. An alteration in normal androgen signalling is thought to be central to the pathogenesis of androgen-independent PCa (7).

It is thought that androgen independence (now called castration resistance) is mediated through two main, overlapping, mechanisms, which are androgen-receptor (AR)-independent and AR-dependent.

*19.1.1 **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 (8,9). Indeed, most active chemotherapeutics in CRPC work by inhibiting microtubule formation. The tumour suppressor gene p53 is more frequently mutated in androgen-independent PCa. Over-expression of bcl-2 and p53 in prostatectomy specimens has been shown to predict an aggressive clinical course (10-12). Clinical trials are underway to target the bcl-2 pathway (13), as the MDM2 oncogene (14) and the PTEN (phosphatase and tensin homolog) suppressor gene may also be involved (15).

19.1.2 ***AR-dependent mechanisms***

Direct AR-dependent mechanisms comprise the main pathway. Ligand-independent AR activation has been suspected, such as the tyrosine kinase activated pathway (IGF-1, KGF, EGF). Epidermal growth factor (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 (16).

Androgen receptor amplification and overexpression are observed in one-third of CRPC tissues (17,19) and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in AR function (3,4,16). At the same time, there is an intracellular increase in androgens from in-situ conversion (20,21). This increase may be secondary to an increase in the intracellular enzymes involved in intracellular androgen synthesis (22).

Because AR mutations are found in only a subpopulation of tumour cells, they are unlikely to be responsible for the entire spectrum of the AR-independent state (23). The AR mutations might be related to the selective pressure of anti-androgens (23). The recent discovery of gene fusion between the androgen-driven TMPRSS2 and the EGR-ETS oncogene family (24) raises the question of oncogene regulation through androgen regulation pathways. In gene fusion, an androgen-responsive element from an androgene-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 (22,25). It is possible that a high intraprostatic cholesterol level can activate specific androgen pathways (1).

19.2 Definition of relapsing prostate cancer after castration

The previously term, 'hormone-refractory prostate cancer' referred to a very heterogeneous disease. It included different patient cohorts with significantly different median survival times (Table 21).

Table 21: Estimated natural mean survival of patients with HRPC presenting with different clinical scenarios

Patient characteristics	**Estimated mean survival**
Asymptomatic PSA	
No metastases	20-36 months
Minimal metastases	18-27 months
Extensive metastases	9-12 months
Symptomatic PSA	
Minimal metastases	14-16 months
Extensive metastases	9-12 months

The precise definition of recurrent or relapsed PCa remains controversial and several groups have recently published practical recommendations for defining CRPC (25-26).

Various different terms have been used to describe prostate cancers that relapse after initial hormonal ablation therapy, including HRPC, androgen-independent cancers and hormone-independent cancers (1). Over the course of the past 5 to 8 years, the term castration-resistant prostate cancer (CRPC) has become more used than the term hormone refractory or androgen independent. This is based predominantly on the implications of recent findings suggesting that advancing prostate cancer is not uniformly refractory to further hormonal manipulation and that androgens and the progression of disease are frequently dependent on - not independent of - androgen-AR interactions. The castrate-resistant, but still hormone-sensitive, PCa (CRPC) has been clearly characterised, with new drugs targeting either the AR, such as MDV3100, or androgen synthesis, via the CYP 17 inhibition like abiraterone acetate or TAK700 (*see below* Section 17.8.5.2) (27). Table 22 lists the key defining factors of CRPC.

Table 22: Definition of CRPC

Castrate serum levels of testosterone (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 a 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 hormonal manipulations†

** Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for CRPC if patients have been treated with antiandrogens in the context of maximum androgen blockade or step up therapy following PSA progression after failure of LHRH treatment.*
† Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) and with nodes ≥ 2 cm in diameter.

19.3 Assessing treatment outcome in androgen-independent PCa

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) (28). 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 osseous metastases.

Osteoblastic bone metastases remain difficult to quantify accurately. Magnetic resonance imaging (MRI) might be useful for assessing axial metastases (29). Since the cause of death in PCa patients is often unreliable, a more valid end-point might be overall survival (OS) rather than a disease-specific one (30).

*19.3.1 **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 new agents for activity, there is conflicting evidence about the role of PSA as a response marker. Both the vaccine trials, Sipuleucel-T (Provenge) (31) and the TRICOM (PROSTVAC) study (32), demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs (33).

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 (34-41).

Nevertheless, it has been reproducibly shown that ≥ 50% PSA decline in pre-treatment PSA following therapy carries a significant survival advantage (42,43). Kelly et al. (42) reported a statistically significant survival advantage in 110 patients with ≥ 50% PSA decline (> 25 months) versus those without a ≥ 50% PSA decline (8.6 months). Smith et al. (43) showed that a PSA decline ≥ 50% for at least 8 weeks resulted in a longer mean survival time of 91 weeks versus 38 weeks in patients showing a smaller PSA reduction.

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) versus 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 (44,45).

*19.3.2 **Other parameters***

The evaluation of molecular markers is just beginning. It includes a possible correlation between the positive findings of reverse transcriptase-polymerase chain reaction (RT-PCR) and poor survival (46), though these data must be corroborated before any clinical recommendations can be made. Another, probably more interesting, tool is the circulating tumour cell count (CTC count), which has been developed in parallel with abiraterone. The CTC count has been clearly related to survival in several trials (47-49) and may become a surrogate marker for survival. The FDA has recently approved an assay for CTC.

In patients with symptomatic osseous lesions, pain reduction or complete pain relief may be used as parameters to assess palliative therapeutic response (50). In a landmark analysis of TAX 327, PSA response

and pain response, but not QoL response, were independently associated with survival (51).

*19.3.3 **Trial end-points***

An increasing number of investigators advocate subjective end-points. However, investigators should currently apply the following:

- Use clearly defined end-points in trials, sufficiently powered to answer the hypothesis.
- Report each response parameter individually, rather than as a complete or partial response.
- Only use PSA response with other clinical parameters of response.
- Consider QoL end-points independently in symptomatic patients.

However, in everyday practice, the evaluation of treatment response must be based on symptom improvement, prolonged survival, or other pre-defined targets.

*19.3.4 **Recommendations for assessing therapeutic response***

The Prostate Cancer Working Group 2 recommends that investigators measure early-response 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 (25). 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.

Recommendations	LE	GR
For PSA: Recognise that a favourable effect on PSA may be delayed for 12 weeks or more, 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 (prior to 12 weeks) in determining PSA response.	1a	A
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 or more weeks later Confirmatory scan: no new lesions: continue therapy • Additional new lesions: progression Subsequent scheduled reassessments: no new lesions: continue. New lesions: progression.		
In non-osseous metastases from CRPC, assessment should adhere to the RECIST criteria.	1b	A
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- to 4-week intervals. Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, 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.	1b	A

HRQoL = health-related Quality of life; RECIST = Response Evaluation Criteria in Solid Tumours.

19.4 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 (52).

Continued testicular androgen suppression in CRPC has a minimal overall effect. The recommendation to continue androgen deprivation therapy (ADT) with LHRH analogues, despite PSA progression, is based on the data of Manni et al. (53). This study 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 (54,55).

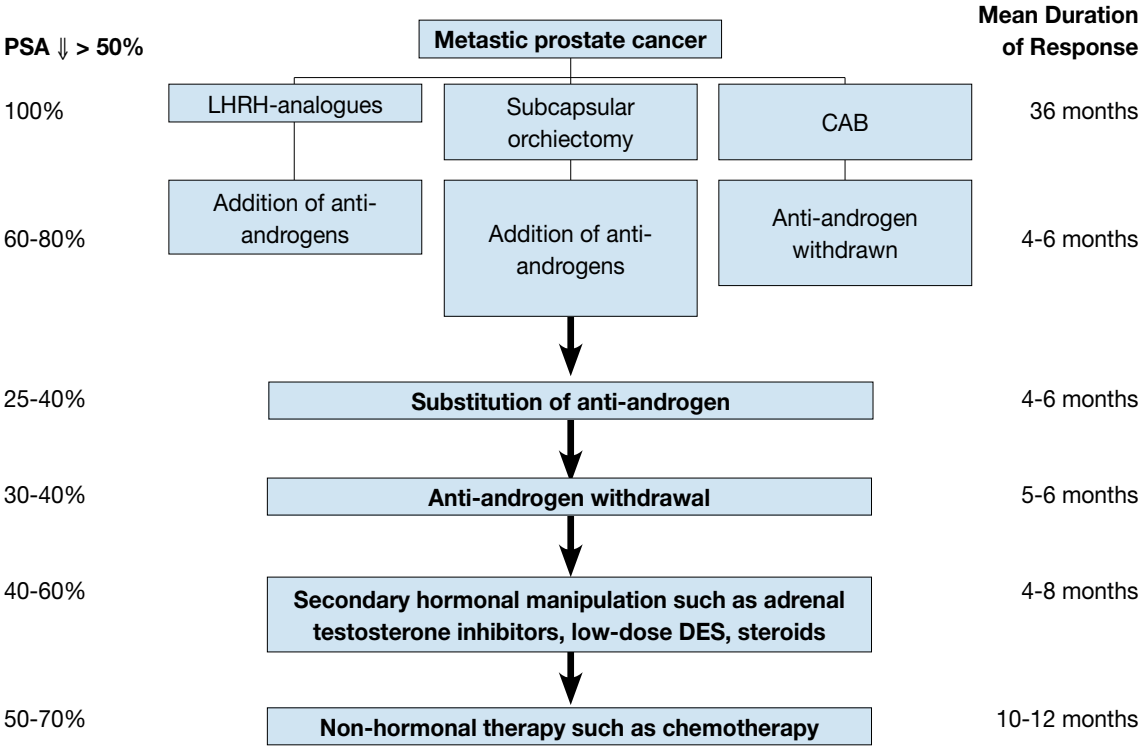
However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. Androgen suppression should therefore be continued indefinitely in these patients.

19.5 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 (56). 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; CAB = complete androgen blockade; DES = diethylstilboesterol.

19.6 Anti-androgen withdrawal syndrome

In 1993, Kelly and Scher (57) reported clinical and PSA responses in men who discontinued flutamide therapy upon the development of progressive disease. The anti-androgen withdrawal syndrome was a critical discovery in understanding the biology of androgen independence, interpreting clinical trials, and treating patients (58-61).

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 (Table 22). Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (62-67). Recently, in the SWOG 9426 trial, PSA progression despite CAB was reported in a subgroup of 210 patients with a tumour stage of M0 or M1 (68). A response was observed in 21%, even though there was no radiographic response. Median progression-free survival (PFS) was 3 months, with 19% (all M0) having 12 months' or greater PFS. Factors associated with increased PFS and OS were a longer period of non-steroidal use, lower PSA at baseline and M0-stage. These results were obtained with patients on CAB following androgen withdrawal treatment. No data were available on the withdrawal effect following second-line anti-androgen treatment.

In conclusion, androgen withdrawal should be systematically considered as a first-line modality in relapsing patients, even if its efficacy is limited (LE: 2).

Table 23: Frequency and duration of PSA response following anti-androgen withdrawal

Anti-androgen	No. of patients	> 50% decrease in PSA No. of patients (%)	Duration (months)
Flutamide	57	16 (28%)	4.0
Flutamide	82	12 (15%)	3.5
Flutamide	39	11 (28%)	3.7
Flutamide	21	7 (33%)	3.7
Bicalutamide	17	5 (29%)	5.0
Combined results	210	44 (21%)	3 (median)

19.7 Treatment alternatives after initial hormonal therapy

Except in patients with non-castration testosterone levels, it is difficult to predict which subset of patients is most likely to respond to secondary hormonal strategies.

19.7.1 ***Bicalutamide***

Bicalutamide is a non-steroidal anti-androgen with a dose response, with higher doses producing a greater reduction in PSA level (69). The largest cohort so far is based on 52 CRPC patients treated with bicalutamide, 150 mg (70). 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 (DHT) for the androgen receptor, a large randomised trial (TARP) is ongoing comparing the effectiveness of bicalutamide 50 mg combined with either dutasteride or placebo in non-metastatic CRPC (71). The addition of an anti-androgen, such as bicalutamide or flutamide, to gonadal suppression at the time of PSA failure appears to result in declining PSA in only a few patients (72,73).

19.7.2 ***Switching to an alternative anti-androgen therapy***

There has been recent interest in another simple modality: the alternative anti-androgen therapy (74). After CAB was stopped in 232 progressing patients (76% being M1b), a withdrawal effect was observed in 31 men (15.1%). A 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 more than 6 months. The higher the PSA at the start of second-line therapy, the shorter was the progression-free survival and the lower was the PSA response rate.

19.7.3 ***Anti-androgen withdrawal accompanied by simultaneous ketoconazole***

The adrenal glands secrete approximately 10% of circulating androgen in humans. Some tumour cells in androgen-independent states must retain androgen sensitivity, as a clinical response is induced by a further decrease in circulating androgen levels following bilateral adrenalectomy or administration of drugs inhibiting adrenal steroidogenesis. Aminoglutethimide, ketoconazole and corticosteroids act mainly via this mechanism (75-79) to produce a PSA response in about 25% of patients for about 4 months. 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 (79).

19.7.4 ***Oestrogens***

Prostate cancer usually expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. In-vitro oestrogens can activate mutant androgen receptors isolated from androgen-independent PCa, while high-dose oestrogens have achieved objective salvage responses. This may be due to the mitotic arrest of direct cytotoxic effects on the cells, perhaps through an apoptotic mechanism (80,81). Recently, diethylstilboestrol (DES) (82-84) achieved a positive PSA response between 24% and 80%, with an overall estimated survival of 63% 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.

19.7.5 ***The future for agents targeting the androgen receptor and endocrine pathways***

In the last 2 years, potential drugs have appeared in early phase I/II trials in CRPC and should be considered as potential major new tools, provided the randomised phase III trials confirm the early results. Furthermore, they confirm that the castrate-resistant status is far from meaning an hormonal-resistant status (see above Section 19.4).

19.7.5.1 MDV3100

The first agent, MDV3100, is a novel anti-androgen which blocks AR transfer to the nucleus, in contrast to currently available drugs where AR is able to transfer to the nucleus. This means that no agonist-like activity should ever occur. At the ASCO 2009 meeting, a phase I/II trial on 140 CRPC was reported (85). In this dose-finding study, a PSA decline > 50% was seen in 57% chemo-naïve patients, and in 45% chemo-refractory patients. Based on these results, a large phase III trial has been recently launched in metastatic CRPC patients after chemotherapy, on more than 1000 patients, with OS being the primary end-point.

At the GU ASCO 2012 the final results of the AFFIRM study were presented demonstrating a significant survival benefit of 4.8 months in patients undergoing MDV3100 treatment as compared to placebo. The median survival was 18.4 months versus 13.6 months ($p < 0.0001$) in the MDV3100 and the placebo group, respectively. The relative risk reduction of death was 37%. The median progression-free was 8.3 months versus 3.0 months ($p < 0.0001$) (86).

19.7.5.2 Abiraterone acetate

The second agent is the CYP17 inhibitor, abiraterone acetate. In CRPC patients, this drug is able to decrease PSA > 50% in 85% chemo-naïve patients (87), by 50% after docetaxel (88,89), and even by 33% after ketoconazole (89). In chemo-naïve patients, a PSA decline of > 90% is seen in up to 40% of patients (87).

The largest cohort so far is based on 96 chemo-naïve men included in a phase I/II trial. At a dose of 1000 mg, a PSA decline > 50% was observed in 67% and > 90% in 19% of patients. A partial response (RECIST-based) was seen in 37% of patients. The median time to progression was about 1 year (6). These very promising results have led to two large phase III trials: one in chemo-refractory patients (n = 1158), the other in chemo-naïve patients (n = 1000, accrual completed). In both trials, OS is the primary endpoint. In the post-chemotherapy trial (COU-301), patients with disease progression after docetaxel-based therapy were randomly assigned to receive abiraterone plus prednisone or prednisone plus placebo, with treatment continuing until disease progression or death. The results from the study demonstrated a significant improvement in overall survival in favour of abiraterone from 10.9 to 14.8 months, with a hazard ratio of 0.646. The PSA response proportion to abiraterone/prednisone was 38% versus 10% in this study, while grade 3 to 4 adverse events leading to discontinuation occurred in 10% of those treated with abiraterone and 13% of those treated with placebo. This study is a confirmation that CRPC remains hormone-driven, even in advanced stages of the disease and represents an outstanding opportunity for the future treatment of CRPC (90).

19.8 Non-hormonal therapy (cytotoxic agents)

Several proven chemotherapeutic options are available for metastatic disease in CRPC (Table 24). Multiple trials are underway, using very different approaches through all the known pathways. A detailed review is far beyond the scope of these guidelines (5), as most drugs are experimental, except perhaps docetaxel.

A significant improvement in median survival of about 2, 2.5 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy (91,92). 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.

Table 24: 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

Study	n	PSA decrease > 50%	Decrease in pain	Survival (months)	Time to progression
TAX 327					
Mitoxantrone, 3 weekly, 12 mg/m^2, Prednisone 5 mg BID		32%	22%	16.5	-
Docetaxel, 3 weekly, 75 mg/m^2 Prednisone 5 mg BID		45%[1]	35%[3]	18.9[1]	-
Docetaxel, weekly, 30 mg/m^2 Prednisone 5 mg BID		48%[1]	31%	17.4	-
SWOG 99-16					
Mitoxantrone, 3 weekly, 12 mg/m^2	336	50%[1]	-	17.5[2]	6.3 months[1]

Docetaxel/EMP, 3 weekly, 60 mg/m^2, EMP 3x280mg/day	338	27%	-	15.6	3.2 months
CALGB 9182					
Hydrocortisone	123	38%[4]	-	12.3	2.3 months
Mitoxantrone/HC, 3 weekly, 12 mg/m^2	119	22%	-	12.6	3.7 months[4]
Tannock et al.					
Prednisone	81	22%	12%	-	43 weeks[1]
Mitoxantrone/Pred, 3 weekly, 12 mg/m2	80	33%	29%[2]	-	18 weeks

EMP = estramustine; HC = hydrocortisone; Pred = prednisone. [1]p < 0.000; [2]p = 0.001; [3]p = 0.01; [4]p < 0.03.

19.8.1 Timing of chemotherapy in metastatic CRPC

The timing of chemotherapy varies in metastatic CRPC. It is advisable to start it immediately in symptomatic patients, if possible every 3 weeks, as this schedule is associated with an improvement in survival. However, a weekly regimen will result in the same symptom improvement and must be considered in patients unable to receive the optimal regimen (LE: 1b), as it is more effective than best supportive care (93). In asymptomatic patients, timing is not so clear and must be discussed individually.

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 (94). 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: good risk (0-1 factor), intermediate (2 factors) and high risk (3-4 factors), leading to three different median OS: 25.7, 18.7 and 12.8 months, respectively (46) . In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (hazard ratio [HR], 2.96) (95,96). Age by itself is not a contraindication to docetaxel (97).

Currently, the only indication for chemotherapy in CRPC non-metastatic patients is inside clinical trials and patients should be advised to participate.

19.8.2 Mitoxantrone combined with corticosteroids

Mitoxantrone combined with corticosteroids (98,99) has been extensively studied primarily in patients with symptomatic osseous lesions due to CRPC. In the CALGB 9182 study (99), 244 patients with symptomatic metastatic CRPC were randomised to receive either mitoxantrone + hydrocortisone, 12 mg/m^2 every 3 weeks, or hydrocortisone alone. No differences were observed with regard to survival, PSA response, and median time to progression. However, the QoL was significantly improved in the combination arm. In another trial (99), 161 men with painful osseous metastases due to CRPC were randomised to receive mitoxantrone + prednisone versus prednisone alone. There was a significant benefit in pain reduction in the combination group (29%) versus prednisone alone (12%, p = 0.01). Furthermore, the duration of palliation was longer in patients who received mitoxantrone (43 weeks vs 18 weeks, p < 0.0001). There were no significant differences with regard to PSA response and median survival time. However, again, QoL was improved significantly due to pain reduction.

19.8.3 Alternative combination treatment approaches

Encouraging results have been seen with alternative treatments evaluated in prospective clinical phase II trials (100-103), including pegylated doxorubicin, vinorelbine, a combination of paclitaxel, carboplatin + estramustine, a combination of vinblastine, doxorubicin + radionuclides, and a combination of docetaxel + mitoxantrone. The lack of representative randomised phase III trials and unknown long-term efficacy are major problems associated with all these studies.

19.8.4 Estramustine in combination therapies

The synergy observed for estramustine combined with other drugs that target microtubule action has generated promising results in prospective clinical trials.

Estramustine + vinblastine is the most studied estramustine combination. Although different doses of estramustine and vinblastine have been used in prospective randomised trials, significant PSA and measurable responses have been reported in three separate studies. Although time to progression and frequency of ≥ 50% PSA decrease was significantly higher in the estramustine + vinblastine treatment arm, median survival

did not differ significantly between the estramustine and the estramustine + vinblastine arms (104). A recent meta-analysis (105) concluded that the addition of estramustine to chemotherapy increased the time to PSA progression and OS. However, there was a significant increased risk of thromboembolic events, up to 7% (106), requiring systematic prevention with coumadin.

19.8.5 ***Oral cyclophosphamide***

Intravenous cyclophosphamide has been tested in many trials. However, there is currently interest in oral cyclophosphamide, which seems to be less toxic than intravenous cyclophosphamide and may have greater activity. A study of oral cyclophosphamide + oral etoposide in 20 patients was similarly encouraging (107,108).

19.8.6 ***Cisplatin and carboplatin***

Cisplatin and carboplatin have activity as single agents against PCa. They also have a well-documented synergy with etoposide or paclitaxel in vitro in other malignancies, such as lung and ovarian cancer. As estramustine is also synergistic with these drugs, combinations of these three agents are now being tested. A combination of estramustine, etoposide and cisplatin (or carboplatin) has significant activity against poorly differentiated CRPC. A combination of estramustine, etoposide and paclitaxel has produced high response rates (102,109).

19.8.7 ***Specific bone targets***

Bone is a primary target for prostatic metastatic cells, leading to a rational for bone-protective drugs, preventing cancer cells from colonising and developing bone. Besides zoledronic acid and denosumab (see above Section 12.7.1), there are other promising drugs, mainly those targeting the endothelin-1 axis. The first of these agents (atrasentan) resulted in clear biological responses, but questionable clinical results (110), possibly secondary to an inappropriate trial design. However, the proof of principle has been made, and second-generation blockers (zibotentan) are under development after initially encouraging phase II trials (111), with large phase III trials in CRPC, either without metastases (> 1000 patients), with metastases (> 500 patients), or with docetaxel (> 1000 patients). Phase 3 trials in patients with CRPC are currently assessing docetaxel with or without atrasentan (NCT00134056) or zibotentan (ENTHUSE M1C; NCT00617669). However, recent results from the ENTHUSE M1 trial (NCT00554229) showed no significant improvement in OS with zibotentan monotherapy in men with mildly symptomatic CRPC (112). Moreover, it has been announced that the ENTHUSE M0 trial of zibotentan monotherapy in patients with non-metastatic CRPC has been discontinued after failing to meet the primary OS end-point. Phase 3 results for zibotentan/docetaxel treatment of bone-metastatic CRPC are still pending.

19.8.8 ***Salvage chemotherapy***

Since all patients who receive docetaxel-based chemotherapy for CRPC will progress, there have been many clinical trials investigating the role of salvage chemotherapy. The results suggest the most appropriate approaches are cabazitaxel (113), intermittent docetaxel chemotherapy (114,115), and potentially molecular-targeted therapy (116,117).

Several groups have used second-line intermittent docetaxel in patients who had clearly responded to first-line docetaxel (114,115,118). 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 (116,117,119-122) though more research is needed in larger groups of patients.

Platinum-based chemotherapeutic regimes have been investigated in patients with CRPC. Although the platinum complex, satraplatin, has shown activity against CRPC and some promise in clinical trials, the FDA rejected it for CRPC in 2008 (119).

Many new drugs, such as gefitinib, bevacizumab (phase III trial CALB 90401 ongoing), oblimersen (phase II trial EORTC 30021), and also a vaccine, G-Vax (122), 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.

Positive results have been recently published from a prospective, randomised, phase III trial comparing the therapeutic efficacy of the taxane derivate, cabazitaxel, + prednisone versus mitoxantrone + prednisone in 755 patients with castration-resistant PCa, who had progressed after or during docetaxel-based chemotherapy (123). Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m2) and mitoxantrone (12 mg/2), respectively. In both treatment arms, patients also received 10 mg prednisone daily for the entire treatment period. Overall survival was the primary endpoint and PFS, treatment response and safety were secondary endpoints. Patients in the cabazitaxel arm experienced a significantly increased OS of 15.1 versus 12.7 months ($p < 0.0001$) in the mitoxantrone arm. The cabazitaxel treatment arm also showed significant improvement

in PFS (2.8 vs 1.4 months, p < 0.0001), as well as in the objective response rate according to RECIST criteria (14.4% vs 4.4%, p < 0.005) and the 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 toxicities (57.4% vs 39.8%, p < 0.0002) (113). Because of this and the risk of neutropenic sepsis associated with cabazitaxel, this drug should be administered by physicians with expertise in handling neutropenia and sepsis, possibly with granulocyte colony-stimulating factor.Whether cabazitaxel can be substituted for front-line docetaxel is the subject of a prospective phase III trial.

Recommendations on hormonal therapy
According to the positive results of this prospective randomised clinical phase III trial (LE: 1), cabazitaxel should be considered in the management of progressive CRPCA following docetaxel therapy.
Based on this second positive trial, in patients with relapse following first-line docetaxel chemotherapy both Cabazitaxel and Abiraterone are regarded as first-choice options for second-line treatment

19.9 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 (124).

*19.9.1 **Painful bone metastases***

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective (125), even as single fraction (126). 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 (127), 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 (128). Palliative treatment with another radioisotope emitter, radium-233, has shown very promising phase II results in patients with painful bone metastases in terms of palliation and OS, and only a mild haematological toxicity (129). Recently, survival results of the randomised phase 3 trial in men with CRPC and symptomatic bone metastases ineligible for or post-progresion to docetaxel with 223Ra (Alpharadin) (NCT00699751) have been reported at the ESMO 2011 meeting.The trial showed a survival advantage for alpharadine versus placebo (11.2 months versus 14.0 months HR 0.695; 95% CI, 0.552-0.875 P = .00185) met its primary endpoint of improved OS. Full data are awaited (130).

*19.9.2 **Common complications due to bone metastases***

Common complications due to skeletal 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 of painful fracture, clearly improving both pain and QoL (131). However, it is still important to offer standard palliative surgery, which can be very effective at managing osteoblastic metastases (132,133). Impending spinal cord compression is an emergency. It must be recognised early and patients educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and an MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression (134). Otherwise, external beam radiotherapy, with or without systemic therapy, is the treatment of choice.

*19.9.3 **Bisphosphonates***

Recently, bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in CRPC to provide effective treatment of skeletal complications and to reduce pain or provide total pain relief. In the largest single phase III trial (135), 643 patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 8 mg or 4 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with only 4 mg of zoledronic acid had fewer skeletal-related events 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 skeletal-related event was longer in the zoledronate group, so 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.

Currently, bisphosphonates can be proposed 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 (135). Patients should have a dental examination before starting a bisphosphonate. 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 (136).

Pain due to osseous 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 in small, open trials only. This data show that bisphosphonates seem to have a low side-effect profile which make them an ideal medication for palliative therapy of advanced CRPC (137-139). 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 anti-emetics).

19.9.4 ***RANK ligand inhibitors***

Denosumab is a fully human monoclonal antibody directed against RANKL, a key mediator of osteoclast formation, function, and survival. Denosumab efficacy against CRPC bone metastases was initially assessed in a phase 2 study. Fifty patients with increased urinary NTX levels despite previous treatment with zoledronic acid were randomised to either continue on intravenous bisphosphonates or receive subcutaneous denosumab. Denosumab normalised NTX levels more frequently than continuing bisphosphonate treatment (140).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 skeletal related events (SREs), as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 versus 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). This was the last of three pivotal trials exploring denosumab treatment of bone metastases, which formed the basis of the recent FDA approval of denosumab for preventing SREs in patients with bone metastases from solid tumours.

19.10 Summary of treatment after hormonal therapy

(Until results from randomised controlled trials on novel agents MDV3100 and abiraterone become available, there are no significant changes in the treatment of prostate cancer after hormonal therapy [27]).

Recommendations	GR
It is recommended to stop anti-androgen therapy once PSA progression is documented.	B
No clear-cut recommendation can be made for the most effective drug for secondary hormonal.	
manipulations because data from randomised trials are scarce.	C

Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.

19.11 Recommendations for cytotoxic and pre/post-docetaxel therapy in CRPC

Recommendations	GR
Patients with CRPCa should be counselled, managed and treated in a multidisciplinary team.	
In non-metastatic CRPCa, cytotoxic therapy should only be used in a clinical trial setting.	B
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	B
Patients should not be started on cytotoxic therapy unless their testosterone serum levels are below 50 ng/dL.	B
Patients should not be started on cytotoxic therapy unless their PSA serum levels are > 2 ng/mL. to assure correct interpretation of therapeutic efficacy.	B
Prior to treatment, the potential benefits of cytotoxic therapy and expected side-effects should be discussed with the patient.	C
In patients with metastatic CRPCa who are candidates for cytotoxic therapy, docetaxel at 75 mg/m^2 every 3 weeks is the drug of choice since it has shown a significant survival benefit.	A

In patients with symptomatic osseous metastases due to CRPCa, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options. If not contraindicated, docetaxel is the preferred agent based on the significant advantage in pain relief.	A
In patients with relapse following first-line docetaxel chemotherapy Cabazitaxel and Abiraterone are regarded as first-choice option for second-line treatment.	A
Second-line docetaxel can be offered to previously responding docetaxel-treated patients. Otherwise treatment is to be tailored to the individual patient. In case patients are not eligible for cabazitaxel or abiraterone, docetaxel is an option.	A
In men with CRPC with symptomatic bone metastases, ineligible for or progressing to docetaxel treatment with 223Ra (Alpharadin) has shown a survival benefit (141).	A

19.12 Recommendations for palliative management of CRPC

Recommendations	GR
Patients with symptomatic and extensive osseous metastases should be informed that further medical treatment will not extend life.	A
Management of these patients has to be directed at improvement of QoL and mainly pain reduction.	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.	A
Bisphosphonates may be offered to patients with skeletal masses (mainly zoledronic acid has been studied) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, in particular jaw necrosis must be avoided.	A
Denosumab may be offered since it has been shown to delay/prevent SREs (pathologic fracture, radiation or surgery to bone, or spinal cord compression) also extending time to first and subsequent on-study SRE. Prior to treatment, the patient must be counseled about the potential benefits and side-effects (toxicity), in particular jaw necrosis.	A
In the management of painful osseous metastatses, early use of palliatative treatments such as radionuclides, external beam radiotherapy and adequate use of analgescis is recommended.	B
In patients with neurological symptoms, spinal surgery or decrompressive radiotherapy might be indicated as ermergency interventions.	A

19.13 References

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20. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

3D-US	three-dimensional ultrasound
ADT	androgen-deprivation therapy
AS	active surveillance
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
AUA	American Urological Association
BDFS	biochemical disease-free survival
BMD	bone mineral density
bNED	actuarial biochemical freedom from disease
CAB	complete (or maximal or total) androgen blockade
CPA	cyproterone acetate
CRT	conformal radiotherapy
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
DES	diethylstilboestrol
DRE	digital rectal anticipation
DHT	dihydrostestosterone
DSS	disease-specific survival
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
eLND	extended lymph node dissection
ELND	elective lymph node dissection
e-MRI	endorectal MRI
EORTC	European Organisation for Research and Treatment of Cancer
EPC	Early Prostate Cancer Trialists' Group
EPCP	Early Prostate Cancer Programme
EPE	extraprostatic extension
ER-®	oestrogen receptor-®
ESRPC	European Randomized Screening for Prostate Cancer
FACT-P	Functional Assessment of Cancer Therapy-prostate
FNAB	fine-needle aspiration biopsy
FSH	follicle-stimulating hormone
GI	gastrointestinal
GR	grade of recommendation
GU	genitourinary
HD EBRT	high-dose EBRT
HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
IAD	intermittent androgen deprivation
IGRT	image-guided radiotherapy
IMRT	intensity modulated radiotherapy
IPSS	International Prostatic Symptom Score
LDAT	long-term ADT
LDR	low-dose rate (LDR)
LE	level of evidence
LET	linear energy transfer
LH	luteinising hormone
LHRH	luteinising hormone-releasing hormone
LHRHa	luteinising hormone-releasing hormone analogue
LND	lymph node dissection
LRP	laparoscopic radical prostatectomy
MRC	Medical Research Council

MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopy imaging
NHT	neoadjvant hormonal therapy
NIH	National Institutes of Health
NVB	neurovascular bundle
OR	odds ratio
OS	overall survival
PAP	prostate acid phosphatase
PCa	prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PIN	prostatic intraepithelial neoplasia
PIVOT	Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative StudiesProgram #407
PLCO	Prostate, Lung, Colorectal and Ovary
PSA	prostate-specific antigen
PSA-ACT	PSA complexed to antichymotrypsin
PSADT	PSA doubling time
PSAV	PSA velocity
PSMA	prostate-specific membrane antigen for messenger RNA
QoL	quality of life
QUALYs	quality of life adjusted gain in life
RALP	robot-assisted radical prostatectomy
RITA	radio-frequency interstitial tumour ablation
RP	radical prostatectomy
RRP	radical retropubic prostatectomy
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results
SLN	sentinel lymph node
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
STAD	short-term androgen deprivation
SVI	seminal vesicle invasion
SWOG	South West Oncology Group
TNM	Tumour Node Metastasis
TZ	transition zone
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UICC	Union Against Cancer
USPIO	ultra-small super-paramagnetic iron oxide particles
VACURG	Veterans Administration Co-operative Urological Research Group
WHO	World Health Organization
WW	watchful waiting

Conflict of interest

All members of the Prostate Cancer Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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. INTRODUCTION

The EAU Guideline Group for renal cell carcinoma (RCC) have prepared these guidelines to help urologists assess the evidence-based management of RCC and to help them incorporate the guidelines recommendations into their clinical practice. Publications concerning RCC are mostly retrospective analyses, which include some larger multicentre studies and well-designed controlled studies. As only a few randomised controlled trials are available, there is some lack of data with a strong evidence base. In recent years, a number of randomised studies have been performed, mostly concerning the medical treatment of metastasised RCC resulting in high evidence-based recommendations.

Where possible, a level of evidence (LE) and/or grade of recommendation (GR) have been assigned (1). Recommendations are graded in order to provide transparency between the underlying evidence and the recommendation given (Tables 1 and 2).

There is clearly a need for re-evaluation at regular intervals by the RCC Guideline Group of the information provided in these guidelines. It has to be emphasised that the current guidelines contain information for the treatment of an individual patient according to a standardised general approach. The information should be considered as providing recommendations without legal implications.

The current document provides a full text update, with a summary of the amendments provided below.

1.1 Summary of the 2010 RCC guidelines update

A new chapter “Other renal tumours” has been added which discusses other tumours of the kidney with the exception of renal pelvic carcinoma. The content of the other chapters has been completely revised based on the findings of a structured literature search.

1.2 Methodology

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, 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 for Medline and Embase. Prior to publication of this document an update search was carried out.

Also other data sources were consulted such as the Database of Abstracts of Reviews of Effectiveness (DARE) as well as relevant reference lists from other guidelines producers (National Institute for Clinical Excellence [NICE], American Urological Association [AUA]).

Publication history information: The RCC Guidelines were first published in 2000, with partial updates in 2001 and 2007 followed by a full text update in 2009, and a partial update in 2010.

Table 1: Level of evidence

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

Modified from Sackett et al. (1).

Table 2: Grade of recommendation

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

Modified from Sackett et al. (1).

1.3 References

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2. EPIDEMIOLOGY AND AETIOLOGY

Renal cell carcinoma represents 2-3% of all cancers (1), with the highest incidence occurring in Western countries. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe, though in Denmark and Sweden a continuing decrease has been observed (2). In 2006, it was estimated that there were 63,300 new cases of RCC and 26,400 kidney cancer-related deaths within the European Union (3). In Europe, overall mortality rates for RCC have increased up until the early 1990s, with rates generally stabilising or declining thereafter (4). There has been a decrease in 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), mortality rates still show an upward trend with increasing rates (4).

Renal cell carcinoma is the commonest solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC types with specific histopathological and genetic characteristics (5). There is a 1.5:1 predominance of men over women, with peak incidence occurring between 60 and 70 years of age. Aetiological factors include lifestyle factors such as smoking, obesity, and hypertension (6-10). Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC (11,12). The most effective prophylaxis is to avoid cigarette smoking and obesity.

Due to the increased detection of tumours by imaging techniques such as ultrasound and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are more often smaller and of lower stage (13-15).

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

	GR
The most important primary prevention for RCC is to eliminate cigarette smoking and to avoid obesity.	B

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3. DIAGNOSIS AND STAGING

3.1 Symptoms

Many renal masses are asymptomatic and non-palpable until the late stages of the disease (1). Currently, more than 50% of RCCs are detected incidentally by using imaging to investigate a variety of non-specific symptom complexes (2-4) (LE: 2b). The classic triad of flank pain, gross haematuria, and palpable abdominal mass is now rare (6-10%) (5,6) (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (Table 3) (LE: 4). A few symptomatic patients present with symptoms due to metastatic disease, such as bone pain or persistent cough (1,7) (LE: 2b).

Table 3: Most common paraneoplastic syndromes

Hypertension
Cachexia
Weight loss
Pyrexia
Neuromyopathy
Amyloidosis
Elevated erythrocyte sedimentation rate
Anaemia

Abnormal liver function
Hypercalcaemia
Polycythaemia

3.1.1 ***Physical examination***

Physical examination has only a limited role in diagnosing RCC. However, the following findings should initiate radiological examinations:

- palpable abdominal mass;
- palpable cervical lymphadenopathy;
- non-reducing varicocele;
- bilateral lower extremity oedema, which suggests venous involvement.

3.1.2 ***Laboratory findings***

The most commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate, haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase, lactate dehydrogenose (LDH), and serum corrected calcium (1,8,9) (LE: 4).

Separate bilateral renal function should be estimated in the following situations (10-12) (LE: 2b):

- When renal function is clinically important, e.g. in patients with a solitary kidney tumour or bilateral tumours;
- When renal function is compromised, as indicated by an increased concentration of serum creatinine;
- In patients at risk of future renal impairment from co-morbid disorders, e.g. diabetes, chronic pyelonephritis, renovascular disease, stone or renal polycystic disease.

3.2 Radiological investigations

Most renal tumours are diagnosed by abdominal ultrasound or CT performed for various reasons (LE: 4). Imaging can be used to classify renal masses into solid or cystic.

3.2.1 ***Presence of enhancement***

For solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement (13) (LE: 3). The traditional approach for detection and characterisation of renal masses is to use ultrasound, CT, or magnetic resonance imaging (MRI). Most renal masses can be diagnosed accurately by using imaging alone. Contrast-enhanced ultrasound can be helpful in specific cases (e.g. chronic renal failure with relative contraindication for iodinated or gadolinium contrast media (14-16) (LE: 3).

3.2.2 ***Computed tomography or magnetic resonance imaging***

Computed tomography or MRI are used to characterise a renal mass. Imaging must be performed both before and after administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield unit (HU) readings from before and after contrast administration. A change of 20 HU or greater is strong evidence of enhancement (17) (LE: 3). To maximise differential diagnosis and detection, the evaluation should include images from the nephrographic phase, because this phase allows optimum depiction of renal masses that typically do not enhance to the same degree as renal parenchyma.

Abdominal CT allows diagnosis of RCC and provides information on:

- function and morphology of the contralateral kidney (10) (LE: 3);
- primary tumour extension with extrarenal spread;
- venous involvement;
- enlargement of locoregional lymph nodes;
- condition of adrenal glands and the liver (LE: 3).

Abdominal contrast-enhanced CT angiography is a useful tool in selected cases to obtain detailed information about the kidney vascular supply (18). If CT results are indeterminate, MRI may provide additional information to:

- demonstrate enhancement in renal masses;
- investigate locally advanced malignancy;
- investigate venous involvement if there is a badly defined extension of inferior vena cava tumour thrombus on CT scan (19-22) (LE: 3).

Magnetic resonance imaging is also indicated in patients with an allergy to intravenous contrast and in

pregnancy without renal failure (23,24) (LE: 3). Evaluation of the tumour thrombus can also be performed with Doppler ultrasound (25) (LE: 3).

*3.2.3 **Other investigations***

Renal arteriography and inferior venacavography have only 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 the treatment decision, e.g. the need to preserve renal function (10-12) (LE: 2a). The true value of positron emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined and currently PET is not a standard investigation (26,27) (LE: 1b).

*3.2.4 **Metastatic RCC investigations***

Chest CT is the most accurate investigation for chest staging (25,28-34) (LE: 3). However, at the very least, routine chest radiography, as a less accurate alternative to chest CT imaging, must be done for metastatic evaluation (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis so that a routine bone or brain CT scan is not generally indicated (35,36). However, if indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be used, such as a bone scan, brain CT, or MRI (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 CR imaging appearance in an attempt to predict the risk of malignancy (38) (LE: 3). The Bosniak system also advocates treatment for each category (Table 4).

Table 4: The Bosniak classification of renal cysts (38**)**

Bosniak category	**Features**	**Work-up**
I	A simple benign cyst with a hairline-thin wall that does not contain septa, calcification, or solid components. It measures water density and does not enhance with contrast material.	Benign
II	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 of < 3 cm, which are sharply marginated and do not enhance.	Benign
IIF	These cysts might 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 that might 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 of ≥ 3 cm. These lesions are generally well-marginated.	Follow-up. A small proportion are malignant.
III	These lesions are indeterminate cystic masses that have thickened irregular walls or septa in which enhancement can be seen.	Surgery or follow-up. Malignant in > 50% lesions.
IV	These lesions are clearly malignant cystic lesions that contain enhancing soft-tissue components.	Surgical therapy recommended. Mostly malignant tumour.

3.3 Renal biopsy

Renal tumour biopsies are increasingly being used in diagnosis, in follow-up surveillance, and in ablative therapies (40-45) (LE: 3). In most series, a core biopsy demonstrates high specificity and high sensitivity for the presence of malignancy (40-44), though it should be noted that 10-20% of biopsies are non-conclusive.

Biopsy aims to determine eventual malignancy, type, and grade of the evaluated renal mass.
A percutaneous mass biopsy is rarely required for large renal masses scheduled for nephrectomy.
The positive predictive value of imaging findings is so high that a negative biopsy result does not alter management (45) (LE: 3).

Biopsy is also indicated in metastatic patients before starting systemic therapy (46) (LE: 3).

3.4 Histological diagnosis

The histological diagnosis in RCC is established after surgical removal of renal tumours or after biopsy specimen examinations (40-42). The Fuhrman classification system for nuclear grade (grade 1, 2, 3 and 4) in RCC (47,48) has been the most generally accepted classification, and is an important, independent prognostic factor for RCC (LE: 3).

According to the World Health Organization (WHO) (49) there are at least three major histological subtypes of RCC:

- clear cell (cRCC, 80-90%);
- papillary (pRCC, 10-15%);
- chromophobe (chRCC, 4-5%) (LE: 3).

These RCC types can be differentiated by histological and molecular genetic changes (Table 5) (LE: 3). Papillary RCC can further be divided into two different subtypes: type 1 and type 2 with an adverse clinical course (Table 5) (50,51) (LE: 3).

Table 5: Major histological subtypes of RCC

Histological subtype	Percentage of RCC	Histological description	Associated molecular genetic changes
Clear cell (cRCC)	80-90%	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.	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.
Papillary (pRCC)	10-15%	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.	The most consistent genetic alterations are trisomies of chromosomes 3q, 7, 8, 12, 16, 17, and loss of the y chromosome.
Chromophobe (chRCC)	4-5%	The cells of chRCC may have pail or eosinophilic granular cytoplasm. Growth usually occurs in solid sheets.	The genetic characteristic is a combination of loss of chromosomes 1, 2, 6, 10, 13, and 17.

3.5 Conclusion

The proportion of small and incidental renal tumours has significantly increased in most countries, though a large number of patients with RCC still present with clinical symptoms, such as palpable mass, haematuria, and paraneoplastic and metastatic symptoms (LE: 3). Accurate staging of RCC with abdominal and chest CT or MRI is obligatory (LE: 3). Chest CT is the most sensitive approach for chest staging. There is no role for routine bone scan or CT of the brain in the standard clinical work-up of asymptomatic patients.

Recently, there has been an increasing indication for fine-needle biopsy for evaluation and ablative therapies in small renal tumours (40-45) (LE: 3).

3.6 Recommendations

	GR
In a patient with one or more laboratory or physical findings, the possible presence of RCC should be suspected.	B
A plain chest x-ray can be sufficient for assessment of the lung in low-risk patients, but chest CT is most sensitive.	A
Abdominal CT and MRI are recommended for the work-up of patients with RCC and are the most appropriate imaging modalities for Tumour Node Metastasis (TNM) classification prior to surgery.	A
In high-risk patients for bone metastases (raised alkaline phosphatase or bone pain), further evaluation using an imaging approach should be done.	A
Evaluation of renal function is recommended.	B
Percutaneous biopsy is always indicated before ablative- and systemic therapy without previous histopathology.	B
Percutaneous biopsy is recommended in surveillance strategies to stratify follow-up.	B

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4. CLASSIFICATION AND PROGNOSTIC FACTORS

4.1 Classification

The TNM stage classification system is generally recommended for clinical and scientific use (1). However, the TNM classification requires continuous improvements (2). The 2009 version has introduced significant changes based on recent prognostication literature (Table 6).

- The pT1 substratification, introduced in 2002, has been validated by several studies and is no longer a matter of controversy (3-5) (LE: 3). Even though it has been less extensively studied, the tumour size stratification of T2 tumours has been recently introduced within the 2009 TNM classification.
- 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).
- Many studies have suggested that adrenal invasion has a very poor prognostic value and that RCCs with this feature should be classified as pT4 tumours (9,10) (LE: 3). This change has been introduced in the latest TNM version (1).
- In previous TNM classifications, the pT3b group included both renal vein and inferior vena cava invasions. As the result of many studies into the independent prognostic value of vena cava compared to renal vein invasion alone (11-13), these two groups have now been separated in the latest version of the TNM classification (1).
- The accuracy of the N1-N2 subclassification has been questioned (14) (LE: 3). For adequate M-staging of patients with RCC, accurate pre-operative imaging (currently, chest and abdominal CT) should be performed (15,16) (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, lymph node, and distant metastasis. These factors are commonly gathered together in the universally used TNM staging classification system (Table 6).

Table 6: The 2009 TNM staging classification system (1)

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm but ≤ 10 cm in greatest dimension
T2b	Tumours > 10 cm limited to the kidney
T3	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

	T3a	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
	T3b	Tumour grossly extends into the vena cava below the diaphragm
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)	
N - Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single regional lymph node	
N2	Metastasis in more than 1 regional lymph node	
M - Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
TNM stage grouping		
Stage I	T1	N0 M0
Stage II	T2	N0 M0
Stage III	T3	N0 M0
	T1, T2, T3	N1 M0
Stage IV	T4	Any N M0
	Any T	N2 M0
	Any T	Any N M1

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 (17). Although affected by intra- and inter-observer discrepancies, it is an independent prognostic factor (18). Recently, 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 (19,20) (LE: 3).

According to the WHO classification (21), 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 (22,23). However, the prognostic information provided by the RCC subtype is lost when stratified to tumour stage (23,24) (LE: 3).

Among papillary RCCs, two subgroups with different outcomes have been identified (25):
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).

The RCC type classification has been confirmed at the molecular level by cytogenetic and genetic analyses (26-28) (LE: 2b).

*4.2.3 **Clinical factors***

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia, and platelet count (29-32) (LE: 3).

*4.2.4 **Molecular factors***

Numerous molecular markers being investigated include: 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, and CD44 (cell adhesion) (33,34) (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 (35).

*4.2.5 **Prognostic systems and nomograms***

Post-operative prognostic systems and nomograms that combine independent prognostic factors have been developed and externally validated (36-42). 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 post-operative histo-prognostic schemes (43). Recently, new pre-operative nomograms with excellent PAs have been designed (44,45). Table 7 summarises the current most relevant prognostic systems.

4.3 Conclusion

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 (LE: 2). Prognostic systems should currently be used in a metastatic setting and are still investigational in localised disease (LE: 2).

4.4 Recommendations

	GR
The current TNM classification system is recommended because it has consequences for prognosis and therapy.	B
The Fuhrman grading system and classification of RCC subtype should be used.	B
A stratification system should be used in a metastatic setting for selecting the appropriate first-line treatment.	B
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.	B
No molecular prognostic marker is currently recommended for routine clinical use.	B

Table 7: Summary of the anatomical, histological, and clinical variables included in the most commonly used prognostic models for localised and metastatic RCC

Prognostic Models		Variables												
		TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	Tumor necrosis	Tumor size	Delay between diagnosis and treatment	LDH	Corrected calcium	Hemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS	X	X			X								
	SSIGN	X				X	X	X						
	Post operative Karakiewicz's nomogram	X			X	X		X						
Metastatic RCC	MSKCC prognostic system			X					X	X	X	X		
	Heng's model			X					X		X	X	X	X

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; RCC = renal cell carcinoma; SSIGN = Stage Size Grade Necrosis; TNM = tumour node metastasis; UISS = University of California Los Angeles integrated staging system.

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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). The common clear cell (cRCC), papillary (pRCC) and chromophobe RCC (chRCC) types account for 85-90% of the renal malignancies. The remaining 10-15% of renal tumours include 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. 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 (2-4).

5.2 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 (5).

5.3 Unclassified RCC

Unclassified RCC is a diagnostic category for RCC that cannot be assigned to any other category of RCC-type carcinoma (1).

5.4 Multilocular cystic RCC (cRCC)

There are no strict histopathological criteria for this subtype. In the WHO 2004 classification (1), multilocular cRCC is an independent entity, but it is essentially a well-differentiated cRCC. This subtype accounts for up to about 3.5% of surgically treated kidney tumours (6). To date, metastases of this tumour have not been

described (6,7). According to the Bosniak classification, which is based on imaging criteria, multilocular cRCC presents as a Bosniak type II or III cystic lesion (8-10). However, this type of Bosniak lesion can also be due to a mixed epithelial and stromal tumour of the kidney (MESTK), a cystic nephroma, 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 procedure of choice for a complex multicystic renal mass with enhanced density is observed (LE: 3) (GR: B) (6,7,9,10).

5.5 Papillary adenoma

Papillary adenomas are tumours with papillary or tubular architecture of low nuclear grade and 5 mm in diameter or smaller (1). Because they are so small, they are only found incidentally in a nephrectomy specimen.

5.6 Renal medullary carcinoma

Renal medullary carcinoma is a devastating malignancy that primarily affects young men with sickle cell trait. It is also extremely rare, comprising approximately 2% of all primary renal tumours in young people aged 10 to 20 years old. Metastatic disease is seen at presentation in 95% of patients (2,11,12).

5.7 Translocation 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 (2). Another rare group of RCCs that show a translocation (t (6; 11) (p21; q12)) has also been reported (2,13).

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 (1,2,14).

5.9 Carcinoma associated with end-stage renal disease

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 in the general population. Compared with sporadic RCCs, the RCCs associated with ESKD and ACKD are characterised by multicentricity and bilaterality, being found in younger patients (mostly male), and by less aggressive behaviour. In transplanted patients, however, it is usually quite aggressive, probably as a result of immunosuppression (15-20).

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 (2,19,20). Tickoo et al. (21) recently described two new renal tumours associated with ESKD: ‘acquired cystic disease-associated RCC‘ and ‘clear-cell pRCC‘. To date, these entities have not generally been accepted. The malignant potential of RCCs in ESKD is still a matter of discussion compared to sporadic RCCs. Patients with ESKD should undergo an annual ultrasound evaluation of the kidneys (16-19).

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 (22). Imaging reveals that most REST cystic lesions are Bosniak type III and less frequently Bosniak type II or IV (8,10). Even though aggressive behaviour has been reported in very few cases, both neoplasms are generally considered to be benign and surgical excision as curative (22).

5.12 Oncocytoma

Renal oncocytomas are benign tumours (1) that comprise about 3-7% of all renal tumours (23). Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard (24). Although only a percutaneous biopsy can lead to a pre-

operative 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) (25). 'Watchful waiting' can be considered in selected cases of histologically verified oncocytoma (LE: 3) (GR: C) (25,26).

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, hereditary leiomyomatosis, tuberous sclerosis, and constitutional chromosome 3 translocation (1,27).

5.14 Mesenchymal tumours

Mesenchymal tumours include different types of 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 epitheloid smooth muscle cells, and abnormal thick-walled blood vessels. It can occur sporadically, which is four times more likely in women. It also occurs in tuberous sclerosis, 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. Epithelioid AML is a potentially malignant variant of AML (1).

The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening (28). The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels (28). The major risk factors for bleeding are tumour size, the grade of angiogenic component of the tumour, and the presence of tuberous sclerosis (28,29).

Primary indications for intervention include symptoms such as pain, bleeding, or suspected malignancy. Prophylactic intervention is justifiable for:

- large tumours (the recommended threshold of intervention is ≥ 4 cm wide (28,30);
- females of childbearing age;
- patients in whom follow-up or access to emergency care may be inadequate (29) (LE: 3) (GR: C).

Most cases of AML can be managed by conservative nephron-sparing approaches, though some cases of AML may require complete nephrectomy (29) (LE: 3). Of the standard surgical interventions, selective arterial embolisation (SAE) and radiofrequency ablation (RFA) can be used (28,31). Although SAE is effective at controlling haemorrhage in the acute setting, it has limited value in the longer-term management of AML (31).

5.15 New histological entities

New histological entities have recently been described, for which there currently is very little clinical data. The entities include:

- thyroid-like follicular tumour/carcinoma of the kidney (32);
- RCC associated with neuroblastoma (1);
- renal angiomyoadenomatous tumour (33);
- tubulocystic carcinoma (34);
- clear cell pRCC (2);
- oncocytic pRCC (2);
- follicular renal carcinoma (2);
- leiomyomatous RCC (2).

Table 8: Summary of other renal tumours with indication of malignant potential and recommendation for treatment (GR: C)

Entity	Malignant potential	Treatment
Sarcomatoid variants of RCC	High	Surgery
Multilocular clear cell RCC	Low, no metastasis	Surgery, NSS*
Papillary adenoma	Benign	Observation
Carcinoma of the collecting ducts of Bellini	High, very aggressive	Surgery, in M+ discussable

Renal medullary carcinoma	High, very aggressive	Surgery
Translocation carcinoma	Intermediate	Surgery, NSS
Mucinous tubular and spindle cell carcinoma	Intermediate	Surgery, NSS
Carcinoma associated with end-stage renal disease	Variable	Surgery
Metanephric tumours	Benign	Surgery, NSS
Renal epithelial and stromal tumours (REST)	Low	Surgery, NSS
Oncocytoma	Benign	Observation/surgery
Hereditary kidney tumours	High	Surgery, NSS
Angiomyolipoma	Benign	Consider treatment when > 4 cm
Unclassified RCC	Variable	Surgery, NSS

**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

	LE	GR
Except for angiomyolipomas, most of these less common renal tumours cannot be differentiated from RCC on the basis of radiology and should therefore be treated in the same way as RCC.	3	C
Bosniak cysts ≥ type III should be surgically treated. When possible, a nephron-sparing procedure should be performed in Bosniak type III.	3	C
In oncocytomas verified on biopsy, follow-up is an option.	3	C
In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered when the tumour > 4cm. When possible, a nephron-sparing procedure should be performed.	3	C
In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.	4	C

5.18 References

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6. TREATMENT OF LOCALISED RCC

6.1 Nephron-sparing surgery (partial tumour resection)

Nephron-sparing surgery (partial tumour resection) for localised RCC has a similar oncological outcome to that of radical surgery (1-5). However, in some patients with localised RCC, nephron-sparing surgery 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 gold standard curative therapy remains radical nephrectomy, which includes removal of the tumour-bearing kidney. Complete resection of the primary tumour by either open (6,7) or laparoscopic surgery (8-13) offers a reasonable chance of curing the disease.

*6.1.1 **Associated procedures***

6.1.1.1 Adrenalectomy

Adrenalectomy is not indicated in the following situations (14-22):

- Pre-operative tumour staging (CT, MRI) shows a normal adrenal gland;
- Intra-operative findings do not give any indication of a nodule within the adrenal gland suspicious of metastatic disease;
- There is no evidence of direct invasion of the adrenal gland by a large upper pole tumour.

6.1.1.2 Lymph node dissection

An extended or radical lymph node dissection does not appear to improve long-term survival following tumour nephrectomy (23). Thus, for staging purposes, the 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.

6.1.1.3 Embolisation

There is no benefit in performing tumour embolisation before routine nephrectomy (24-26). 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 (27-31). Embolisation prior to the resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss (32-34). In selected patients with painful bone or paravertebral metastases, embolisation can help to relieve symptoms (35).

6.1.1.4 Conclusions

- Patients with low-stage RCC (T1) should undergo nephron-sparing surgery. Radical nephrectomy is no longer the gold standard treatment in these cases (1-5) (LE: 2b).
- 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 by a larger upper pole tumour (14-22) (LE: 3).
- Extended lymphadenectomy does not improve survival in RCC patients and should be restricted to staging purposes with dissection of palpable and enlarged lymph nodes (23) (LE: 1b).
- RCCs with tumour thrombi have a higher stage and grade of disease (LE: 2b). Distant and lymph node metastases are twice as common in these patients (LE: 3). The increase in biological aggressiveness of the disease has a larger influence on clinical prognosis than the cranial extension of an intracaval thrombosis (36-40) (LE: 3).

6.1.1.5 Recommendations

	GR
Surgical therapy is the only curative therapeutic approach for the treatment of RCC. For T1 tumours, nephron-sparing surgery should be performed whenever possible. Extended lymphadenectomy does not improve survival and can be restricted to staging purposes.	A
Adrenalectomy (together with nephrectomy) is not needed in most patients, except when there is a large upper pole tumour and direct invasion of the adrenal gland is likely or when a normal adrenal gland cannot be excluded.	B
Embolisation can be a beneficial palliative approach in patients unfit for surgery and suffering from massive haematuria or flank pain.	C

6.1.2 ***Indications for nephron-sparing surgery***

Standard indications for nephron-sparing surgery are divided into the following categories:

- absolute – anatomical or functional solitary kidney;
- relative – functioning opposite kidney is affected by a condition that might impair renal function in the future;
- elective – localised unilateral RCC with a healthy contralateral kidney.

Relative indications include hereditary forms of RCC, which carry a high risk of developing a tumour in the contralateral kidney.

For elective indications, nephron-sparing surgery for tumours limited in diameter (T1a) provides recurrence-free and long-term survival rates similar to those observed after radical surgery (1-5,41,42) (LE: 2b). For larger tumours (T1b), partial nephrectomy has demonstrated feasibility and oncological safety in carefully selected patients (43-47).

6.1.3 ***Complications***

- The complication rates observed with nephron-sparing surgery are slightly higher but still very tolerable when compared with radical nephrectomy (48) (LE: 1b).
- Nephron-sparing surgery carried out for absolute rather than elective indications carries an increased complication rate and a higher risk of developing locally recurrent disease, probably due to the larger tumour size (49-51) (LE: 3).

6.1.4 ***Prognosis***

- In patients with a sporadic solitary renal tumour of up to 4-5 cm maximum diameter and a normal contralateral kidney, long-term renal function is better preserved with a nephron-sparing approach than with nephrectomy (52).
- There is a strong indication that, due to better preservation of renal function, nephron-sparing surgery

results in an improved overall survival when compared with radical nephrectomy (53-55) (LE: 3).
- If the tumour is completely resected, the thickness of the surgical margin does not impact on the likelihood of local recurrence (56-58) (LE: 3).

*6.1.5 **Conclusions***

- Nephron-sparing surgery has a slightly higher complication rate compared with radical surgery.
- However, nephron-sparing surgery is a safe procedure from the oncological point of view. Whenever technically feasible, nephron-sparing surgery is therefore considered to be the standard of care for T1a/b stage RCC (1-5,41-47).
- In the long term, a nephron-sparing approach results in improved preservation of renal function, decreased overall mortality, and reduced frequency of cardiovascular events (53-55).

*6.1.6 **Recommendations***

	GR
Whenever technically feasible, nephron-sparing surgery is the standard procedure for solitary renal tumours up to a diameter of 7 cm.	A
A minimal tumour-free surgical margin following partial resection of RCC is sufficient to avoid local recurrence.	B
There is an increased risk of intrarenal recurrences in larger-size (> 7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin. Follow-up should be intensified in these patients.	C

6.2 Laparoscopic surgery

Since its introduction, laparoscopic nephrectomy for RCC has become an established surgical procedure worldwide. Whether done retro-peritoneally or trans-peritoneally, the laparoscopic approach must follow established open surgical oncological principles.

*6.2.1 **Laparoscopic radical nephrectomy***

Laparoscopic radical nephrectomy is the standard of care for patients with T2 tumours and smaller renal masses not treatable by nephron-sparing surgery (59-63). Long-term outcome data indicate that laparoscopic radical nephrectomy has equivalent cancer-free survival rates to those of open radical nephrectomy (10,12,13,61,62,64-68).

6.2.1.1 Conclusions

- Laparoscopic radical nephrectomy appears to have a lower morbidity compared to open surgery, though this is based on only a few studies using a standardised quality-of-life evaluation (69) (LE: 3).
- Tumour control rates appear equivalent for T1-T2 tumours (10,12,13,61,62,64-68) (LE: 3).

6.2.1.2 Recommendations

	GR
Laparoscopic radical nephrectomy is recommended in T2 renal cell cancer.	B
Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial resection is indicated.	B

*6.2.2 **Partial laparoscopic nephrectomy***

In experienced hands and selected patients, laparoscopic partial nephrectomy is an alternative to open nephron-sparing surgery. The optimal indication for laparoscopic nephron-sparing surgery is a relatively small and peripheral renal tumour (4).

During laparoscopic partial resection, the intra-operative ischaemia time is longer than with open partial nephrectomy (4,70,71). Long-term renal function depends on the duration of the intra-operative ischaemia time (72).

Laparoscopic nephron-sparing surgery has a higher complication rate compared to open surgery. However, the oncological outcome in available series with limited follow-up appears to be similar to the outcome achieved with open nephron-sparing surgery (4,73,74).

In patients with a solitary kidney, laparoscopic partial nephrectomy results in a prolonged warm ischaemia time and a higher complication rate. Temporary or permanent dialysis is more likely to be necessary (4,72,75).

6.2.2.1 *Robotic-assisted partial nephrectomy*

Robotic-assisted partial nephrectomy is a novel technique that is still undergoing evaluation (76-80).

6.2.2.2 *Conclusion*

Partial nephrectomy by laparoscopic surgery is technically feasible (LE: 2b).

6.2.3 ***Recommendations***

	GR
Open partial nephrectomy currently remains the standard of care.	C
Laparoscopic partial nephrectomy should be performed by experienced surgeons.	C
Open partial resection is recommended for renal masses in a solitary kidney.	C

6.3 Therapeutic approaches as alternative to surgery

6.3.1 ***Surveillance***

In patients presenting with small renal masses, who undergo active surveillance, there appears to be no correlation between local tumour progression and an increased risk of metastatic disease. Both short- and intermediate-term oncological outcomes indicate that it is an appropriate strategy to initially monitor small renal masses followed, if required, by treatment for progression (73,81,82).

6.3.2 ***Percutaneous approaches***

Suggested alternatives to the surgical treatment of RCC have included image-guided percutaneous and minimally invasive techniques, e.g. percutaneous RFA, cryoablation, microwave ablation, laser ablation, and high-intensity focused ultrasound ablation (HIFU) (LE: 2b).

Possible advantages of these and other techniques include reduced morbidity, out-patient therapy, and the ability to treat high-risk surgical candidates (LE: 2b).

Indications for minimally invasive techniques, including RFA, are:

- small, incidentally found, renal cortical lesions in elderly patients;
- patients with a genetic predisposition for developing multiple tumours;
- patients with bilateral tumours;
- patients with a solitary kidney at high risk of complete loss of renal function following surgical tumour resection (LE: 2b).

Contraindications to the above-mentioned procedures include:

- poor life expectancy of < 1 year;
- multiple metastases;
- low possibility of successful treatment due to size or location of tumour. In general, tumours > 3 cm or tumours in the hilum, near the proximal ureter or the central collecting system are not typically recommended for ablative techniques via a percutaneous approach.

Absolute contraindications include:

- irreversible coagulopathies;
- severe medical instability, such as sepsis.

6.3.2.1 *Radiofrequency ablation and cryoablation*

Of all the available ablative techniques, RFA and cryoablation are the most intensively investigated approaches in terms of how practical they are to use, complication rate, and oncological safety.

Before an ablative approach, a pre-treatment biopsy to clarify the histology of the renal mass should be carried out. The available literature indicates that the pathology is unknown in a significantly higher proportion of patients undergoing RFA (40%) versus 25% in patients undergoing cryotherapy.

Compared to RFA, cryoablation is more likely to be performed laparoscopically. The laparoscopic approach is more effective but has a higher complication rate. Repeat ablation is necessary more frequently following RFA. Local tumour progression is significantly higher with RFA. Cancer-specific survival rates for cryotherapy and RFA are poorer than survival rates for surgical procedures (83-86).

6.3.2.2 *Conclusions*

- Radiofrequency and cryoablation are the only minimally invasive approaches for the treatment of small renal tumours with medium follow-up data.

- Although the oncological efficacy is not yet known, currently available data strongly suggest that cryoablation, when performed laparoscopically, results in fewer re-treatments and improved local tumour control compared with RFA (LE: 3).
- For both RFA and cryoablation, recurrence rates are higher than with nephron-sparing surgery (83-86) (LE: 3).

6.3.2.3 Recommendations

	GR
Patients with small tumours and/or significant co-morbidity who are unfit for surgery should be considered for an ablative approach, e.g. cryotherapy and radiofrequency ablation.	A
Pre-treatment biopsy has to be carried out as standard.	C
Other image-guided percutaneous and minimally invasive techniques, such as microwave ablation, laser ablation, and high-intensity focused ultrasound ablation are still experimental in character. The experience obtained with radiofrequency ablation and cryoablation should be considered when using these related techniques.	B

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 (87-91) (LE: 1b). Prognostic algorithms might identify patients likely to derive the largest clinical benefit from adjuvant vaccination therapy.

*6.4.1 **Conclusion***

Adjuvant therapy with cytokines does not improve survival after nephrectomy (LE: 1b).

*6.4.2 **Recommendation***

	GR
Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.	A

6.5 Surgical treatment of metastatic RCC (tumour nephrectomy)

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For the majority of patients with metastatic disease, tumour nephrectomy is palliative and other systemic treatments are necessary. In a meta-analysis of two randomised studies, comparing nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to tumour nephrectomy (92). Nephrectomy in patients with metastatic disease is indicated for patients who are both suitable for surgery and have good performance status (93). At present, only limited data are available addressing the value of cytoreductive nephrectomy combined with targeting agents.

*6.5.1 **Conclusion***

Tumour nephrectomy in combination with interferon-alpha (IFN-alpha) improves the survival of patients with metastatic RCC (mRCC) and good performance status (LE: 1b).

*6.5.2 **Recommendation***

	GR
Tumour nephrectomy is recommended for metastatic RCC patients with good performance status when combined with IFN-alpha.	A

6.6 Resection of metastases

Complete removal of metastatic lesions contributes to an improvement of clinical prognosis. Immunotherapy, where there has been complete resection of metastatic lesions or isolated local recurrences, does not contribute to an improvement in clinical prognosis (93-97) (LE: 2b).

*6.6.1 **Conclusion***

There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis

(LE: 3). Therefore; the possibility of metastasectomy has to be continuously re-evaluated, even together with a targeted systemic therapy.

6.6.2 ***Recommendation***

	GR
In patients with synchronous metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status. The clinical prognosis is worse in patients who have surgery for metachranous metastases.	B
Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or a limited (solitary lesion) number of metachranous metastases in order to improve the patient's prognosis.	B

6.7 Radiotherapy for metastases in RCC

Radiotherapy can be used for selected symptomatic patients with non-resectable brain or osseous lesions who do not respond to systemic treatment approaches (98,99).

6.7.1 ***Conclusion***

Radiotherapy of metastases from RCC can induce a significant relief from symptoms with pain reduction, e.g. a single bony deposit (LE: 2b).

6.7.2 ***Recommendation***

	GR
In individual cases, radiotherapy for the treatment of brain metastases (whole brain irradiation or stereotactic approach) and osseous lesions can induce a relief from symptoms due to mRCC (100,101).	B

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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 chemotherapies. Chemotherapy seems to be moderately effective only if 5-fluorouracil (5FU) is combined with immunotherapeutic agents (1).

*7.1.1 **Conclusion***

Only 5FU in combination with immunotherapy seems to be effective in patients with mRCC (LE: 3).

Recommendation

	GR
Chemotherapy as monotherapy should not be considered effective in patients with mRCC.	B

7.2 Immunotherapy

*7.2.1 **Interferon-alpha monotherapy and combined with bevacizumab***

In randomised studies, IFN-alpha has proven superiority for survival over hormonal therapy in patients with mRCC (2). Interferon-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 compared with a placebo-equivalent (3,4). The positive effect of IFN-alpha is particularly important in mRCC patients with clear-cell histology, good-risk Motzer criteria and lung metastases only (4). In a prospective randomised study, IFN-alpha showed equivalence in efficacy to the combination IFN-alpha + IL2 + 5FU (5).

A combination of bevacizumab + IFN-alpha recently demonstrated increased response rates and progression-free survival in first-line therapy compared to IFN-alpha monotherapy (6). All recent randomised studies comparing anti-angiogenic drugs in a first-line setting to IFN-alpha monotherapy have demonstrated a superiority for either sunitinib, bevacizumab + IFN-alpha or temsirolimus (6-9).

Table 9: MSKCC (Motzer) criteria to predict survival of patients with advanced RCC; depending on the presence or absence of 5 distinct risk factors (3)

Risk factors[1]	Cut Point Used
Karnofsky performance status	< 80
Time from diagnosis to treatment with IFN-alpha	< 12 months
Hemoglobin	< Lower limit of laboratory's reference range
Lactate dehydrogenase	> 1.5 x the upper limit of laboratory's range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)

[1]Favourable (low) risk, 0 risk factor; intermediate, 1-2 risk factors; poor (high) risk ≥ 3 risk factors.

7.2.1.1 Conclusions

- Interferon-alpha monotherapy is no longer recommended as first-line therapy for mRCC (LE: 1b).
- Interferon-alpha monotherapy still has a role only in selected cases (good performance status, clear-cell type, lung metastases only) (LE: 2).

*7.2.2 **Interleukin-2***

Interleukin-2 (IL-2) has been used to treat mRCC since 1985 with response rates ranging from 7-27% (9-11).

The optimal IL-2 regimen is not clear, but long-term (> 10 years) complete responders have been achieved with high-dose bolus IL-2 (12). The toxicity of IL-2 is substantially higher than that of IFN-alpha. Only clear cell type RCC responds to immunotherapy. Interleukin-2 has not been validated in controlled randomised studies compared with best supportive care (4).

7.2.2.1 Conclusions

- Interleukin-2 has more side-effects than INF-alpha.
- High-dose IL-2 gives durable complete responders in a limited number of patients.
- Interleukin-2 can be considered as monotherapy in selected patients with a good prognosis profile.

7.2.2.2 Recommendations

	GR
Monotherapy with IFN-alpha or high-dose bolus IL-2 can only be recommended as a first-line treatment for mRCC in selected cases with clear-cell histology and good prognostic factors.	A
Bevacizumab + IFN-alpha is recommended as first-line therapy in low- and intermediate-risk patients. Only selected patients with mRCC, revealing a good risk profile, and clear-cell subtype histology, show clinical benefit from immunotherapy with IL-2.	B
Cytokine combinations, with or without additional chemotherapy, do not improve overall survival compared with monotherapy.	A

7.3 Angiogenesis inhibitor drugs

Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC (Table 9).

In sporadic clear cell RCC, HIF accumulation due to von Hippel Landau (VHL) inactivation, results in overexpression of VEGF and PDGF (platelet-derived growth factor), both of which promote neo-angiogenesis (13-15). 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-alpha;
- pazopanib (Votrient®);
- temsirolimus (Torisel®);
- everolimus (Afinitor®).

Several other new agents targeting angiogenesis are under investigation, as well as combinations of these new agents with each other or with cytokines.

*7.3.1 **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 a prior systemic immunotherapy or in patients unfit for immunotherapy. The trial reported a 3-month improvement in progression-free survival in favour of sorafenib (16). Survival seems to improve in patients crossed over from placebo to sorafenib treatment (17).

7.3.2 ***Sunitinib***

Sunitinib is an oxindol tyrosine kinase (TK) inhibitor. It selectively inhibits PDGFR, VEGFR, c-KIT and FLT-3 and has anti-tumour and anti-angiogenic activity. Phase II trials with sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response rate in 34-40% of patients and stable disease > 3 months in 27-29% of patients (18).

In a recent phase III trial of first-line monotherapy comparing treatment with sunitinib versus IFN-alpha, sunitinib achieved a longer progression-free survival than IFN-alpha (11 versus 5 months, $p < 0.000001$). Results suggested monotherapy with IFN-alpha was inferior compared to sunitinib in low- and intermediate-risk patients with mRCC (19). Overall survival was 26.4 and 21.8 months in the sunitinib and IFN-alpha arms, respectively ($p = 0.05$) (19). In patients crossed over from IFN-alpha to sunitinib ($n = 25$), median survival times were 26.4 versus 20.0 months for sunitinib and IFN-alpha, 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-alpha group ($p = 0.003$).

7.3.3 ***Bevacizumab monotherapy and combined with interferon-alpha***

Bevacizumab is a humanised monoclonal antibody that binds isoforms of VEGF-A. Bevacizumab, 10 mg/kg every 2 weeks, in patients refractory to immunotherapy showed an increase in overall response (10%) and in progression-free survival versus placebo (20). A recent double-blind phase III trial ($n = 649$) in mRCC compared bevacizumab + IFN-alpha to IFN-alpha monotherapy (6). The median overall response was 31% in the bevacizumab + IFN-alpha group versus 13% in the IFN-alpha-only group ($p < 0.0001$). Median progression-free survival increased significantly from 5.4 months with IFN-alpha to 10.2 months for bevacizumab + IFN-alpha ($p < 0.0001$), but only in low-risk and intermediate-risk patients. No benefit was seen in high-risk patients. No mature data are yet available on overall survival.

7.3.4 ***Pazopanib***

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-KIT. In a prospective randomised trial of pazopanib versus placebo in treatment-naïve mRCC patients and cytokine-treated patients, there was a significant improvement in progression-free survival and tumour response (9.2 vs 4.2 months) (20).

7.3.5 ***Mammalian target of rapamycin (mTOR) inhibitors***

7.3.5.1 Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR) (21). Patients with high-risk mRCC were randomised to receive first-line treatment with temsirolimus or IFN-alpha monotherapy or in combination. In the temsirolimus group, overall survival was 10.9 months versus 7.3 months in the IFN-alpha group ($p < 0.0069$). However, overall survival in the temsirolimus + IFN-alpha group was not significantly improved (8).

7.3.5.2 Everolimus

Everolimus is an oral mTOR inhibitor. A recent phase III study compared everolimus plus best supportive care (BSC) versus placebo plus BSC in patients who had failed previous anti-VEGFR treatment. Median progression-free survival was 4 months with everolimus versus 1.9 months with placebo ($p < 0.001$) (13,22).

Table 10: 2010 EAU evidence-based recommendations for first- and second-line systemic therapy in mRCC

Treatment	Risk or prior treatment	Recommended agent
1st-line therapy	Low- or intermediate-risk	Sunitinib
		Bevacizumab + IFN-alpha
		Pazopanib
	High risk	Temsirolimus
2nd-line therapy	Prior cytokine	Sorafenib
		Pazopanib
	Prior VEGFR	Everolimus
	Prior mTOR(-)	Clinical trials

7.3.6 Conclusions

	LE
Tyrosine kinase inhibitors (TKIs) increase progression-free survival and or overall survival as both first- and second-line treatment of mRCC.	1b
Sorafenib has proven efficacy as second-line treatment after failure of cytokine therapy or in patients unfit for cytokines.	1b
Sunitinib is more effective than IFN-alpha in treatment-naïve, low- and intermediate-risk tumours.	1b
The association between bevacizumab and IFN-alpha is more effective than IFN-alpha in treatment-naïve, low- and intermediate-risk tumours.	1b
Pazopanib is superior to placebo in both naïve mRCC patients as post-cytokine patients.	1b
Temsirolimus monotherapy in poor-risk mRCC patients is more effective than IFN-alpha or temsirolimus + IFN-alpha.	1b
Everolimus prolongs progression-free survival in patients who have failed treatment with TKIs.	
The role of the new drugs is still under development and combination studies are ongoing. To date, no data are available indicating the new agents have a curative effect. These agents appear to promise to stabilise mRCC for a prolonged period of time. However, their promise has to be balanced against their toxicity profile and the patient's quality of life.	4

7.3.7 Recommendations for systemic therapy for mRCC

Recommendations	GR
Sunitinib is recommended as first-line therapy in low- and intermediate-risk patients.	A
Bevacizumab + IFN-alpha is recommended as first-line therapy in low- and intermediate-risk patients.	A
Sorafenib is recommended as a second-line treatment for mRCC after cytokine failure.	A
Pazopanib is recommended as first-line and after cytokine failure.	A
Temsirolimus is recommended as first-line treatment in high-risk patients.	A
Everolimus is recommended as second-line treatment after failure of tyrosine kinase inhibitors.	A

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8. SURVEILLANCE FOLLOWING RADICAL OR PARTIAL NEPHRECTOMY OR ABLATIVE THERAPIES FOR RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- post-operative complications;
- renal function;
- local recurrence after partial nephrectomy or ablative treatment;
- recurrence in the contralateral kidney;
- development of metastases.

The method and timing of investigation has been the subject of many publications. There is no consensus on surveillance after treatment for RCC and in fact no evidence that early versus later diagnosis of recurrence improves survival. However, follow-up is important to increase our knowledge of RCC and should be performed by the urologist, who should record the time elapsed to recurrence or development of metastasis.

Post-operative complications and renal function are readily assessed by 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 a post-operative deterioration. Renal function (1,2) and non-cancer survival (3-5) can be optimised by performing 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 because 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 surveillance is to identify local recurrence or metastases early. This is particularly important with ablative therapies, such as cryotherapy and RFA. Even though the local recurrence rate is higher than conventional surgery, the patient may still be cured by repeat ablative therapy or radical nephrectomy (10) (LE: 3). In metastatic disease, more extended tumour growth can reduce the possibility of surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, within 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 follow-up, taking into account the risk of a recurrence or metastases developing. Although no randomised evidence exists, there are large studies examining prognostic factors with long follow-up from which some conclusions can be drawn (11-13) (LE: 4).

- When the likelihood of relapse is low, chest x-ray and ultrasound may be appropriate. However, the sensitivity of chest x-ray for small metastases is poor and ultrasound has limitations.
- When the risk of relapse is intermediate or high, CT of the chest and abdomen is the investigation of choice, though the significant morbidity of radiation dose with repeated CT scans should be taken into account (14).

Depending on the availability of new effective 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 by 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 detected when small. Furthermore, for tumours < 4 cm, there is no difference between partial or radical nephrectomy in recurrence during 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 recurrence, metastases, and subsequent death. These systems have been compared and validated (20) (LE: 2). Using prognostic variables, several stage-based surveillance regimes have been proposed (21,22), but these do not include ablative therapies. A post-operative nomogram is available to give the likelihood of freedom from recurrence at 5 years (23). Most recently, a pre-operative 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 to monitor patients

after treatment for RCC, recognising not only the patient risk profile, but also the efficacy of the treatment given (Table 11).

Table 11: Proposed algorithm for surveillance following treatment for RCC taking into account patient risk profile and treatment efficacy

Risk profile	Treatment	Surveillance						
		6 months	1 year	2 years	3 years	4 years	5 year	After 5 years
Low	RN/PN only	CXR and US	CXR and US	CXR and US	CXR and US	CXR and US	CXR and US	Discharge
Intermediate	RN/PN/cryo/ RFA	CT	CXR and US	CT	CXR and US	CXR and US	CT	Yearly CXR and US
High	RN/PN/cryo/ RFA	CT	CT	CT	CT	CT	CT	CXR/CT alternate years

RN = radical nephrectomy; PN = partial nephrectomy; CXR = chest x-ray; US = ultrasound of kidneys and renal bed; CT = computed tomography of chest and abdomen; cyro = cryotherapy; RFA = radiofrequency ablation.

8.3 Conclusions

Surveillance after treatment for RCC should be based on a patient's risk factors and the type of treatment delivered. The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable.

- For low-risk disease, the use of CT can be infrequent (LE: 4).
- In the intermediate-risk group, an intensified follow-up that includes CT scans at regular time intervals should be performed according to a risk-stratified nomogram (LE: 4).
- In high-risk patients, the follow-up examinations should include routine CT scans (LE: 4).

8.4 Recommendation

	GR
The intensity of the follow-up programme for an individual patient should be adapted according to the risk of tumour recurrence and the type of treatment.	C

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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
eGFR	estimated glomerular filtration rate
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
LDH	lactate dehydrogenase
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
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 Carcinoma Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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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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 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 nonseminoma, 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 fetal 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-analysis studies, Cochrane evidence, and the recommendations of the European Germ Cell Cancer Collaborative Group 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*

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

* *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*

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

**Modified from Sackett et al. (32).*

Publication history

The content of these guidelines has not changed 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 edition contains 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/.

For 2013, a revised version is scheduled which will address the findings of the Third European Consensus Conference on the Diagnosis and treatment of Germ Cell Cancer.

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 the 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 orchioepididymitis, with consequent delay of the correct diagnosis (1,2). Ultrasound 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 ultrasound 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 athrophy, inhomogeneous parenchyma). The solely presence of microlithiasis is not an indication for a regular scrotal ultrasound (46).

In the absence of other risk factors (< 12 ml (atrophy), maldescent testis), testicular microlithiasis is not an indication for biopsy or further (ultrasound) screening (45,47).

Magnetic resonance imaging (MRI) offers higher sensitivity and specificity than ultrasound 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 cm^2 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 for 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 testis. 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, selfphysical 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 thoracic computed tomography (CT) scan.

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 scan. The supraclavicular nodes are best assessed by physical examination.

Abdominopelvic CT scanning 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 scans do not seem to improve the sensitivity.

Magnetic resonance imaging produces similar results to CT scanning in the detection of retroperitoneal nodal enlargement (75,76). Again, the main objections to its routine use are its high cost and limited access to it. Nevertheless, MRI can be helpful when abdominopelvic CT or ultrasound are inconclusive (75), when CT scan 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 scan 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). The CT scan has high sensitivity but low specificity (75).

There is no evidence to support the use of the fluorodeoxyglucose-PET (FDG-PET) scan 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 scan of the skull is advisable in patients with NSGCT and multiple lung metastasis and poor prognosis IGCCG risk group. Table 3 shows the recommended test at staging.

Table 3: Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	Alpha-fetoprotein hCG LDH	A
Abdominopelvic CT scan	All patients	A
Chest CT scan	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan	In case of symptoms	
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and high beta-hCG values	

Further investigations	
Fertility investigations: Total testosterone LH FSH Semen analysis	B
Sperm banking should be offered	A

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])

pT	**Primary tumour[1]**	
	pTX	Primary tumour cannot be assessed (see note 1)
	pT0	No evidence of primary tumour (e.g. histological scar in testis)
	pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
	pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis
	pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
	pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
	pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N	**Regional lymph nodes clinical**	
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	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
	N2	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
	N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
pN	**Pathological**	
	pNX	Regional lymph nodes cannot be assessed
	pN0	No regional lymph node metastasis
	pN1	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
	pN2	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
	pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M	**Distant metastasis**	
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Non-regional lymph node(s) or lung
	M1b	Other sites
S	**Serum tumour markers**	
	Sx	Serum marker studies not available or not performed
	S0	Serum marker study levels within normal limits

	LDH (U/l)	hCG (mIU/ml)	AFP (ng/ml)
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.

LDH, lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.
[1]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

Stage 0	pTis	N0	M0	S0,SX
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1
Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage IIC	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

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)*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate prognosis group	
Non-seminoma (28% of cases) 5 years PFS 75% 5-year survival 80%	• Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	*Any of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma No patients classified as poor prognosis	

**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

	For seminoma	For non-seminoma
Pathological (for stage I)		
Histopathological type	• Tumour size (> 4 cm) • Invasion of the rete testis	• Vascular/lymphatic in or peri-tumoural invasion • Proliferation rate > 70% • Percentage of embryonal carcinoma > 50%
Clinical (for metastatic disease)		
• Primary location • Elevation of tumour marker levels • Presence of non-pulmonary visceral metastasis		

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 be preferably 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.

5. GUIDELINES FOR THE DIAGNOSIS AND STAGING OF TESTICULAR CANCER

	GR
1. Testicular ultrasound is mandatory assessment	A
2. 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
3. Serum determination of tumour markers (AFP, hCG, and LDH must be performed before and after orchidectomy for staging and prognostic reasons	A
4. 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 studies of surveillance have been conducted during the past decade, the largest study coming from Canada with > 1,500 patients (102). 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 (103).

In patients with low risk (tumour size ≤ 4 cm and no rete testis invasion) the recurrence under surveillance is as low as 6% (104).

Chemotherapy according to 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 (105).

The overall cancer-specific survival rate reported with surveillance performed by experienced centres is 97-100% for seminoma stage I (103,105). 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 (106-108). Therefore, adjuvant carboplatin therapy using a dosage of one course AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma (103,106-108). Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% (109,110), but further experience and long-term observations 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% (111-114). After modern radiotherapy, nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs) (111-114). Based on the results of a large randomised MRC trial, Fossa et al. (111,112) 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 (112). 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% (111). The main concern surrounding adjuvant radiotherapy is the increased risk of radiation-induced second non-germ cell malignancies (115-119).

A scrotal shield can be of benefit during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis (118).

*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 (120).

*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 (121).

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
1. Surveillance is the recommended management option (if facilities available and patient compliant)	A*
2. Carboplatin-based chemotherapy (one course at AUC 7) can be recommended.	B
3. Adjuvant treatment is not recommended for patients at very low risk.	A
4. Radiotherapy is not recommended as adjuvant treatment.	A

**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 (122-126). 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 (127) 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 (128,129).

*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 (130-135). In these series, involving more than 200 patients, some with a median follow-up of nearly 8 years (130), 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 (136). 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 (137).

It is important to be aware of the slow-growing retroperitoneal teratomas after primary chemotherapy (138).

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 (139). With a low frequency of follow-up CTs (such as has been proven effective for the surveillance strategy in non-seminoma CS1), the costs of follow-up can be considerably reduced (140).

*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 (130-135,141-144). 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 patients, 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 (145). 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. Still, a randomised trial between 1 and 2 courses of PEB is accruing patients. 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 (146-148). If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites (92,128,149-151).

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 (92,123,128,151,152). The presence of vascular invasion seems to be a very robust parameter, and is clinically usable even without centralised review by an expert panel (142,151). 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 (142,151,153,154).

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 (155-157). 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 (128,152,158). 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 (152,155,156).

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 (152). 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 specialized laparoscopic centre (159-162). 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 (163). 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 (145).

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 (164). An ultrasound 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 (165), or by RPLND (140). 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

CS1 risk-adapted treatments based on vascular invasion or surveillance without using risk factors are recommended treatment options.

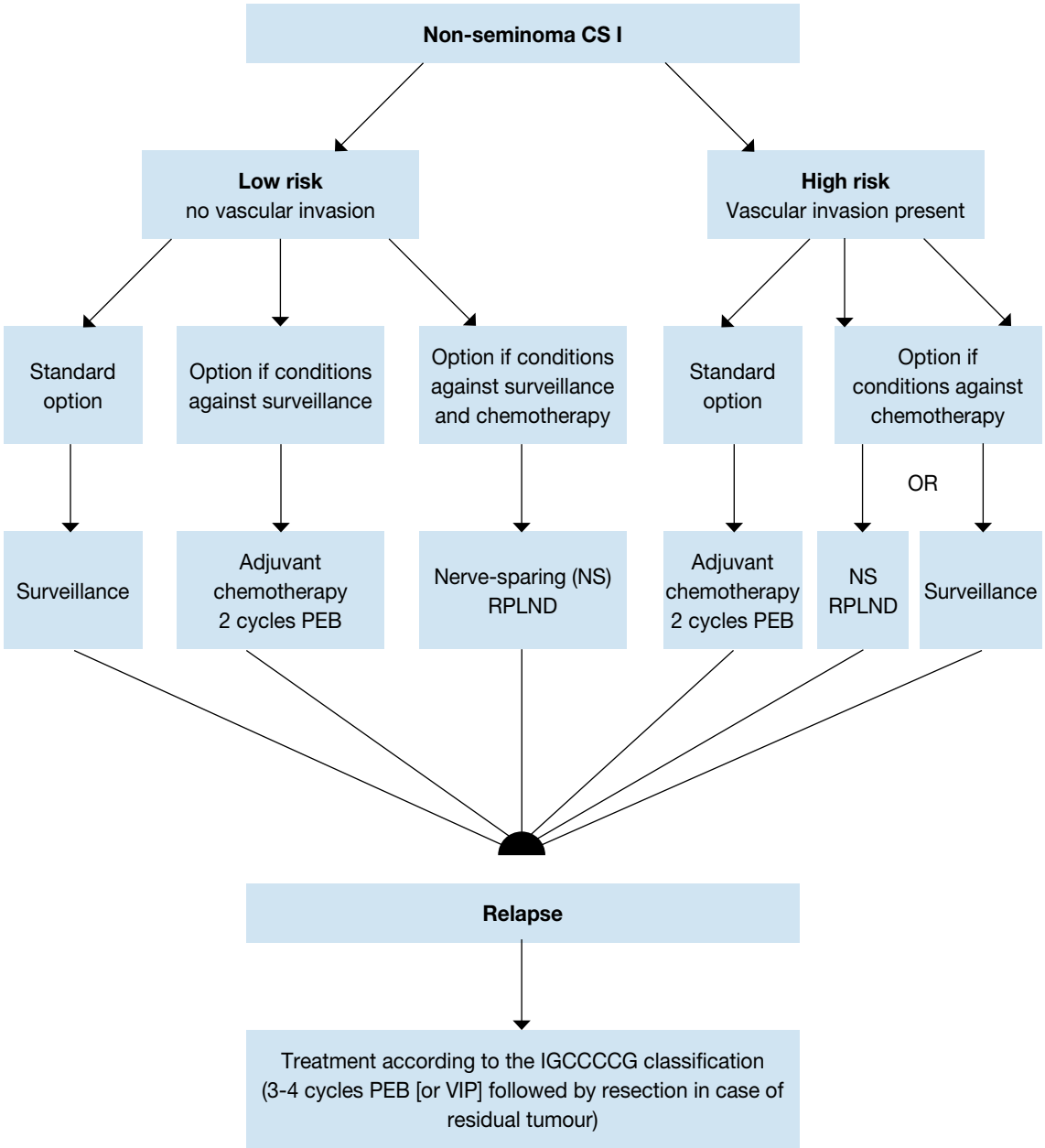
Table 7: Risk-adapted treatments for CS1 based on vascular invasion

	GR
CS1A (pT1, no vascular invasion): low risk	
1. 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.	A*
2. In low-risk patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy or nerve-sparing RPLND are treatment options If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered.	A
CS1B (pT2-pT4): high risk	
1. Primary chemotherapy with two courses of PEB should be recommended (one course of PEB within a clinical trial or registry).	A*
2. Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy should be considered.	A

**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)



PEB = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLNPD = 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 5202 non-seminoma and 660 seminoma cases (Table 5) (166).

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% (167,168). Conversely, dose reduction to 27Gy has been associated with 11% of relapses (105).

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 (169). Single-agent carboplatin is not an alternative to standard EP or PEB chemotherapy (170).

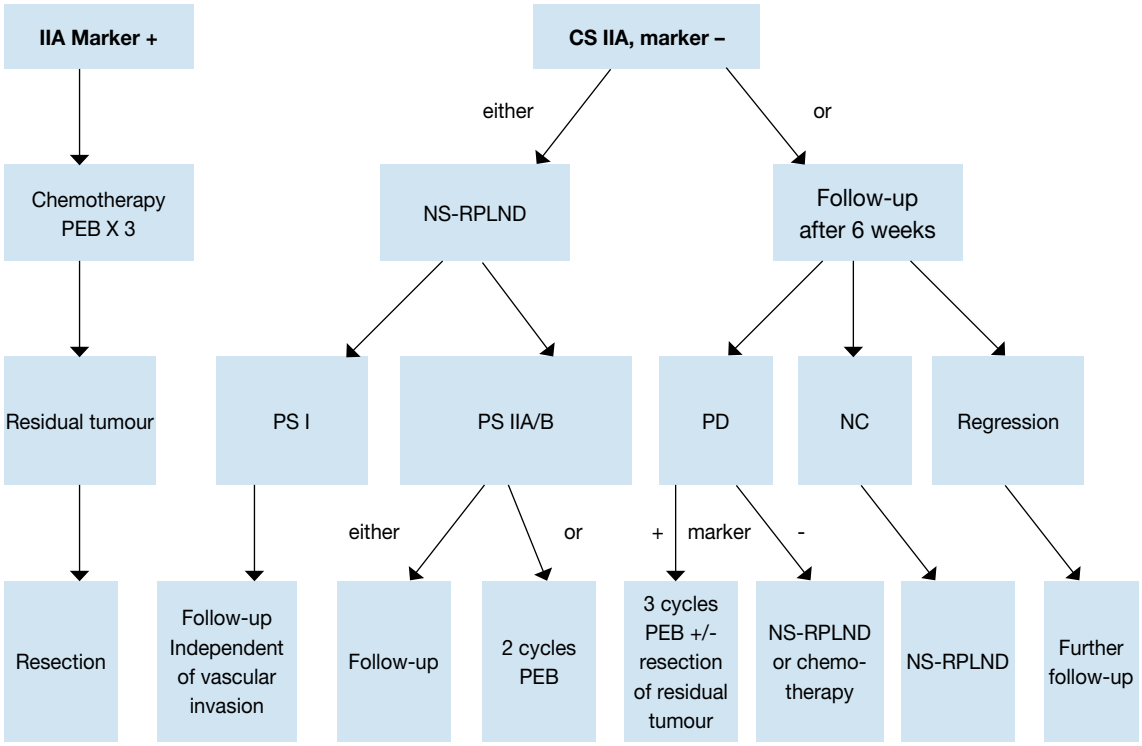
*7.1.2 **Stage IIA/B non-seminoma***

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 (171,172).

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 (173-175) (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 (176). The cure rate with either approach will be close to 98% (158,177-182).

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.

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 (183-185). 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 4 cycles are used (186).

Table 8: PEB regimen (interval 21 days)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

*Plus hydration.
PEB = cisplatin, etoposide, bleomycin.

For patients with a 'good prognosis', according to the IGCCCG Classification (166), standard treatment consists of three cycles of PEB, and only in very selected cases where bleomycin is contraindicated, four cycles of EP (166,185-189). 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 (189,190). 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/mm^3 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 (187,191).

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 (166,192).

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 (193,194). 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 (195-197). 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 (195). More aggressive chemotherapy may also be investigated in a very poor prognostic group (e. g. primary mediastinal germ cell tumours or synchroneous brain metastasis).

Since a matched-pair analysis resulted in a better survival rate (198-200), 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 (201).

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) (166,202,203). 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 (204).

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 (198,205). 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 (206,207).

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 (208-214).

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 (215).

On progression, salvage therapy is indicated (chemotherapy, salvage surgery, radiotherapy) (216-220). 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 (221-228). The long-term relapse rate in this patient group is 6-9%, however, one third of the late relapsing patients will not survive (228).

In the case of any visible residual mass and marker normalisation, surgical resection is indicated. In patients with lesions < 1 cm, there still is an increased risk of residual cancer or teratoma (229) 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 (221,228-237).

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 (222-224,236-246).

The extent of surgery should be based on the risk of relapse of an individual patient and quality of life issues (231). 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 (247). There is growing evidence that "template" resections in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients (248,249). However, the mere resection of the residual tumour (so called "lumpectomy") should not be performed.

The histology may diverge in different organ sites (239). Resection of contralateral pulmonary lesions is not mandatory in case pathologic examination of the lesions from the first lung shows complete necrosis (250).

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 specialized centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Patients treated within such centres benefit with a significant reduction in perioperative mortality from 6% to 0.8% (26,251). In addition, specialised urologic surgeons are capable to reduce the local recurrence rate from 16% to 3% (252) 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) (247,253) (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 vey 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 (235,240).

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 (254). 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 (255). 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 (256-258). 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 VeIP chemotherapy (interval 21 days)

Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP	20 mg/m^2	Days 1-5
Cisplatin*	75-100 mg/m^2	Days 1-5
Etoposide	1.2 g/m^2	Days 1-5
Ifosfamide†		
TIP		
Paclitaxel	250 mg/m^2 [xx]	24 hour continuous infusion day 1
Ifosfamide†	1.5 g/ m^2	Days 2-5
Cisplatin*	25 mg/m^2	Days 2-5
VeIP		
Vinblastin	0.11 mg/kg	Days 1 + 2
Ifosfamide†	1.2 g/m^2	Days 1-5
Cisplatin*	20 mg/m^2	Days 1-5

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; VeIP = vinblastine, ifosfamide, cisplatin.
**Plus hydration.*
†Plus mesna protection.
[xx] An MRC schedule uses paclitaxel at 175mg/m2 in a 3 hour infusion (259).

Conventionally dosed salvage chemotherapy may achieve long-term remissions in 15-40% of patients, depending on individual risk factors (207,260-262).

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 (263).

Table 10: IGCCCG-2 (Lorch-Beyer) Score Construction (257)

Points Variable	-1	0	1	2	3
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	3 months		
AFP salvage		Normal	< 1000	1000	
HCG salvage		< 1000	1000		
LBB		No	Yes		

AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; 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 (257)

	N	%	HR	2-years PFS	3-years OS
Score (N=1435)					
Very Low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very High	105	7.3	8.95	11.5	14.7
Missing	159				

IGCCCG = International Germ Cell Cancer Collaborative Group; OS = overall survival; PSF = progression-free survival.

Salvage therapy with VeIP is probably not superior to other conventionally dosed cisplatin-based combination regimens (250,253,254). Recently, paclitaxel and gemcitabine have proved to be active in the treatment of refractory germ cell tumours; both drugs are synergistic with cisplatin (264-266).

Depending on the presence of adverse prognostic factors, the results of salvage therapy after first-line cisplatin-based treatment are unsatisfactory (207,267). 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 (259,268-271).

High dose chemotherapy offered no advantage as first salvage treatment according to the results of the randomised IT 94 trial in good prognosis patients (255). 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 (256,261,272,273). 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 (274,275).

*7.4.3 **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 nonseminoma. If technically feasible, all nonseminoma 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 (139,276). 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 experimented pathologist is required to avoid misinterpretation of the therapeutic morphological changes in the germ cell neoplasms (277). 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 (278).

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) (206,232,240,243,279-288).

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%) (289,290). 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 (291). 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

	GR
1. 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.	A
2. In stage IIA/B witout 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.	B
3. In metastatic NSGCT (> stage IIC) with a good prognosis, three courses of PEB is the primary treatment of choice.	A
4. 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.	A
5. 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.	A
6, 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.	A
7. 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.	B
8. Seminoma stage IIC and higher should be treated with primary chemotherapy according to the same principles used for NSGCT.	A

EP = eposide, cisplatin; GR = grade of recommendation; NSGCT = non-seminomatous germ cell tumour; PEB = cisplatin, eposide, 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 (292).

- 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 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 chest X-ray has been recently questioned in the follow-up of patients with disseminated disease after complete remission (293,294).
- CT of the chest has a higher predictive value than chest X-ray (294).
- 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 (295). 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 MRT. However, MRT is a protocol-dependent method and, thus, should be performed in the same institution with a standardized protocol.
- With special expertise, ultrasound 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 (296-298). The follow-up tables presented below (tables 12 through 15) present the minimum follow-up criteria and should therefore be considered as a GR A.

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 (5,131,151,154,177,299-302).
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% (112,113). Relapse occurs mainly in the retroperitoneum: approximately 70% of patients have evident metastases in the retroperitoneum, and 10% in the mediastinum and lungs (303). Sometimes the only indication is an elevated level of tumour markers.

A randomised trial of two versus five CT scans 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 (141). 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

Procedure	**Year**			
	1	**2**	**3-5**	**6-10**
Physical examination	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	Once/year	Once/year
Chest X-ray	Twice	Twice		
Abdominopelvic CT scan	Twice (at 3 and 12 months)			

CT= computed tomography scan.

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 (304).

For low-risk stage I non-seminoma, two abdominopelvic CT scans during the first year seem sufficient

to detect relapses at an early stage (141). The significance of additional CT scans 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 CT scans. 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 (305). In the Indiana series, only one relapse in 559 cases was reported (306). 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 (87,307). 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 (163). 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

Procedure	Year			
	1	**2**	**3-5**	**6-10**
Physical examination	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	Once/year	Once/year
Chest X-ray	Twice	Twice		
Abdominopelvic CT scan	Once	Once		

CT = computed tomography scan.

*8.2.3 **Follow-up after adjuvant chemotherapy***

Prospective reports with long-term follow-up after adjuvant chemotherapy have shown a low relapse rate (131,132,299,300) of about 3%. 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) (163). 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-orchidectomy 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 (308). The treatment options post-orchidectomy 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 (309-311).

*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 (112-114,312,314). The rate of relapse is 1-2% and the most common time of presentation is within 18 months of treatment (112,115,311,314,315), although late relapses have also been described (316). 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 (311,317,318). Up to 50% of patients can develop moderate toxicity grade I-II (308). 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

Procedure	Year			
	1	2	3-4	5-10
Physical examination	3 times	3 times	Once/year	Once/year
Tumour markers	3 times	3 times	Once/year	Once/year
Chest X-ray	Twice	Twice		
Abdominopelvic CT scan	Twice	Twice		

CT = computed tomography scan.

*8.3.2 **Follow-up during surveillance***

The actuarial risk of relapse at 5 years ranges between 6% (low risk) and 20% (118,329-323). 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 (102,324). 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 (102,137,325-328). Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years (329) (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 (329,330). 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 (158). In general, the primary tumour bulk governs the outcome for patients with NSGCT (331). 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 (171,172,178).

In advanced metastatic germ cell tumours, the extent of the disease is correlated 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 (332,333). Complete response rates to chemotherapy are in the order of 50-60% (332); another 20-30% of patients could be rendered disease-free with post-chemotherapy surgery (334).
The main reasons for failure of therapy in advanced NSGCT are (331,335,336):

- 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

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Chest X-ray	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT scan*†	Twice	Twice	as indicated	as indicated
Chest CT scan†‡	As indicated	As indicated	As indicated	As indicated

Brain CT scan§	As indicated	As indicated	As indicated	As indicated

CT = computed tomography scan.

**Abdominal CT scanning 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 scan should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET scanning can be performed.
‡A chest CT scan is indicated if abnormality is detected on chest X-ray 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 ultrasound 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), ultrasound of both testes, and CT scan of chest and abdomen. On ultrasound, 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 ultrasound 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), ultrasound of both testes and CT scan of chest and abdomen.

Sertoli cell tumours are generally hypoechoic on ultrasound, 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 scans 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 is correlated 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.

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10.2 Non-germ cell tumours

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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive to the most common abbreviations.

AFP	alpha-fetoprotein
AUC	area under curve
Cg A	chromogranine A
CI	confidence interval
CS	clinical stage
CT	computed tomography
EAU	European Association of Urology
EBM	evidence-based medicine
EP	etoposide, cisplatin
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	follicle-stimulating hormone
GI	gastrointestinal
G-CSF	granulocyte colony-stimulating factor
GR	grade of recommendation
hCG	human chorionic gonadotrophin
HPF	high-power field
IGCCCG	International Germ Cell Cancer Collaborative Group
LE	level of evidence
LH	luteinising hormone
LDH	lactate dehydrogenase
MRC	Medical Research Council
MRI	magnetic resonance imaging
NSGCT	non-seminomatous germ cell tumour
PA	para-aortic
PEB	cisplatin, etoposide, bleomycin
PEI	cisplatin, etoposide, ifosfamide
PET	positron emission tomography
PFS	progression-free survival
PS	pathological stage
PLAP	placental alkaline phosphatase
PVB	cisplatin, vinblastine, bleomycin
RPLND	retroperitoneal lymph node dissection
SWENOTECA	Swedish-Norwegian Testicular Cancer Project
Tin	testicular intraepithelial neoplasia
	pathological definition: undifferentiated intratubular germ cell carcinoma
TIP	paclitaxel, ifosfamide, cisplatin
TNM	Tumour Node Metastasis
UICC	International Union Against Cancer
ULN	upper limit of normal
VelP	vinblastine, ifosfamide, cisplatin
WHO	World Health Organization
VIP	(VP-16) etoposide, ifosfamide, cisplatin

Conflict of interest

All members of the Testicular Cancer Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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

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European
Association
of Urology

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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 Group 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 EAU Annual 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*

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

**Modified from Sackett et al. (3).*

Table 2: Grade of recommendation*

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

**Modified from Sackett et al. (3).*

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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

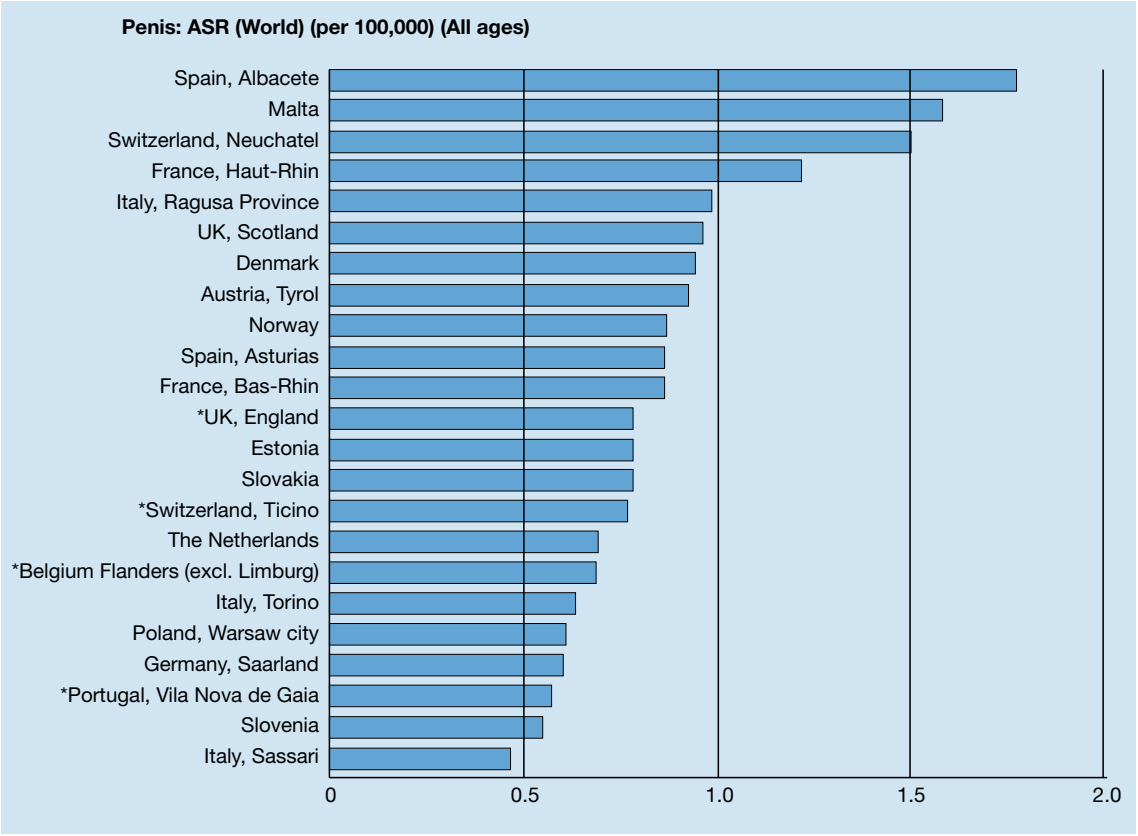
In Western countries, primary malignant penile cancer is uncommon, with an incidence of less than 1.00 per 100,000 males in Europe and the United States (1,2). However, there are significant geographical variations, within Europe (Figure 1) reporting an incidence greater than 1.00 per 100,000 men (3). 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).*

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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 condyloma 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).

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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

Clinical classification	
T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma, not associated with destructive invasion
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b	Tumour invades subepithelial connective tissue without with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2 *	Tumour invades corpus spongiosum/corpora cavernosa
T3	Tumour invades urethra
T4	Tumour invades other adjacent structures
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification The pT categories correspond to the T categories. The pN categories are based upon biopsy or surgical excision.	
pN - Regional lymph nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of regional lymph node metastasis
pM - Distant metastasis	
pM0	No distant metastasis
pM1	Distant metastasis
G - Histopathological grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

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.

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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

Lesions sporadically associated with SCC of the penis • Cutaneous horn of the penis • Bowenoid papulosis of the penis • Balanitis xerotica obliterans (lichen sclerosus et atrophicus)
Lesions at high risk of developing SCC of the penis (up to one-third transform to invasive SCC) • Penile intraepithelial neoplasia (carcinoma *in situ*): erythroplasia of Queyrat and Bowen's disease

Table 5: Penile SCC

Types of SCC • Classic • Basaloid • Verrucous and its varieties: - Warty (condylomatous) carcinoma - Verrucous carcinoma - Papillary carcinoma - Hybrid verrucous carcinoma - Mixed carcinomas (warty basaloid and adenobasaloid carcinoma) • Sarcomatoid • Adenosquamous
Growth patterns of SCC • Superficial spread • Nodular or vertical-phase growth • Verrucous

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).

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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 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 ultrasound (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 isosulphan blue and/or Tc99m-colloid sulphur 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 scans cannot detect micrometatases (21). No further studies have been performed to confirm the promising results reported with nanoparticle-enhanced MRI (22), but positron emission tomography (PET)/CT imaging 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 ^{18}fluorodeoxyglucose (FDG) PET/CT scanning 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 punction). 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.

*7.2.5 **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 ^{18}FDG-PET/CT have some minor limitations (0.5 cm) (31). The use of molecular biological techniques is experimental (37-41).

7.3 Distant metastases

An assessment of distant metastases should be performed in patients with positive inguinal nodes (23-35) (LE: 2b). Positron emission tomography/CT is reliable for identification of pelvic and distant metastases in patients with positive inguinal nodes (31). Routine blood analysis and chest x-rays 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.

7.4 Guidelines for the diagnosis and staging of penile cancer

Recommendations	**GR**
Primary tumour	C
Physical examination, recording morphological and physical characteristics of the lesion. Cytological and/or histological diagnosis.	
Inguinal lymph nodes	C
Physical examination of both groins, recording nodal morphological and physical characteristics: - If nodes are non-palpable, DSNB is indicated; if DSNB not available, ultrasound-guided FNAC/risk factors. - If nodes are palpable, FNAC for cytological diagnosis.	
Regional metastases (inguinal and pelvic nodes)	C
A pelvic CT scan/PET-CT scan is indicated in patients with metastatic inguinal nodes.	
Distant metastases (beside inguinal and pelvic nodes)	C
PET/CT scan also allows evidence of distant metastasis. If PET/CT is not available, abdominal CT scan and chest x-ray are advisable, and in symptomatic M1 patients a bone scan is also advisable.	
Biological laboratory	C
Determinations for penile cancer are investigational and not for clinical use.	

CT = computed tomography; DSNB = dynamic sentinel node biopsy; FNAC = fine-needle aspiration cytology; PET = positron emission tomography.

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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**
Local excision with (or without) circumcision.	3
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.	2b
Mohs' micrographic surgery (for verrucous carcinoma) (6).	3
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).	4

*8.1.2 **Category T1b tumours of the glans with deeper infiltration (> 1 mm)***

These tumours can be treated with the following techniques:	**LE**
Wide local (laser) excision plus reconstructive surgery or total glans resurfacing with or without skin transplantation (8).	2b
Neoadjuvant chemotherapy [vinblastine, bleomycin, and methotrexate (VBM)] followed by CO_2 laser excision and spontaneous glans re-epithelialisation (3).	2b
Radiotherapy (*see* section 8.1.7).	
Glansectomy (2,8-11).	2b

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

Primary tumour	**Conservative treatment is to be considered whenever possible**	**LE**	**GR**
Category Tis, Ta, T1a (G1, G2)	CO_2 or Nd:YAG laser surgery, wide local excision, glans resurfacing, or glans resection, depending on size and location of the tumour.	2b	C
	Mohs' micrographic surgery or photodynamic therapy for well differentiated superficial lesions (Tis, G1 Ta).	3	C
Categories: T1b (G3) and T2 (glans only)	Glansectomy, with or without tips amputation or reconstruction.	2b	B
Category T2 (invasion of the corpora)	Partial amputation.	2b	B
Category T3 (invasion of urethra)	Total amputation with perineal urethrostomy.	2b	B

Category T4 (other adj. structures)	Eligible patients: neoadjuvant chemotherapy followed by surgery in responders. Alternative: external radiation.	3	C
Local disease recurrence after conservative therapy	Salvage surgery, consisting of penis-sparing treatment in small recurrences.	2b	B
	Larger recurrence: some form of amputation.	2b	B
Radiotherapy	Organ-preserving treatment in selected patients with T1-T2 of glans or coronal sulcus, lesions < 4 cm.	2b	B
Chemotherapy	Neoadjuvant, before surgery.	3	C
	Palliation in advanced or metastatic disease.	3	C

CO_2 = 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***

Ultrasound-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 sentinal 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. 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).

Conclusion

Adjuvant chemotherapy is recommended in patients with pN2-3 tumours (33) (GR: C), and neoadjuvant chemotherapy followed by radical surgery is advisable in those with non-resectable or recurrent lymph node metastases (36-38) (GR: C).

*8.2.6 **The role of radiotherapy***

Prophylactic radiotherapy in patients with N0 tumours is not recommended (39) (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***

Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**LE**	**GR**
No palpable inguinal nodes	Tis, Ta G1, T1G1: surveillance.	2a	B
	> T1G2: DSNB. (NB: Inguinal LAD if histology is positive).	2a	B
	If DSNB not available: risk factors / nomogram decision-making.	3	C

Palpable inguinal nodes	Ultrasound-guided FNAB (DSNB is unsuitable for palpable nodes).	2a	B
	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.	2a	B
	Unilateral pelvic LAD if unilateral lymph node metastases with prolonged inguinal incision.	2b	B
	Bilateral pelvic LAD if bilateral inguinal metastases.	2a	B
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).	2b	B
Patients with fixed or relapsed inguinal nodes	Neo-adjuvant chemotherapy is strongly recommended in patients with unresectable or recurrent lymph node metastases.	2a	B
	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.	2a	B
	Prophylactic radiotherapy in clinical N0 patients is not indicated.	2a	B

DSNB = dynamic sentinel node biopsy; FNAB = fine-needle aspiration biopsy; LAD = lymphadenectomy.

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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 ultrasound imaging 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). Ultrasound and immediate FNAB have been encouraging in finding occult metastases (6,7), and it seems reasonable to add ultrasound 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 ultrasound 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 ultrasound 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

	Interval of follow-up		**Examinations and investigations**	**Maximum duration of follow-up**	**GR**
	Years 1 and 2	Years 3, 4 and 5			
Recommendations for follow-up of the primary tumour					
Penile preserving treatment	3 months	6 months	Regular physician or self-examination	5 years	C
Amputation	6 months	1 year	Regular physician or self-examination	5 years	C
Recommendations for follow-up of the inguinal lymph nodes					
'Wait-and-see'	3 months	6 months	Regular physician or self-examination	5 years	C

pN0	6 months	1 year	Regular physician or self-examination Ultrasound with FNAB	5 years	C
pN+	3 months	6 months	Regular physician or self-examination Ultrasound with FNAB	5 years	C

FNAB = fine-needle aspiration biopsy.

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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 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 medium 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.

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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

5-FU	5-fluorouracil
BMP	cisplatin, methotrexate and bleomycin
CT	computed tomography
DFS	disease-free survival
DSNB	dynamic sentinel node biopsy
EAU	European Association of Urology
FDA	[US] Food and Drug Administration
FDG	fluorodeoxyglucose
FNAB	fine-needle aspiration biopsy
FNAC	fine-needle aspiration cytology
GR	grade of recommendation
HPV	human papillomavirus
LAD	lymphadenectomy
LE	level of evidence
MRI	magnetic resonance imaging
Nd:YAG	neodynium:yttrium-aluminum-garnet
PET	positron emission tomography
PF	cisplatin and fluorouracil
SCC	squamous cell carcinoma
SNB	sentinel node biopsy
TC99m	technetium 99m
TNM	tumour, node, metastasis
VBM	vinblastine, bleomycin, methotrexate

Conflict of interest

All members of the Penile Cancer Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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

Management of Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

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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 Guideline on LUTS suggestive of BPO (3) to the more contemporary and precise EAU Guideline on Male LUTS, including BPO.

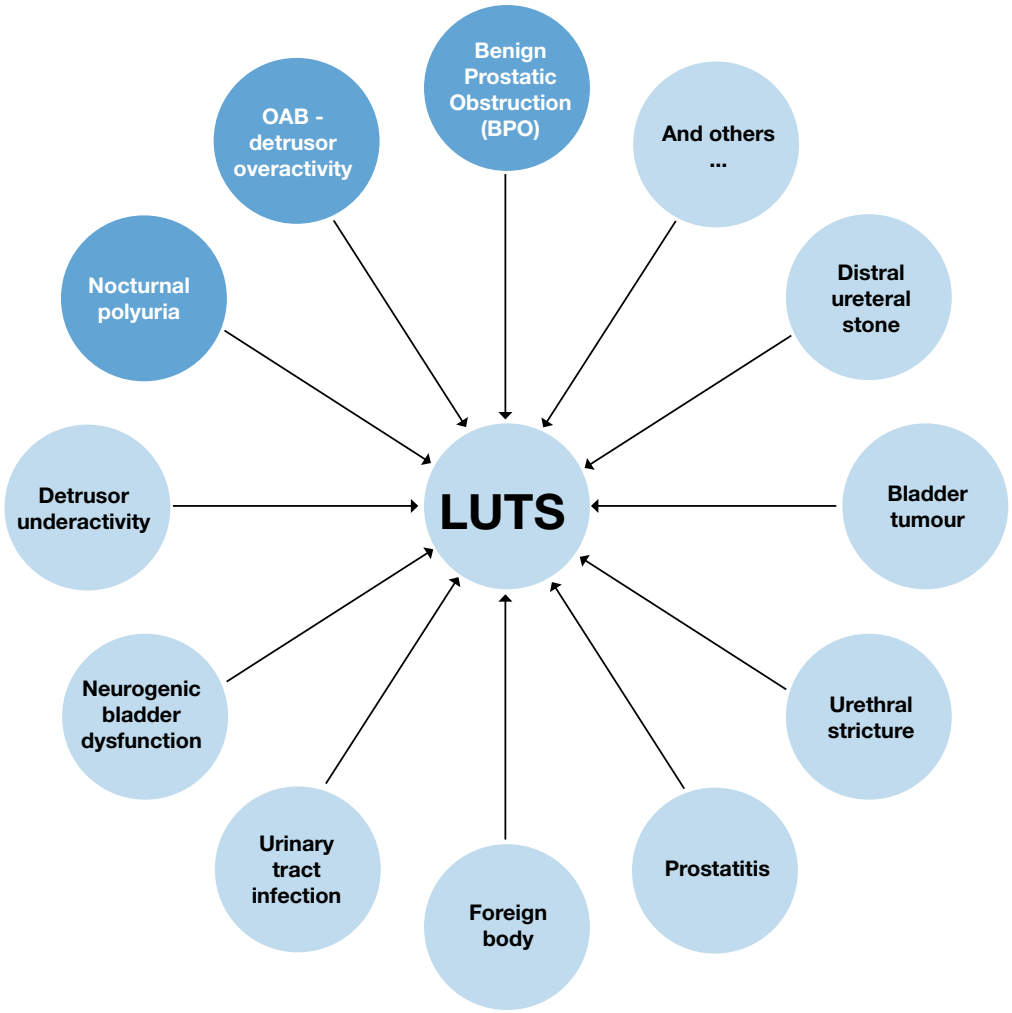

Figure 1: Multifactorial aetiology of lower urinary tract symptoms (LUTS). The EAU Guideline on Male LUTS mainly covers LUTS secondary to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO), detrusor overactivity or overactive bladder (OAB), and nocturia due to nocturnal polyuria. Other causes of male LUTS are covered by separate EAU Guidelines.

Because patients seek help for LUTS and not an underlying attribute of the prostate such as BPH or BPE, this updated guideline has 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 guideline 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 urinary incontinence, urogenital infections, ureteral stones, or malignant diseases of the lower urinary tract have been published elsewhere.

The recommendations of this guideline 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 liscensed since the literature search.

Databases: PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed/) Web of Science (http://apps.webofknowledge.com) Cochrane (http://www.cochrane.org/)		
Language: English		
Literature Search: conducted 1st February - 1st March 2010		
Search Period: 1966 - 1st January 2010		
Search limits …	for group search terms … **(AND)**	in combination with investigated drugs, operations, or synonyms **(AND)**
humans **AND** adult men **AND** review **OR** randomised clinical trials **OR** clinical trials **OR** meta-analysis	- lower urinary tract symptoms - benign prostatic hyperplasia - detrusor overactivity - overactive bladder - nocturia - nocturnal polyuria	- alpha-adrenoceptor antagonist - adrenergic alpha-1 receptor antagonists - alpha-blocker - alfuzosin - doxazosin - tamsulosin - terazosin - 5α-reductase inhibitor - dutasteride - finasteride

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 guideline panel consisted of urologists, a pharmacologist, and an epidemiologist and statistician who have been working on the topic for the last 4 years. The guideline is primarily written for urologists but can also be used by general practitioners, patients, or other stakeholders. The guideline panel intends to update the content and recommendations, according to the given structure and classification systems, every 2 years.

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2. ASSESSMENT

Systematic diagnostic work-up should be done by history, validated symptom questionnaires (e.g. IPSS), both ideally proactively, physical examination, uinanlysis, blood analysis, ultrasound of the prostate, bladder and kidneys, uroflowmetry and ultrasound 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 over night) 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.

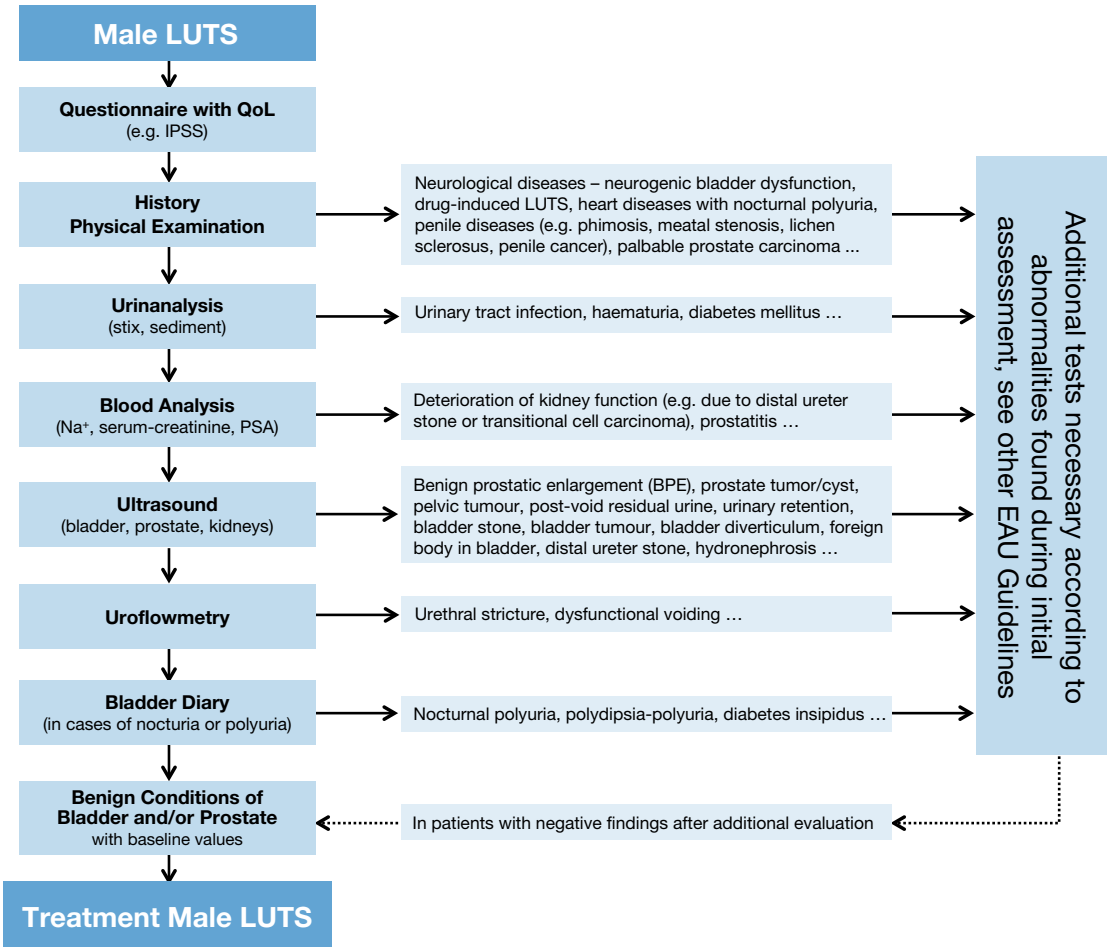

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older. Systematic work-up can exclude other diseases or conditions also associated with LUTS. The assessment may be interrupted or stopped when relevant pathologies have been identified.

Benign prostatic obstruction (BPO) 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. WW 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)

Trial	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
Brown et al. (2007) (7)	52	Standard care	67	-1.3	-	-	1b
		Standard care plus self-management	73	-5.7 * †	-	-	

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine.

** 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

	LE	GR
Men with mild symptoms are suitable for watchful waiting.	1b	A
Men with lower urinary tract symptoms should be offered lifestyle advice prior to or concurrent with treatment.	1b	A

3.7 References

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4. DRUG TREATMENT

4.1 α_1-adrenoceptor antagonists (α_1-blockers)

4.1.1 Mechanism of action

Historically, it was assumed that α_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 α_1A-adrenoceptors (1). However, it has been shown that α_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 α_1-adrenoceptors located outside the prostate (e.g. in the urinary bladder and/or spinal cord) and other α-adrenoceptor subtypes (α_1B- or α_1D-adrenoceptors) as mediators of beneficial effects of α_1-blockers. α_1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and central nervous system are considered to be mediators of side-effects during α-blocker treatment, and all three receptor subtypes seem to be involved. This concept has favoured the use of α_1A-selective adrenoceptor antagonists. However, it remains to be determined whether α_1A-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 α_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 α_1-blockers licensed in Europe for treating symptoms of BPH

Drug	t_{max} (hours)	t½ (hours)	Recommended daily dose
Alfuzosin IR	1.5	4-6	3 x 2.5 mg
Alfuzosin SR	3	8	2 x 5 mg
Alfuzosin XL	9	11	1 x 10 mg
Doxazosin IR	2-3	20	1 x 2-8 mg
Doxazosin GITS	8-12	20	1 x 4-8 mg
Silodosin	2.5	11-18	1 x 4-8 mg
Tamsulosin MR	6	10-13	1 x 0.4 mg
Tamsulosin OCAS	4-6	14-15	1 x 0.4 mg
Terazosin	1-2	8-14	1 x 5-10 mg

t_{max} = time to maximum plasma concentration; t½ = elimination half-life; IR = immediate release; SR = sustained release; GITS = Gastrointestinal Therapeutic System; MR = Modified Release; OCAS = Oral Controlled Absorption System.

4.1.3 ***Efficacy***

Indirect comparisons between α_1-blockers, and limited direct comparisons, demonstrate that all α_1-blockers have a similar efficacy in appropriate doses (4). Controlled studies have shown that α_1-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_{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 runin period), an IPSS improvement of up to 50% and Q_{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. α_1-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 α_1-blocker efficacy in studies with follow-up periods of $\leq$ 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). α_1-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 α_1-blockers appears to be maintained over at least 4 years.

Table 3: Randomised, placebo-controlled trials with α_1-blockers in men with LUTS (drugs in chronological order; selection of trials)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)	PVR change (%)	LE
Jardin et al. (1991) [14]	24	Placebo Alfuzosin 3 x 2.5 mg	267 251	-32 [a] -42 [a,b]	+1.3 [a] +1.4 [a]	-9 -39 [a,b]	1b
Buzelin et al. (1997) [15]	12	Placebo Alfuzson 2 x 5 mg	196 194	-18 -31 [a,b]	+1.1 +2.4 [a,b]	0 -17 [a,b]	1b
van Kerrebroeck et al. (2000) [16]	12	Placebo Alfuzosin 3 x 2.5 mg Alfuzosin 1 x 10 mg	154 150 143	-27.7 -38.1 [a,b] -39.9 [a,b]	+1.4 +3.2 [a,b] +2.3 [a,b]	- - -	1b
MacDonald and Wilt (2005) [17]	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9 [b] (Boyarski) [†] -1.8 [b] (IPSS) [†]	+1.2 [b]	-	1a
Kirby et al. (2001) [18]	13	Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS	155 640 651	-34 [a] -45 [a,b] -45 [a,b]	+1.1 [a] +2.6 [a,b] +2.8 [a,b]	- - -	1b
McConnell et al. (2003) [8]	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39 [b]	+1.4 +2.5 [a,b]	- -	1b
Chapple et al. (1996) [19]	12	Placebo Tamsulosin MR 1 x 0.4 mg	185 364	-25.5 -35.1 [a,b]	+0.6 +1.6 [a,b]	-13.4 -22.4 [a]	1b
Lepor (1998) [20]	13	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin MR 1 x 0.8 mg	253 254 247	-28.1 -41.9 [a,b] -48.2 [a,b]	+0.5 +1.8 [a,b] +1.8 [a,b]	- - -	1b
Chapple et al. (2005) [21]	12	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8 mg	350 700 354 707	-32 -43.2 [b] -41.7 [b] -42.4 [b]	- - - -	- - - -	1b
Wilt et al. (2002) [22]	4-26	Placebo Tamsulosin 1 x 0.4-0.8 mg	4122	-12 [b] (-1.1 Boyarski [†]) -11 [b] (-2.1 IPSS [†])	+1.1 [b]	-	1a

Brawer et al. (1993) [23]	24	Placebo Terazosin 1 x 1-10 mg	72 69	-11 -42 [a,b]	+1.2 +2.6 [a,b]	- -	1b
Roehrborn et al. (1996) [24]	52	Placebo Terazosin 1 x 1-10 mg	973 976	-18.4 -37.8 [a,b]	+0.8 [a] +2.2 [a,b]	- -	1b
Wilt et al. (2000) [25]	4-52	Placebo Terazosin	5151	-37 [b] (-2.9 Boyarski †) -38 [b] (IPSS †)	+1.7 [b]	-	1a

Q_{max} = maximum urinary flow rate (free uroflowmetry); PVR = post-void residual urine; 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 α_1-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 α_1-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 (odds ratio for vascular-related adverse events 3.3, 3.7, 1.7 and 1.4, respectively; the latter two not reaching statistical significance; [5]). In particular, patients with cardiovascular co-morbidity and/or vasoactive co-medication may be susceptible to α-blocker-induced vasodilatation (9). This includes anti-hypertensive drugs, such as α-adrenoceptor antagonists, diuretics, Ca^{2+}-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists, but also phosphodiesterase (PDE) inhibitors prescribed for erectile dysfunction or male LUTS (9).

Despite the long-standing and widespread use of α_1-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 α_1-blockers, most reports have been related to tamsulosin. Whether this reflects a greater risk with tamsulosin than with other α_1-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 α_1-blockers (11). It therefore appears prudent not to initiate α_1-blocker treatment prior to cataract surgery, while existing α_1-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 erectile dysfunction often co-exist, medical BPH treatment should not further impair sexual function. A systematic review concluded that α_1-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 α_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 α_1A-selective drugs, such as silodosin, carry a greater risk (13), however, all α_1-blockers are dosed to block α_1A-adrenoceptors effectively. Hence, the mechanism underlying abnormal ejaculation remains to be elucidated.

*4.1.5 **Practical considerations***

α_1-blockers are often considered the first-line drug treatment of moderate-to-severe male LUTS. All α_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, α_1-blockers can be considered for intermittent use in patients with fluctuating intensity of symptoms not needing long-term treatment.

*4.1.6 **Recommendations***

	LE	GR
α_1-blockers should be offered to men with moderate-to-severe lower urinary tract symptoms	1a	A

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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

Drug	t_{max} (hours)	t ½	Recommended daily dose
Dutasteride	1-3	3-5 weeks	1 x 0.5 mg
Finasteride	2	6-8 hours	1 x 5 mg

t_{max} = time to maximum plasma concentration; t½ = elimination half-life.

*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_{max} 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_{max} 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_1-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). IPSS 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_1-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

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [4]	52	Placebo	305	-16.5 [a]	+1.4	+1.3	1b
		Finasteride 1 x 5 mg	310	-19.8 [a]	+1.6	-16.9 [b]	
Kirby et al. (2003) [5]	52	Placebo	253	-33.1	+1.4	-	1b
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
Andersen et al. (1995) [6]	104	Placebo	346	+1.5	-0.3	+11.5 [a]	1b
		Finasteride 1 x 5 mg	348	-14.9 [a,b]	+1.5 [a,b]	-19.2 [a,b]	
Nickel et al. (1996) [7]	104	Placebo	226	-4.2	+0.3	+8.4 [a]	1b
		Finasteride 1 x 5 mg	246	-13.3 [a,b]	+1.4 [a,b]	-21	

McConnell et al. (1998) [8]	208	Placebo	1503	-8.7	+0.2	+14 [a]	1b
		Finasteride 1 x 5 mg	1513	-22 [a,b]	+1.9 [a,b]	-18 [a,b]	
Marberger et al. (1998) [9]	104	Placebo	1452	-9.8 [†]	0.8	+9	1b
		Finasteride 1 x 5 mg	1450	-21.4 [†b]	+1.4 [b]	-15 [b]	
McConnell et al. (2003) [10]	234	Placebo	737	-23.8	+1.4 [a]	+24 [a]	1b
		Finasteride 1 x 5 mg	768	-28.4 [a,b]	+2.2 [a,b]	-19 [a,b]	
Roehrborn et al. (2002) [11]	104	Placebo	2158	-13.5 [a]	+0.6	+1.5 [a]	1b
		Dutasteride 1 x 0.5 mg	2167	-26.5 [a,b]	+2.2 [a,b]	-25.7 [a,b]	
Roehrborn et al. (2008) [12]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4 [a]	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5 [a]	+1.9	-28 [b]	
Roehrborn et al. (2010) [13]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2 [a]	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3 [a]	+2.0	-28 [b]	

Q_{max} = 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***

	LE	**GR**
5α-reductase inhibitors should be offered to men who have moderate-to-severe lower urinary tract symptoms and enlarged prostates (> 40 mL) or elevated prostate specific antigen concentrations (> 1.4 – 1.6 µg/L). 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.	1b	A

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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 (M^1-M^5) have been described in humans, of which the M^2 and M^3 subtypes are predominantly expressed in the detrusor. Although approximately 80% of these muscarinic receptors are M^2 and 20% M^3 subtypes, only M^3 seems to be involved in bladder contractions in healthy humans (1,2). The role of M^2 subtypes remains unclear. However, in men with neurogenic bladder dysfunction and in experimental animals with neurogenic bladders or bladder outlet obstruction M^2 receptors seem to be involved in smooth muscle contractions as well (3).

The detrusor is innervated by parasympathic 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):

- darifencacin 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

Drug	t_{max} [h]	t ½ [h]	Recommended daily dose
Darifencacin	7	13 - 19	1 x 7.5-15 mg
Fesoterodine	5	7	1 x 4-8 mg
Oxybutynin IR	0.5 - 1	2 - 4	3-4 x 2.5-5 mg
Oxybutynin ER	5	16	2-3 x 5 mg
Propiverine	2.5	13 - 20	2-3 x 15 mg
Propiverine ER	7	20	1 x 30 mg
Solifenacin	4 - 6	45 - 68	1 x 5-10 mg
Tolterodine IR	1 - 3	2-10	2 x 1-2 mg
Tolterodine ER	4	6 - 10	1 x 4 mg
Trospium chloride	4 - 6	5 - 15	3 x 10-15 mg 2 x 10-20 mg

IR = immediate release; ER = extended release; t_{max} = time to maximum plasma concentration; t½ = elimination half-life;
** oral bioavailability increased by about 50% for the parent compound, whereas that of the active metabolite is decreased by about 30%; † absolute bioavailability dependent on genotype for CPY 2D6 ranging from 17% in extensive metabolisers to 65% in poor metabolisers.*

*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 (6). A sub-analysis of an open-label trial of 2,250 male or female patients with overactive bladder symptoms treated with tolterodine showed that age but not gender has a significant impact on urgency, frequency, or urgency incontinence (7).

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 (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, urgency incontinence, and IPSS were all significantly reduced compared to baseline values after 12-25 weeks (8, 9). In an open-label study with α_1-blocker nonresponders, each answer of the IPSS questionnaire was improved during tolterodine treatment irrespective of storage or voiding symptoms (8). Randomised, placebo-controlled trials demonstrated that tolterodine can significantly reduce urgency incontinence and daytime or 24-hour frequency compared to placebo. It was also demonstrated that urgency related voiding is significantly reduced by tolterodine (10-12). 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 (13).

Table 7: Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with overactive bladder symptoms (trials in chronological order)

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency [%]	Nocturia [%]	Urgency incontinence [%]	IPSS [%]	LE
Kaplan et al. (2005) [8]	25	Tolterodine 1 x 4 mg/d (after α-blocker failure)	43	-35.7[a]	-29.3[a]	-	-35.3[a]	2b
Roehrborn et al. (2006) [16]	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1 x 4 mg/d	77	-12	-	-71[b]	-	
Kaplan et al. (2006) [11]	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-10.8[b]	-18.8	-	-	
Kaplan et al. (2006) [17]	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-85[b]	-54	
Dmochowski et al. (2007) [12]	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-8.7[b]	-18.8	-	-	
Höfner et al. (2007) [9]	12	Tolterodine 1 x 4 mg/d	741	-20[a]	-42.9 a	-100	-37.9[a]	2b
Herschorn et al. (2009) [14]	12	Placebo	124	-10.2	-	-59.3	-	1b
		Fesoterodine 1 x 4 mg/d	111	-13.2[b]	-	-84.5[b]	-	
		Fesoterodine 1 x 8 mg/d	109	-15.6[b]	-	-100[b,c]	-	

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 post-void residual 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) (14). The incidence of urinary retention in men without bladder outlet obstruction 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 bladder outlet obstruction, antimuscarinic drugs are not recommended due to the theoretical decrease of bladder strength which might be associated with post-void residual urine or urinary retention. A 12-week placebo-controlled safety study dealing with men who had mild to moderate bladder outlet obstruction (median bladder outlet obstruction index, BOOI, in the placebo or tolterodine group 43 and 49 cm H_2O, respectively) demonstrated that tolterodine significantly increased the amount of post-void residual urine (49 vs. 16 mL) but was not associated with increased events of acute urinary retention (3% in both study arms) (15). 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 bladder outlet obstruction 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 post-void residual urine is advised.

4.3.6 *Recommendations*

	LE	GR
Muscarinic receptor antagonists might be considered in men with moderate to severe lower urinary tract symptoms who have predominantly bladder storage symptoms.	1b	B
Caution is advised in men with bladder outlet obstruction.	4	C

4.3.7 *References*

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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, lipoxygenase, growth-factor stimulated proliferation of prostatic cells, α-adrenoceptors, 5α-reductase, muscarinic cholinoceptors, 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 bladder outlet obstruction 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_{max}), post-void residual 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 ß-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_{max} and post-void residual urine. A meta-analysis calculated weighted mean differences of -4.9 IPSS points, +3.9 mL/s in terms of Q_{max} and -28.6 mL in terms of post-void residual urine in favour of ß-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_{max} was +2.5 mL/s and of post-void residual 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_{max}, post-void residual 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 Prostaserene™) was compared as mono or combination preparations either with placebo, other plant extracts (*Pygeum africanum*, *Utica dioica*), the 5-reductase inhibitor finasteride, or the α_1-blocker tamuslosin. 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_{max}, or prostate size reduction. Similar levels of IPSS or Q_{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 diocia***: 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_{max} and post-void residual 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_{max}, and post-void residual urine significantly improved compared to placebo.
- ***Combination preparations***: Trials have been carried out, especially with the extract combination of *Sabal serrulata* and *Utica dioica* (PRO 160/120, Prostatgutt™ forte). A 24-weeks placebo-controlled trial demonstrated a significant improvement in IPSS in the phytotherapy arm (-2 IPSS points difference) (16); Q_{max} reduction was similar in both groups. 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 Q_{max} in both groups (17).

Table 8: Trials with plant extracts in patients with BPH-LUTS (selection; in alphabetical order)

Trials	Duration (weeks)	Treatment	Patients (n)	Change in symptoms (IPSS) †	Change in Q_{max} [mL/s]	PVR [mL]	LE
Bach (2000) (6)	52	placebo Cucurbita pepo (Prosta Fink™forte)	243 233	-5.5 -6.7[a]	n.s. n.s.	n.s. n.s	1b
Berges et al. (1995) (8)	24	placebo *Hypoxis rooperi* (Harzol™)	100 100	-2.3 -7.4[a]	+1.1 +5.2[a]	-16.8 -35.4[a]	1b
Klippel et al. (1997) (9)	26	placebo *Hypoxis rooperi* (Azuprostat™)	89 88	-2.8 -8.2[a]	+4.3 +8.8[a]	-4.1 -37.5[a]	1b
Wilt et al. (2000) (7)	4-26	placebo Hypoxis rooperi	475	-4.9[b]	+3.9[b]	-28.6[b]	1a
Wilt et al. (2002) (10)	4-18	placebo *Pygeum africanum* (β-sitosterol)	1562	RR 2.07[b]	+2.5[b]	-13.2[b]	1a
Wilt et al. (2000) (11)	12-24	placebo *Secale cereale* (Cernilton™)	444	RR 2.4[b]	-1.6	-14.4	1a
Wilt et al. (2002) (18)	4-48	placebo Serenoa repens/ Sabal cerrulata	3139	-1.41[b]	+1.86[b]	-23[b]	1a
Bent et al. (2006) (19)	52	placebo Serenoa repens	113 112	-0.7 -0.7	-0.01 +0.42	-19 -14	1b
Carraro et al. (1996) (20)	26	finasteride *Serenoa repens* (Permixon™)	545 553	-6.2 -5.8	+3.2* +2.7	- -	1b
Debruyne et al. (2002) (21)	52	tamsulosin *Serenoa repens* (Permixon™)	354 350	-4.4 -4.4	+1.9 +1.8	- -	1b
Schneider & Rübben (2004) (14)	52	placebo *Urtica dioica* (Bazoton uno™)	122 124	-4.7 -5.7[a]	+2.9 +3.0	-4 -5	1b
Safarinejad (2005) (15)	26	placebo Urtica dioica	316 305	-1.5 -8.0[a]	+3.4 +8.2[a]	0 -37	1b
Lopatkin et al. (2005) (16)	24	placebo *Sabal cerrulata* + *Urtica dioica* (Prostatgutt™ forte)	126 127	-4 -6[b]	+1.9 +1.8	- -	1b
Sökeland & Albrecht (1997) (17)	48	finasteride *Sabal cerrulata* + *Urtica dioica* (Prostatgutt™ forte)	244 245	-5.6 -4.8	+2.8 +2.0	-17.1 -10.2	1b

IPSS = International Prostate Symptom Score; Q_{max} = maximal urinary flow rate (free uroflowmetry); PVR = post-void residual urine; 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*, erectile dysfunction 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***

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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. AVP increases water re-absorption as well as urinary osmolality and decreases water excretion as well as total urine volume. AVP 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

Drug	t_{max} (hours)	t ½ (hours)	Recommended daily dose
Desmopressin	1-2	3	1 x 0.1-0.4 mg orally before sleeping

t_{max} = time to maximum plasma concentration; t½ = 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

Trials	Duration (weeks)	Treatment, i.e. oral daily dose before bedtime unless otherwise indicated	Patients (n)	Change nocturnal urine volume (mL/min)	Change nocturnal voids (n)	Time to first void (hours)	LE
Asplund et al. (1998) [4]	3	1 x 0.1 mg 1 x 0.2 mg 2 x 0.2 mg	23* 23* 23*	-0.5 (-31%) -0.7 (-44%) -0.6 (-38%)	- - -	- - -	2b
Cannon et al. (1999) [5]	6	Placebo 1 x 20 µg intranasal 1 x 40 µg intranasal	20 20 20	- - -	+0.1 (+3%) -0.3 (-10%) -0.7 (-23%)[a]	- - -	1b
Asplund et al. (1999) [6]	2	Placebo 1 x 0.1-0.4 mg	17* 17*	-0.2 (-11%) -0.8 (-44%)[a]	-0.2 (-11%) -0.8 (-42%)[a]	+0.2 +1.6	1b
Chancellor et al. (1999) [7]	12	1 x 20-40 µg intranasal	12	-	-1.8 (-50%)	-	2b
Mattiasson et al. (2002) [8]	3	Placebo 1 x 0.1-0.4 mg	65 86	-0.2 (-6%) -0.6 (-36%)[a]	-0.5 (-12%) -1.3 (-43%)[a]	+0.4 +1.8[a]	1b
Kuo 2002 [9]	4	1 x 0.1 mg	30*	-	-2.72 (-48.5)	-	2b
Rembratt et al. (2003) [10]	0.5	1 x 0.2 mg	72*	-0.5	-1.0	+1.9	2b
van Kerrebroeck et al. (2007) [11]	3	Placebo 1 x 0.1-0.4 mg	66 61	- -	-0.4 (-15%) -1.25 (-39%)[a]	+0.55 +1.66[a]	1b
Lose et al. (2004) [12] ‡	52	1 x 0.1-0.4 mg	132	-	-2	+2.3	2b

**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***

	LE	**GR**
Desmopressin can be used for the treatment of nocturia secondary to nocturnal polyuria.	1b	A

*4.5.7 **References***

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4.6 Combination therapies

4.6.1 α_1-blockers + 5α-reductase inhibitors

4.6.1.1 Mechanism of action

Combination therapy of α_1-blockers and 5α-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 α_1-blocker (alfuzosin, doxazosin, tamsulosin, or terazosin; pharmacokinetic properties see Section 3.1.2) together with a 5α-reductase inhibitor (dutasteride or finasteride; pharmacokinetic properties see Section 3.2.2). The α_1-blocker exhibits clinical effects within hours or days, whereas the 5α-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 α_1-blocker, 5α-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 α_1-blocker was superior to finasteride in symptom reduction, whereas the combination treatment was not superior to the α_1-blocker alone. In studies which included a placebo arm, the α_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_{max} improvement and superior to α_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_{max} starting from month 9 and superior to α_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 α_1-blockers or 5α-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 α_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 α_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 α_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 α_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 α_1-blockers in combination with either dutasteride or finasteride (9). Dutasteride patients discontinued α_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, 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 prostaterelated 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 α_1-blocker alone might also reduce the risk of symptom progression.

Table 11: Randomised trials using α_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.)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Symptom change (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [1]	52	Placebo	305	-16.5 [a]	+1.4	+1.3	1b
		Terazosin 1 x 10 mg	305	-37.7 [a,b,d]	+2.7 [b,d]	+1.3	
		Finasteride 1 x 5 mg	310	-19.8 [a]	+1.6	-16.9 [b,c]	
		Terazosin 1 x 10 mg + finasteride 1 x 5 mg	309	-39 [a, b ,d]	+3.2 [b,d]	-18.8 [b,c]	
Debruyne et al. (1998) [2]	26	Alfuzosin 2 x 5 mg	358	-41.2 [d]	+1.8	-0.5	1b
		Finasteride 1 x 5 mg	344	-33.5	+1.8	-10.5 [c]	
		Alfuzosin 2 x 5 mg + finasteride 1 x 5 mg	349	-39.1 [d]	+2.3	-11.9 [c]	
Kirby et al. (2003) [3]	52	Placebo	253	-33.1	+1.4	-	1b
		Doxazosin 1 x 1-8 mg	250	-49.1 [b,d]	+3.6 [b,d]	-	
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	265	-49.7 [b,d]	+3.8 [d]	-	
McConnell et al. (2003) [4]	234	Placebo	737	-23.8 [a]	+1.4 [a]	+24 [a]	1b
		Doxazosin 1 x 1-8 mg	756	-35.3 [a,b,d]	+2.5 [a,b]	+24 [a]	
		Finasteride 1 x 5 mg	768	-28.4 [a,b]	+2.2 [a,b]	-19 [a,b,c]	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	786	-41.7 [a,b,c,d]	+3.7 [a,b,c,d]	-19 [a,b,c]	

Roehrborn et al. (2008) [5]	104	Tamsulosin 1 x 0.4 mg Dutasteride 1 x 0.5 mg Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1611 1623 1610	-27.4 -30.5 -39.2 [c,d]	+0.9 +1.9 +2.4 [c,d]	0 -28 [c] -26.9 [c]	1b
Roehrborn et al. (2010) [6]	208	Tamsulosin 1 x 0.4 mg Dutasteride 1 x 0.5 mg Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1611 1623 1610	-23.2 -32.3 -38 [c,d]	+0.7 +2.0 +2.4 [c]	+4.6 -28 [c] -27.3 [c]	1b

Q_{max} = maximum urinary flow rate (free uroflowmetry); IPSS = International Prostate Symptom Score; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo; c = significant compared to α_1-blocker monotherapy; d = significant compared to 5α-reductase inhibitor monotherapy.

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 α_1-blocker and 5α-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 α_1-blockers or 5α-reductase inhibitor monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{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 α_1-blocker after 6 months might be considered in men with moderate LUTS.

4.6.1.6 Recommendations

	LE	GR
Combination treatment with α_1-blocker together with 5α-reductase inhibitor should be offered to men with moderate-to-severe lower urinary tract symptoms, enlarged prostates (> 40 mL), and reduced Q_{max} (men likely to develop disease progression). Combination treatment is not recommended for short-term therapy (< 1 year).	1b	A

4.6.1.7 References

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4.6.2 α_1-blockers + muscarinic receptor antagonists

4.6.2.1 Mechanism of action

Combination therapy of an α_1-blocker together with a muscarinic receptor antagonist aims to antagonise both α_1-adrenoceptor and muscarinic cholinoreceptors (M^2 and M^3) 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 α_1-blocker (alfuzosin, doxazosin, tamsulosin, or terazosin; pharmacokinetic properties chapter 3.1.2) together with a muscarinic receptor antagonist (darifencacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, or trospium chloride; pharmacokinetic properties chapter 3.3.2). However, only the combinations of the α_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 α_1-blockers and muscarinic receptor antagonists in adult male patients with LUTS (1-8). Additionally, one trial was published using the α_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 α_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 α_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 α_1-blockers or placebo alone. Furthermore, the combination treatment significantly reduced urgency 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 α_1-blocker treatment by adding a muscarinic receptor antagonist to the existing α_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 α_1-blockers

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency [%]	Nocturia [%]	IPSS [%]	LE
Saito et al. (1999) [1]	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5	-	1b
		Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20 mg/d	75	-44.7	-44.4[a]	-	
Lee et al. (2005) [3]	8	Doxazosin 1 x 4 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin 1 x 4 mg/d + propiverine 1 x 20 mg/d	131	-27.5[a]	-46.7	-50.7	
Kaplan et al. (2006) [4]	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-54	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9[b]	
		Tolterodine 1 x 4 mg/d + tamsulosin 1 x 0.4 mg/d	217	-27.1[b]	-39.9[b]	-66.4[b]	
MacDiarmid et al. (2008) [5]	12	Tamsulosin 1 x 0.4 mg/d + placebo	209	-	-	-34.9	1b
		Tamsulosin 1 x 0.4 mg/d + oxybutynine 1 x 10 mg/d	209	-	-	-51.9[b]	
Kaplan et al. (2005) [7] ‡	25	Tolterodine 1 x 4 mg/d	43	-35.7[a]	-29.3 [a]	-35.3	2b
Yang et al. (2007) [8] ‡	6	Tolterodine 2 x 2 mg/d	33	-	-	-35.7[a]	2b
Kaplan et al. (2009) [11] ‡	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2[a]	-	-29	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d	202	-9.1[a]	-	-31.8	

IPSS = International Prostate Symptom Score
‡ persisting LUTS during α_1-blocker treatment (add-on approach)
a = significant compared to baseline ($p \leq 0.05$, indexed wherever evaluated)
b = 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 α_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 post-void residual urine was low (+6 to +24 mL) some men developed higher post-void residuals or even urinary retention (0.9 to 3.3%). It remains unknown which men are at risk of developing post-void residual 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 α_1-blocker and muscarinic receptor antagonist. Measuring of post-void residual urine is recommended during combination treatment to assess increase or urinary retention.

4.6.2.6 Recommendations

	LE	GR
Combination treatment with α_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.	1b	B
Combination treatment should cautiously be prescribed in men who are suspicious of having bladder outlet obstruction.	2b	B

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4.7 Emerging drugs

4.7.1 Phosphodiesterase (PDE) 5 Inhibitors (with or without α_1-blockers)

4.7.2 ***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. NO 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. PDE 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). NO 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).

*4.7.3 **Available drugs***

Three selective oral PDE5 inhibitors (sildenafil citrate [sildenafil], tadalafil, and vardenafil hcl [vardenafil]) have been licensed in Europe for the treatment of erectile dysfunction 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 PDE5 inhibitors differ primarily in their pharmacokinetic profiles (5). All PDE5 inhibitors 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. PDE5 inhibitors 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: PDE5 inhibitors licensed in Europe for treating erectile dysfunction; key pharmacokinetic properties and doses used in clinical trials

Drugs	t_{max} (hours)	t ½ (hours)	Daily doses in clinical trials of patients with male LUTS
Sildenafil	1 * (0.5-2)	3-5	1 x 25-100 mg
Tadalafil	2 (0.5-12)	17.5	1 x 2.5-20 mg
Vardenafil	1 * (0.5-2)	4-5	2 x 10 mg

*t_{max} = time to maximum plasma concentration; t½ = elimination half-life; * dependent on food intake (i.e. slower resorption of the drug and an increase in tmax by approximately 1 hour after a fatty meal).*

*4.7.4 **Efficacy***

A post-hoc analysis of patients with erectile dysfunction treated with sildenafil initially showed that the PDE5 inhibitor 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 PDE5 inhibitors have been published during the last years and have investigated changes in symptoms (IPSS), uroflowmetry parameters (Q_{max}), and post-void residual urine (6-16). The maximum trial duration was 12 weeks. These trials demonstrated that all PDE5 inhibitors significantly and consistently reduced IPSS by approximately 17-35% (Table 14). Both bladder storage and voiding symptoms decreased equally during treatment with PDE5 inhibitors. Post-void residual urine remained unchanged in most of the trials. Q_{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_{max} and Q_{ave} following oral administration of 50 or 100 mg sildenafil in up to 76% of men (mean Q_{max} increase 3.7-4.3 mLs or 24-38%) (17,18). PDE5 inhibitors significantly improved QoL compared to placebo-treated patients.

Three trials compared the efficacy of PDE5 inhibitors (sildenafil or tadalafil) with or without α_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_{max}, and post-void residual urine to a greater extent than the single drug alone of each class (Table 14), although the difference compared to PDE5 inhibitor or α_1-blocker alone was only statistically significant in one of the three trials (12).

Table 14: Efficacy of PDE5 inhibitors in adult men with LUTS who participated in clinical trials with EBM

Trials	Duration (weeks)	Treatment	Patients	IPSS	Qmax (mL/s)	PVR (mL]	LE
McVary et al. 2007 [8] ‡	12	Placebo	180	-1.93	+0.16	-	1b
		Sildenafil 1 x 50-100 mg/ day or 1 x 50-100 mg before sexual intercourse	189	-6.32 *	+0.32	-	
Kaplan et al. 2007 [9]‡	12	Alfuzosin 1 x 10 mg/day	20	-2.7 (-15.5%) †	+1.1 †	-23 †	1b
		Sildenafil 1 x 25 mg/day	21	-2.0 (-16.9%) †	+0.6	-12	
		Alfuzosin 1 x 10 mg/day + sildenafil 1 x 25 mg/day	21	-4.3 (-24.1%) †	+4.3 †	-21 †	
McVary et al. 2007 [10]	12	Placebo	143	-1.7 (-9.3%)	+0.9	-2.6	1b
		Tadalafil 1 x 5-20 mg/day	138	-3.8 (-21.7%) *	+0.5	+1.4	
Roehrborn et al. 2008 [11]	12	Placebo	212	-2.3 (-13.3%)	+1.2	+4.81	1b
		Tadalafil 1 x 2.5 mg/day	209	-2.7 (-22.2%) *	+1.4	+12.1	
		Tadalafil 1 x 5 mg/day	212	-4.9 (-28.2%) *	+1.6	+6.6	
		Tadalafil 1 x 10 mg/day	216	-5.2 (-29.1%) *	+1.6	+10.6	
		Tadalafil 1 x 20 mg/day	209	-5.2 (-30.5%) *	+2.0	-4	
Bechara et al. 2008 [12]	6	Tamsulosin 1 x 0.4 mg/day	15	-6.7 † (-34.5%)	+2.1 †	-35.2 †	1b
		Tamsulosin 1 x 0.4 mg/day + tadalafil 1 x 20 mg/day	15	-9.2 †a (-47.4%)	+3.0 †	-38.7 †	
Liguori et al. 2009 [13] ‡	12	Alfuzosin 1 x 10 mg/day	22	-5.2 † (-27.2%)	+1.7 †	-	1b
		Tadalafil 1 x 20 mg every 2 days	21	-1.3 (-8.4%)	+1.2 †	-	
		Alfuzsosin 1 x 10 mg/day + tadalafil 1 x 20 mg every 2 days	23	-6.3 † (-41.6%)	+3.1 †	-	
Porst et al. 2009 [14]‡	12	Placebo	115	-2.1	+1.9	-6.8	1b
		Tadalafil 1 x 2.5 mg/day	113	-3.6 *	+1.4	+8.6 *	
		Tadalafil 1 x 5 mg/day	117	-4.2 *	+1.7	-1.8	
		Tadalafil 1 x 10 mg/day	120	-4.7 *	+1.3	+3.8	
		Tadalafil 1 x 20 mg/day	116	-4.7 *	+2.0	-14	
Stief et al. 2008 [15]	8	Placebo	113	-3.6 (-20%)	+1.0	+1.92	1b
		Vardenafil 2 x 10 mg	109	-5.8 (-34.5%) *	+1.6	-1.0	

*IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine; ‡ trial included patients with both erectile dysfunction and LUTS; * significant compared to placebo ($p \leq 0.05$); † significant compared to baseline ($p \leq 0.05$ (indexed wherever evaluated); [a] significant compared to α1-blocker (tamsulosin, $p < 0.05$).*

4.7.5 *Tolerability and safety*

PDE5 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 PDE5 inhibitors. The probability of developing priapism or acute urinary retention is considered minimal.

PDE5 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 PDE5 inhibitors should not be used in patients who are taking the α_1-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 PDE5 inhibitors. Sildenafil and vardenafil are also contraindicated in patients with retinitis pigmentosa. Caution is advised if PDE5 inhibitors 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 PDE5 inhibitor.

4.7.6 *Practical considerations*

To date, PDE5 inhibitors have been officially licensed only for the treatment of erectile dysfunction 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 PDE5 inhibitors in the context of other available potent drugs (e.g. α_1-blockers, 5α-reductase inhibitors, or muscarinic receptor antagonists) remains to be determined. Insufficient information is available about combinations between PDE5 inhibitors and other LUTS medications.

4.7.7 *Recommendations*

	LE	GR
PDE5 inhibitors reduce moderate to severe male lower urinary tract symptoms.	1b	
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.		A

4.7.8 *References*

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4.8 Other new drugs

Several new drugs are currently under clinical investigation (phase II-III trials) of which none has been licensed for male LUTS so far. These new drugs target:

- the prostate, e.g. gonodotrophin-releasing hormone antagonists, oestrogen receptor antagonists, apoptosis-inducing agents, vaccines, vitamin D agonists, or androgen replacement therapies;
- the bladder, e.g. β_3-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 benign prostatic obstruction (BPO) and, secondly, to reduce lower urinary tract symptoms (LUTS).

TURP 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 who 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

TURP 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 followup (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_{max} increase following TURP was 125% with an absolute mean improvement of +9.7 mL/s (95% CI: 8.6-11.2 mL/s) (10). All RCTs comparing TUIP with TURP 12 months after the procedure reported a lower mean or median Q_{max} following TUIP with an overall mean Q_{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% (96% 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 post-operative 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 long-standing 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 erectile dysfunction (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 post-operative 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_{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 a 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_{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 post-operative 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. Post-operative 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 post-operative retrograde ejaculation (57 vs 60%) (24) or erectile dysfunction (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*

	LE	GR
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.	1a	A
Bipolar TURP achieves short-term results comparable to monopolar TURP.	1a	A
TUIP is the surgical therapy of choice for men with LUTS secondary to BPO and prostate sizes < 30 mL without middle lobes.	1a	A

BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

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_{max})

Trials	Intervention	Patients (n)	Absolute decrease (%) in symptoms at 12 months		Q_{max} (mL/s) at 12 months		Blood transfusion	Re-operation rate at 12 months	LE
			absolute	[%]	absolute	[%]	[%]	[%]	
Dorflinger et al. (1992) (28)	TURP	31	-11.6 [a]	-88 [a]	+22.9 [a, b]	+294 [a, b]	13	3.2 [b]	1b
	TUIP	29	-12.6 [a]	-85 [a]	+16.3 [a]	+223 [a]	0 [c]	20.7	
Jahnson et al. (1998) (29)	TURP	43	-13 [a]	-82 [a]	+19.5 [a, b]	+229 [a, b]	2.4	7.1 [b]	1b
	TUIP	42	-11.8 [a]	-77 [a]	+13.8 [a]	+148 [a]	0	23.2	
Riehmann et al. (1995) (30)	TURP	61	-9.5 [a]	-67 [a]	no significant difference between groups			16	1b
	TUIP	56	-10 [a]	-63 [a]				23	
Saporta et al. (1996) (31)	TURP	20	-9.4 [a]	-63 [a]	+17.3 [a]	+266 [a]		0 [b]	1b
	TUIP	20	-9.3 [a]	-64 [a]	+14.6 [a]	+197 [a]		15	
Soonwalla et al. (1992) (32)	TURP	110			+20.1 [a]	+251 [a]	34.5		1b
	TUIP	110			+19.5 [a]	+246 [a]	0 [c]		
Tkoocz et al. (2002) (12)	TURP	50	-12 *[a]	-70*	6.9 *[a]	+255 [a]			1b
	TUIP	50	-13 *[a]	-77*	7.6 *[a]	+222 [a]			
Lourenco et al. (2009) (33)	TURP	345	no significant difference between groups		no significant difference between groups		28.3	7.2 [b]	1a
	TUIP	346					1.1 [c]	18	
Yang et al. (2001) (11)	TURP	403	-11.2 to -13	-63 to -82	+17.3 to +22.9 [b]	+266 to +352 [b]	25.1	5.5	1a
	TUIP	392	-10 to -13.5	-63 to -83	+13.8 to +16.3	+189 to +223	0.87 [c]	9.3	

** 24 month post-operatively; a significantly different compared to baseline; b significantly different in favour of TURP; c significantly different in favour of TUIP*

5.1.8 *References*

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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. Post-operative 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 scissor 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 urinary tract infection 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_{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

Studies	Duration (weeks)	Patients (*n*)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Kuntz et al. 2008 (9)	260	32	-18.2	86	21.4	677	-287	98			1b
Skolarikos et al. 2008 (8)	78	60	-12.5	63	7	86	-77	86	-86	88	1b
Naspro et al. 2006 (7)	104	39	-13.2	62	15.9	291					1b
Varkarakis et al. 2004 (12)	151	232	-23.3	84	16.5	329	-104	90			3
Gratzke et al. 2007 (13)		868			13	218	-128	88	85	88	2b

IPSS = international prostate symptom score; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry)

Table 17: Tolerability and safety of open prostatectomy

	Peri-operative mortality (%)	Post-operative stress incontinence (%)	Re-operation for BPO (%)
Kuntz *et al*. 2008 (9)	0	0	0
Skolarikos *et al*. 2008 (8)	0		0
Naspro *et al*. 2006 (7)	0	2.5	0
Varkarakis *et al*. 2004 (12)	0	0	
Gratzke *et al*. 2007 (13)	0.2		

BPO = benign prostatic obstruction.

5.2.6 *Recommendations*

	LE	GR
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.	1b	A

5.2.7 *References*

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5.3 Transrethral 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 α-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 Q_{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 Q_{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 Q_{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 Q_{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, transurethral resection (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. TURP 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 (erectile dysfunction, 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 bladder outlet obstruction 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_{max}), post-void residual urine (PVR), and prostate volume (PVol)

Trials	Duration (weeks)	Patients (n)	Change IPSS (absolute [%])	Change Q_{max} (mL/s, [%])	Change QoL (absolute [%])	Change PVR (absolute [%])	Change PVol (absolute [%])	LE
Hoffman et al. (2007) (3)	52	322	-12.7[a] (-65.0)	5.6[a] (70.0)	-2.4[a] (58.5)	NA	NA	1a
Gravas et al. (2005) (4)	52	183	-14.5[a] (-69.0)	8.4[a] (109.0)	-2.97[a] (70.9)	NA	-17.0 [a] (-33.0)	1b
Mattiasson et al. (2007) (19)	260	100	-13.6[a] (-61.5)	3.8[a] (50.0)	-3.2[a] (-74.4)	-36.0 (-34.0)	-4.0 (-8.1)	1b
Floratos et al. (15)	156	78	-8.0[a] (-40.0)	2.7[a] (29.3)	-2.0[a] (-50.0)	NS	NA	1b
Thalmann et al. (2002) (17)	104	200	-20.0[a] (-87.0)	7.0[a] (116.6)	-4.0[a] (-80.0)	-143 [a] (-84.1)	-17.7 [a] (-30.7)	2b
Miller et al. (2003) (18)	260	150	-10.6[a] (-47.0)	2.4[a] (37.0)	-2.3[a] (-54.7)	NA	NA	2b
Trock et al. (2004) (23)	208	541	-8.9[a] (-42.7)	2.8[a] (35.0)	-2.1[a] (-50.1)	NA	NA	2b

a = significant compared to baseline (indexed whenever evaluated); NS = not significant; NA = not available.

5.3.6 *Recommendations*

	LE	GR
Transuretrual 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 transuretrual resection of the prostate with lower re-treatment rates compared to transretrual microwave therapy	1a	A

5.3.7 *References*

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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 Q_{max} 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 Q_{max} 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 Q_{max}, 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). Post-operative 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, erectile dysfunction, urinary incontinence). However, there remain concerns about the durability of the effects achieved by TUNA™.

*5.4.6 **Recommendations***

	LE	GR
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.	1a	A

Table 19: Summary of comparative level of evidence (LE) 1 data (TUNA™ vs TURP) (12)

	TUNA™	TURP	TUNA™ vs TURP 95% CI	LE
Symptoms (IPSS): mean (% improvement)				
3 months (8,10)	-12 (56%)	-14 (62%)	-2 (-0.9 to 3.1)	1b
1 year (9-11)	-12 (55%)	-15.5 (70%)	3.4 (2.1 to 5.2)[a]	1b
3 years (9,11)	-10 (45%)	-15 (67%)	4.8 (4.2 to 5.4)[a]	1b
Quality of life scores: mean (% improvement)				
3 months (8,10)	-4.5 (54%)	-3.7 (48%)	-0.8 (-1.3 to 0.5)	1b
1 year (9-11)	-4 (50%)	-4.3 (56%)	0.63 (0.1 to 1.2)[a]	1b
3 years (9,11)	-4.2 (50%)	5.2 (67%)	1 (0.2 to 1.9)[a]	1b
Q_{max} (mL/s): mean (% improvement)				
3 months (8,10)	4.7 (54%)	11.5 (150%)	-5.8 (-6.3 to -5.4)[a]	1b
1 year (9-11)	6.5 (76%)	12.2 (160%)	-5.9 (-7.7 to -4.1)[a]	1b
3 years (9,11)	5.6 (66%)	10.8 (141%)	-5.3 (-6.8 to -3.9)[a]	1b
PVR (mL): mean (% improvement)				
1 year (10,11)	-20 (22%)	-42 (41%)	22 (-18 to 27)[a]	1b

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate; PVR = post-void residual urine. a = TURP significantly better compared with TUNA™.

5.4.7 ***References***

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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 analyzed available RCTs comparing HoLEP and TURP (10,11), reported a significantly longer operation time with HoLEP (Table 20). Symptom improvements were comparable, but Q_{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 post-operative 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: Post-operative 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_{max}), post-void residual urine (PVR), and prostate volume

Trials	Duration	Patients	Surgery	Change symptoms (IPSS)		Change Q_{max} (mL/s)		Change PVR (mL)		Change prostate volume (mL)		LE
	(months)	(n)		absolute	[%]	absolute	[%]	absolute	[%]	absolute	[%]	
Le Duc et al. (1999) (1)	6	42	HoLRP	-18.4	-84	+15.1	+170					1b
		43	TURP	-17.9	-78	+13.2	+145					
Westenberg et al. (2004) (7)	48	43	HoLRP	-14.7 [a]	-67 [a]	+13.4 [a]	+151 [a]	- 61.1 [a] †	-70 [a] †	- 15 [a] †	-34 [a] †	1b
		30	TURP	-16.4 [a]	-71 [a]	+9.4 [a]	+103 [a]	- 50.4 [a] †	-60 [a] †	- 17 [a]	-39 [a] †	
Fraundorfer et al. (1998) (8)	1	14	HoLEP	-14.0	-66	+18.2	+260					3
Gilling et al. (2008) (9)	72	38	HoLEP	-17.2	-67	+10.9	+135	-71.7 †	-68 †	- 31.3 †	-54 †	3
Tan et al. (2007) (10)	12	232	HoLRP	-17.5 to -21.7	-81 to -83	+13.4 to +23.0	+160 to +470	-232.7	-98			1a
		228	TURP	-17.7 to -18.0	-76 to -82	+10.1 to +21.8	+122 to +370	-189.4	-88			
Lourenco et al. (2008) (11)	12	277	HoLRP	-17.7 to -21.7	-82 to -92	+13.4 to +23.0 [b]	+160 to +470 [b]					1a
		270	TURP	-17.5 to -18.7	-81 to -82	+10.1 to +21.8	+122 to +370 [a]					
Kuntz et al. (2008) (12)	60	42	HoLEP	-19.1	-86	+ 20.5	+540	-269.4	-96			1b
		32	OP	-18.0	-86	+ 20.8	+578	-286.7	-98			
Heinrich et al. (2007) (13)	6	140	KTP (80 W)	-10.9 [a]	-55	+ 5.6	+ 43	-65 [a]	-74 [a]			3
Ruszat et al. (2008) (14)	12	302	KTP (80 W)	-11.9 [a]	-65 [a]	+ 10.2 [a]	+121 [a]	-173 [a]	-83 [a]			3
	48	88	KTP (80 W)	-10.9 [a]	-60 [a]	+ 10.2 [a]	+121 [a]	-179 [a]	-86 [a]			
Hamann et al. (2008) (15)	12	157	KTP (80 W)	-13.4 [a]	-65 [a]	+ 10.7 [a]	+135 [a]	-103.4 [a]	-78 [a]			3
Reich et al. (2005) (16)	12	51	KTP (80 W) OA	-13.7 [a]	-68 [a]	+ 14.9 [a]	+222 [a]	-122 [a]	-83 [a]			3

Ruszat et al. (2007) (17)	24	116	KTP (80 W) OA	-13.0	-70	+ 11.3	+140	-103	-80			3
		92	KTP (80 W) CG	-12.7	-71	+12.0	+168	-160	-78			
Ruszat et al. (2006) (18)	24	16	PVP RUR	-11.1	-72			-280	-88			3
		19	PVP NUR	-12.1	-65	+16.2	+228	-131	-85			
Rajbabu et al. (2007) (19)	24	38	KTP (80 W)	-17.2 [a]	-75 [a]	+11.3 [a]	+141 [a]	-85 [a]	-63 [a]			3
Bouchier-Hayes et al. (2006) (20)	12	38	KTP (80 W)	-14.0 [a]	-50 [a]	+12.0 [a]	+167 [a]	-120 [a]	-82 [a]			1b
		38	TURP	-12.9 [a]	-50 [a]	+8.6 [a]	+149 [a]	-82 [a]	-69 [a]			
Bachmann et al. (2005) (21)	6	55	KTP (80 W)	-12.9 [a]	-71 [a]	+11.2 [a]	+162 [a]	-133 [a]	-91 [a]			3
		31	TURP	-12.5 [a]	-72 [a]	+12.2 [a]	+177 [a]	-106 [a]	-88 [a]	-21	-45	
Bouchier-Hayes et al. (2008) (23)	12	46	KTP (80 W)	-16.4 [a]	-65 [a]	+9.8 [a]	+111 [a]	-107 [a]	-83 [a]	-30	-63	1b
		39	TURP	-14.5 [a]	-57 [a]	+10.5 [a]	+118 [a]	-93 [a]	-84 [a]	-27	-44	
Horasanli et al. (2008) (24)	6	39	KTP (80 W)	-5.8	-31	+4.7	+156	-104	-57			1b
		37	TURP	-13.8 [b]	-68 [b]	+11.5 [b]	+225 [b]	-154 [b]	-87 [b]			

† 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 vaporised 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_2O) and detrusor pressure at Q_{max} (Pdetmax; 75 vs. 36.6 cm H_2O) 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 a RCT is only 12 months; this trial indicated that 532 nm laser vaporisation 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 vaporisation 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 vaporisation than the TURP group, with a mean (range) of 13 (0–24) hours versus 44.7 (6–192) hours. Additionally, the length of hospital stay was significantly shorter with laser vaporisation, with a mean (range) of 1.09 (1–2) and 3.6 (3–9) days in the laser vaporisation 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 aluminum 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 vaporisation), and thulium:YAG laser prostatectomy. Only a few articles have been published on thulium:YAG prostatectomy, which may be used as a vaporising, 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

	LE	GR
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.	1b	A
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.	3	B
With regard to long-term complication rates, results are only available for HoLEP, and are comparable to TURP.	1b	A

TURP = transurethral resection of the prostate; LUTS = lower urinary tract symptoms; BPO = benign prostatic obstruction.

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5.6 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 ultrasonography 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 bulbar segment. This bulbar segment results in a significantly lower migration rate with BPS-2 (5%) compared with BPS-1 (85%), but the bulbar segment also caused significant discomfort (10). BPS-2 also has better symptom scores and voiding function than BPS-1, but only Q_{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_{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_{max} ranging from 8.8 to 20 mL/s. At 12 years of follow-up, the mean IPSS, Q_{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_{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***

	LE	GR
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.	3	C

Table 21: Efficacy of stents: key studies

		Symptoms		Q_{max} (mL/s)		Failure rate (follow-up in months)	LE
Stent	***n***	**Pre-operative**	**Post-operative**	**Pre-operative**	**Post-operative**		
Urolume (P) (2)	91	14.1	4.7	9.3	17.1	Overall	3
	44	R	4.6	R	13.7	15.5% (18 mos)	
Memotherm (P) (5)	123	24.0	6.1*	7.4	16.1*	4% (48 mos)	3
TITAN (P) (6)	85	15.9[a]	9.331	8.59*	11.431	Overall	3
	59	18.0	5.21	R	11.34	19% (24 mos)	
Spanner (T) (7)	30	22.3	7.1	8.2	11.6	0% (2 mos)	3
Memokath (T-P) (8)	211	20.3	8.22	NA	NA	23% (7 y)3	3
Horizon Bell-shaped (T) (9)	108	22.0	15.0	9.1	9.6	46% (3 mos)	3

Q_{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.*

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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 (Qmax +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 post-operatively 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 (9,12).

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

Trials	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		Level of evidence
			Absolute	%	mL/s	%	mL	%	mL	%	
Goya *et al.* 1999 (5)	12	10	-10.9[a]	-47	+5.1[a]	+64	-79.8[a]	-62	-2.1	-4	3
Savoca *et al.* 2001 (15)	24	8	-11[a]	-52	+5[a]	+46	-103[a]	-79	n/a	n/a	3
Ditrolio *et al.* 2002 (6)	52	15	-1 6.5	-74	+6.2	+109	n/a	n/a	-21.6	-45	3
Plante *et al.* 2002 (7)	52	5	-9.6[a]	-41	+3.2	+32	-7.6	-6.4	-15.8[a]	-30	2b
Chiang *et al.* 2003 (16)	12 (24)	11	-9.2[a]	-52	+8.2[a]	+155	-203.2[a]	-88	-2.2	-5	3
Goya *et al.* 2004 (8)	156	34	-8.7[a]	-40	+4.4[a]	+65	-65[a]	-70	+2.1	+4	3
Grise *et al.* 2004 (9)	52	115 (94)	-10.3[a]	-50	+3.5[a]	+35	n/a	n/a	-7.4[a]	-16	2b
Mutaguchi *et al.* 2006 (10)†	64	16	Spontaneous voiding in 87.5% Mean PVR 60 mL						-19.7[a]	-34	3
Larson *et al.* 2006 (11)	52	65	-9.4[a]	-44	+2.8[a]	+33	n/a	n/a	n/a	n/a	3
Plante *et al.* 2007 (12)*	24	79	-10.6 to -13.4[a]	-47 to -55	+3.2 to +8.1[a]	+37 to +94	-1.2 to -27.3[a]	-1 to -26	-5.6 to -11.2[a]	-13 to -25	2b
Magno *et al.* 2008 (13)	52	36	-13.3[a]	-47	+9.2[a]	+154	-286.4[a]	-99	-12.7	-19	3
Sakr *et al.* 2009 (14)	208	35	-12.1[a]	-55	+11[a]	+186	-32.6[a]	-47	-2.8[a]	-5	3

*Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Qmax), post-void residual urine (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%);
- urinary tract infection or epididymitis;
- urinary retention.

Less frequently reported (< 5%) adverse events included:

- decreased libido;
- retrograde ejaculation;
- urgency urinary incontinence;
- urethral stenosis;
- erectile dysfunction.

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

	LE	GR
Intra-prostatic ethanol injections for LUTS due to BPO are still experimental.	3	
Intra-prostatic ethanol injections should be performed only in clinical trials.		C

LUTS = lower urinary tract symptoms; BPO = benign prostatic obstruction.

5.7.1.7 References

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*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 α_1-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_{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_{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_{max} and PVR. Retreatment rates with BTX-A were as high as 29% (11).

Table 23: Results of intra-prostatic botulinum toxin (Botox™) injections for treating LUTS/BPH, BPO or urinary retention

Trials	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		Level of evidence
			Absolute	%	mL/s	%	mL	%	mL	%	
Maria *et al.* 2003 (7)*	52	30	-14.4[a,b]	-62	+6.9[a,b]	+85	-102[a,b]	-81	-32[a,b]	-61	1b
Chuang *et al.* 2005 (8)*	40	16	-9.8[a]	-52	+5.3[a]	+73	-41	-60	-3[a]	-16	3
Kuo 2005 (5)†	24	10	Spontaneous voiding in 100% of patients		+4.0[a]	+53	-206[a]	-85	-17[a]	-24	3
Chuang *et al.* 2006 (9)*	52	41	-11[a]	-57	+4.1[a]	+59	-68	-42	-7[a]	-13	3
Park *et al.* 2006 (10)*	24	23	-9.3[a]	-39	+2.0[a]	+28	-49[a]	-45	-7[a]	-14	3
Chuang *et al.* 2006 (4)	12	8	-15[a]	-79	+6.5[a]	+73	-155.5	-88	-12.1[a]	-20	3
Silva *et al.* 2008 (14)†*	12 (24)	21 (10)	Spontaneous voiding in 80% of patient		+11.4	n/a	Mean PVR 66 mL		-20[a]	-29	3
Brisinda *et al.* 2009 (11)*	120	77	-13[a]	-54	+5.9[a]	+69	-65[a]	-71	-27.2[a]	-50	3
Kuo and Liu 2009 (12)*	52	30	-7.1[a]	-46	+2.3[a]	+27	+21	+23	-13[a]	-14	1b
Silva *et al.* 2009 (15)†*	72	11	Spontaneous voiding in 100% of patients		+10.5	n/a	Mean PVR 58 mL		-9.2[a]	-11	3
Nikoobakht *et al.* 2010 (13)‡	52	72	-11.3[a]	-57	+7.7[a]	+122	-34[a]	-68	n/a		3

*Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Q_{max}), post-void residual urine (PVR), and prostate volume. a = significant compared with baseline (indexed whenever evaluated); b = significant compared with placebo (saline solution) or α1-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 post-operative 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 post-operative 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

	LE	GR
Intra-prostatic botulinum toxin injections for lower urinary tract symptoms due to benign prostatic obstruction or urinary retention are still experimental.	3	
Intra-prostatic botulinum toxin injections should be performed only in clinical trials.		C

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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.

Treatment	Onset	LUTS	Uroflowmetry (Q_{max})	Prostate size	PVR	Disease progression
Conservative treatments						
Watchful waiting, behavioural treatment	months	+	+	-	-	?
α-adrenoceptor antagonists	days	++	++	-	- / +	+++ (symptoms)
5α-reductase inhibitors	months	+	++	+ - ++	-	+++ (retention)
Muscarinic receptor antagonists	weeks	++ (storage symptoms)	-	-	+ (increase)	?
Plant extracts	weeks	+	- / +	-	-	+
α-adrenoceptor antagonists + 5α-reductase inhibitors	days	++	++	+ -++	- / +	+++ (symptoms + retention)
α-adrenoceptor antagonists + muscarinic receptor antagonists	days	++	++	-	- / +	?
PDE5-inhibitors	weeks	++	-	-	-	?
Surgical treatments	After catheter removal					
TURP–TUIP	hours	++++	++++	+++	++++	++++
Open prostatectomy	hours	++++	++++	++++	++++	++++
TUMT	weeks	+++	+++	++	++	+++
TUNA	weeks	+++	+++	++	+	++
HoLEP	hours	++++	++++	++++	++++	++++
KTP	days	+++	+++	++	++	+++
Prostate stents	hours	++	++	-	+++	?
Ethanol injections prostate	weeks	++	++	+	+	?
Botulinum toxin injections prostate	weeks	++	+++	+	+	?

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.

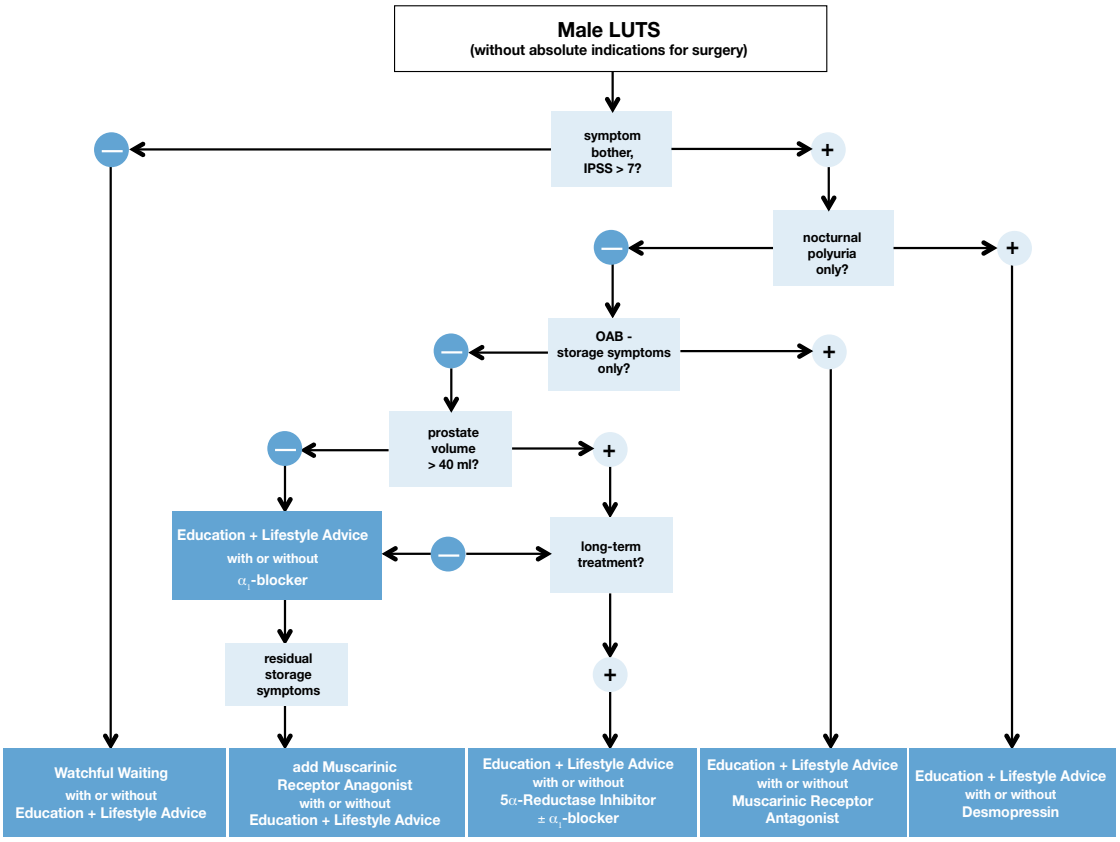

Figure 3: Treatment algorithm of male lower urinary tract symptoms (LUTS) using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation (◊). Minus (–) indicate the absence and plus (+) the presence of the condition.

Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent urinary tract infections, bladder stones or diverticula, treatment-resistant macroscopic hematuria 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.

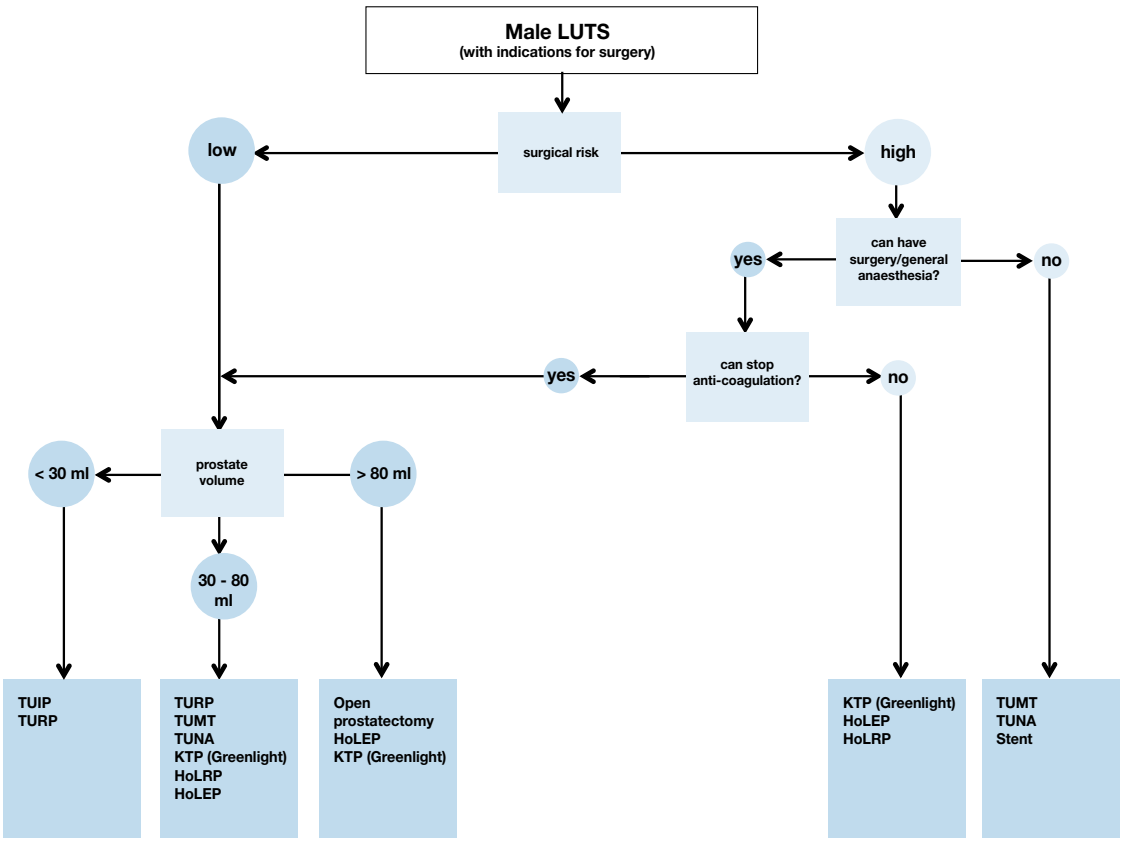

Figure 4: Treatment algorithm of bothersome lower urinary tract symptoms (LUTS) refractory to conservative/medical treatment or in cases of absolute operation indications. Note that this flowchart has been stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size; however, the choice of the surgical techniques also depends on patients' preferences, willingness to accept surgery-associated side effects, availability of the armamentarium, and surgeon's experience with the operation technique.

HoLEP = Holmium Laser Enucleation of the Prostate; HoLRP = Holmium Laser Resection of the Prostate; KTP = K^+-titanyl-phosphate laser ("greenlight"); TUIP = Transurethral Incision of the Prostate; TUMT = Transurethral Microwave Therapy; TUNA = Transurethral Needle Ablation of the prostate; TURP = Transurethral Resection of the Prostate.

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 post-void residual 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:

- I-PSS;
- Uroflowmetry and post-void residual urine volume.

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 post-void residual 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 post-void residual urine volume.

6.4 Recommendations

	LE	GR
Follow-up for all conservative or operative treatment modalities is based on empirical data or theoretical considerations but not on evidence based studies.	3-4	C

7. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AVP	arginine vasopressin
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
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 urine
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	transuretrual incision of the prostate
TUMT	transretrual microwave therapy
TUNA™	transuretrual needle ablasion
TURP	transurethral resection of the prostate
WW	watchful waiting

Conflict of interest

All members of the Male LUTS working group 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 kept on file in the European Association of Urology Central Office database. 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, E. Amar, I. Eardley, F. Giuliano, D. Hatzichristou, K. Hatzimouratidis, F. Montorsi, Y. Vardi

European Association of Urology

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1. BACKGROUND

1.1 Introduction

Erectile dysfunction (ED, impotence) and premature ejaculation (PE) are the two main complaints in male sexual medicine. 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 (1).

The update is based on a review of available scientific information, current research, and clinical practice in the field (1,2). The Expert Panel has also identified critical problems and knowledge gaps, setting priorities for future clinical research.

Level of evidence (LE) and grade of recommendation (GR) have been included in these guidelines when possible. The aim of this practice is to provide transparency between the underlying evidence and the recommendation made (3).

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2. DIAGNOSIS

2.1 Epidemiology and risk factors

Erection is a neurovascular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism (1).

Erectile dysfunction has been defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it affects physical and psychosocial health and has a significant impact on the quality of life (QoL) of sufferers and their partners and families (2).

*2.1.1 **Epidemiology***

Recent epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large-scale, community-based study of ED was the Massachusetts Male Aging Study (MMAS). The study reported an overall prevalence of 52% ED in non-institutionalised 40- to 70-year-old men in the Boston area in the USA (3); specific prevalences for minimal, moderate, and complete ED were 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years old, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% (4). In the National Health and Social Life Survey (NHSLS), the prevalence of sexual dysfunctions (not specific ED) was 31% (5). The incidence rate of ED (new cases per 1,000 men annually) was 26 in the MMAS study (6), 65.6 (mean follow-up of 2 years) in a Brazilian study (7), and 19.2 (mean follow-up of 4.2 years) in a Dutch study (8). Differences between these studies can be explained by differences in methodology and in the ages and socio-economic status of the populations studied.

*2.1.2 **Risk factors***

Erectile dysfunction shares common risk factors with cardiovascular disease (e.g. lack of exercise, obesity, smoking, hypercholesterolaemia, metabolic syndrome), some of which can be modified. 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 of ED over an 8-year follow-up period of regular exercise (9). 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 (10). Significant improvements in body mass index (BMI) and physical activity scores, as well as in erectile function, were observed in the lifestyle intervention group. These changes were highly correlated with both weight loss and activity levels.

However, it should be emphasised that controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED.

*2.1.3 **Post-radical prostatectomy erectile dysfunction (ED)***

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localised prostate cancer (PCa) 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 PCa in younger patients (11-13). Research has shown that about 25-75% of men experience post-operative ED (14).

Post-RP ED is multifactorial. Cavernosal nerve injury induces pro-apoptotic (loss of smooth muscle) and pro-fibrotic (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 pre-operative potency is a major factor associated with the recovery of erectile function after surgery, patients being considered for a nerve-sparing radical prostatectomy (NSRP) should ideally be potent (15). 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 post-operative ED (16,17).

2.2 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 several new treatment options for ED, including new pharmacological agents for intracavernous, intraurethral, and, more recently, oral use (18-20). Treatment strategies have also changed following the poor outcomes seen in long-term follow-up of reconstructive vascular surgery (21,22).

An increasing number of men are seeking help for ED due to the great media interest in ED and the availability of effective and safe oral drug therapy. However, there are many physicians evaluating and treating ED without appropriate background knowledge and clinical experience. Thus, some 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. Given this situation, these EAU guidelines for the diagnosis and treatment of ED are a necessity.

2.3 Conclusions on epidemiology and risk factors

Conclusions	LE
Erection is a neurovascular phenomenon under hormonal control in a physiologenic environment.	2b
ED is common worldwide.	3
ED shares several risk factors with cardiovascular disease.	3
Lifestyle modification (intensive exercise and a decrease in body mass index) can improve erectile function.	1b
ED is a symptom, not a disease. Some men may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
Radical prostatectomy is a common cause of ED.	3

ED = erectile dysfunction.

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2.5 Diagnosis

2.5.1 ***Basic work-up***

The first step in evaluating ED is always a detailed medical and psychological history of patients and partners

(1,2). Often it is not possible to include the partner at 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, hormonal, anatomical, drug-induced, or psychogenic (Table 1) (3) and taking a 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, particularly when patients do not find it easy to talk about their problem. It will also make it easier to explain the diagnosis and therapeutic approach to the patient and his partner.

Table 1: Pathophysiology of ED

Vasculogenic
- Cardiovascular disease
- Hypertension
- Diabetes mellitus
- Hyperlipidaemia
- Smoking
- Major surgery (radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
- Multiple sclerosis
- Multiple atrophy
- Parkinson's disease
- Tumours
- Stroke
- Disk disease
- Spinal cord disorders
Peripheral causes
- Diabetes mellitus
- Alcoholism
- Uraemia
- Polyneuropathy
- Surgery (pelvis or retroperitoneum, radical prostatectomy)
Anatomical or structural
- Peyronie's disease
- Penile fracture
- Congenital curvature of the penis
- Micropenis
- Hypospadias, epispadias
Hormonal
- Hypogonadism
- Hyperprolactinemia
- Hyper- and hypo-thyroidism
- Cushing's disease
Drug-induced
- Antihypertensives (diuretics and beta-blockers are the most common causes)
- Antidepressants
- Antipsychotics
- Antiandrogens
- Antihistamines
- Recreational drugs (heroin, cocaine, methadone)
Psychogenic
- Generalised type (e.g. lack of arousability and disorders of sexual intimacy)
- Situational type (e.g. partner-related, performance-related issues or due to distress)

2.5.1.1 Sexual history

The sexual history may include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. A detailed description should be made of the rigidity and duration of both erotic and morning erections and of problems with arousal, ejaculation, and orgasm. Validated questionnaires, such as the International Index for Erectile

Function (IIEF), help to assess all sexual function domains (erectile function, orgasmic function, sexual desire, ejaculation, intercourse, and overall satisfaction), as well as the impact of a specific treatment modality (4).

2.5.1.2 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 Peyronie's disease, prostatic enlargement or cancer, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics, diminished sexual desire, and changes in mood) (2). A rectal examination should be performed in every patient older than 50 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 (*see* Section 2.5.2).

2.5.1.3 Laboratory testing

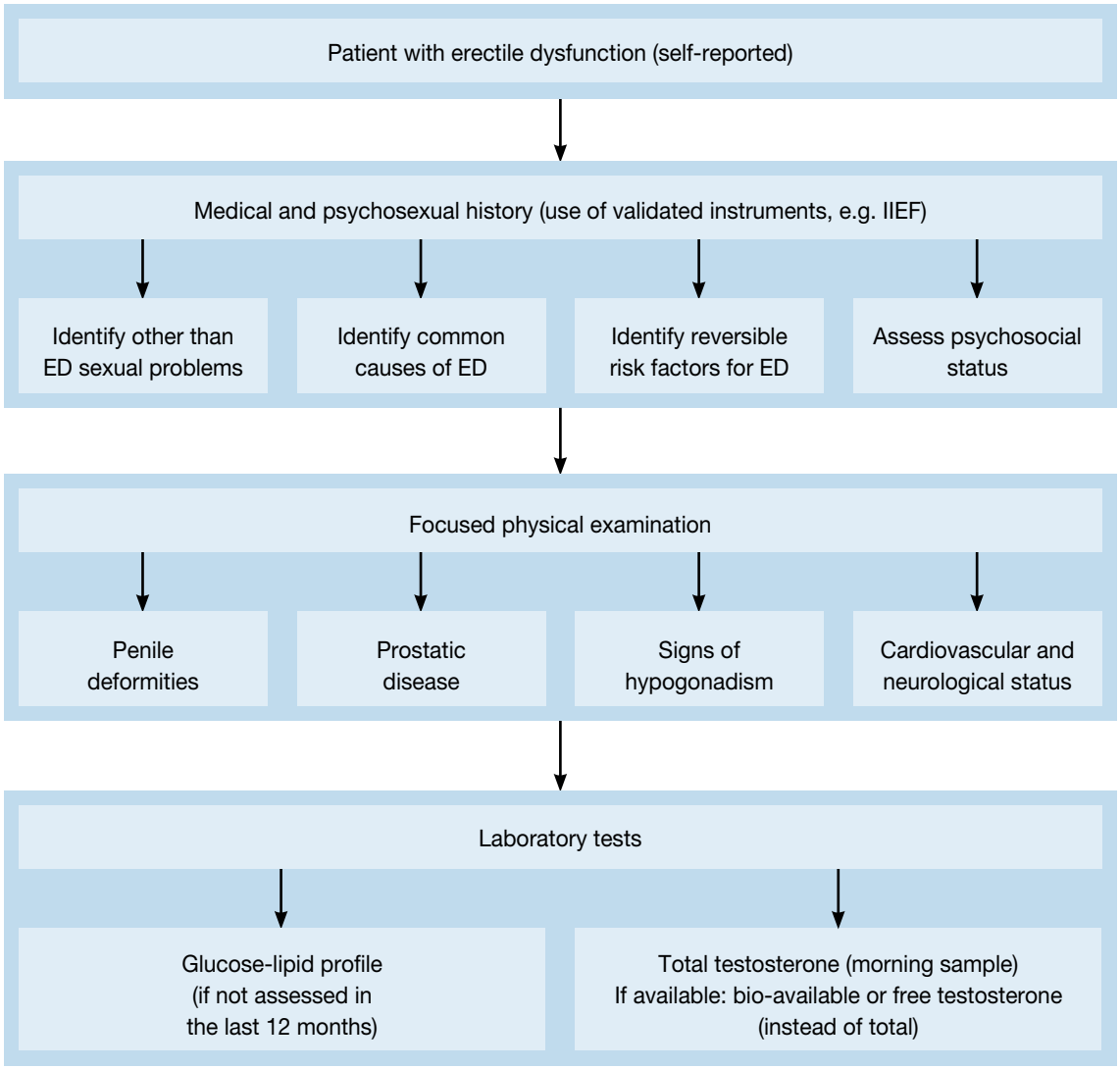
Laboratory testing must be tailored to the patient's complaints and risk factors. All patients must undergo a fasting glucose and lipid profile if not assessed in the previous 12 months. Hormonal tests must include a morning sample of total testosterone. Tests that measure bioavailable or calculated-free testosterone are preferred to total testosterone tests because they are better at establishing hypogonadism.

Additional laboratory tests must be considered only in selected patients, e.g. prostate-specific antigen (PSA) for detection of prostate cancer.

Additional hormonal tests, e.g. prolactin, follicle-stimulating hormone (FSH), luteinising hormone (LH), must be carried out when low testosterone levels are detected. If any abnormality is observed, referral to another specialist may be necessary (5,6).

Figure 1 gives the minimal diagnostic evaluation (basic work-up) in patients with ED.

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

2.5.2 *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. Recent epidemiological studies have emphasised the association between cardiovascular and metabolic risk factors and sexual dysfunction in both men and women (7).

There has been an intensive investigation of the pharmacological properties of phosphodiesterase type 5 (PDE5) inhibitors, including their effects on cardiac smooth muscle activity and overall cardiovascular safety. The EAU Guidelines recommendations given here for using PDE5 inhibitors in PE have been adapted from previously published recommendations from consensus conferences on sexual dysfunction and cardiac risk (8,9).

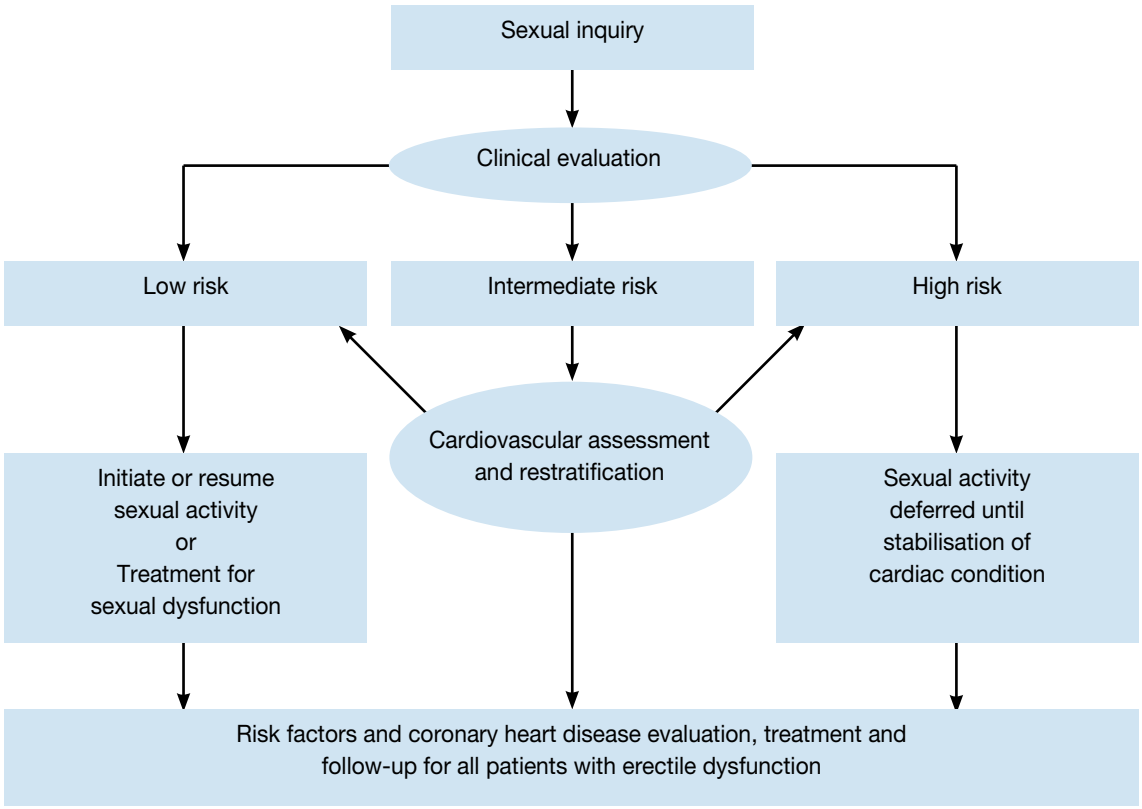
Patients with ED can be stratified into three cardiovascular risk categories (Table 2), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, determined when taking the patient's history.

Table 2: Cardiac risk stratification

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

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



2.5.2.1 *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 six or more '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.

2.5.2.2 *Intermediate-risk 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.

2.5.2.3 *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 moderately to severely 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.

2.5.3 ***Specialised diagnostic tests***

Most patients with ED can be managed within the sexual care setting, but some patients may need specific diagnostic tests (Tables 3 and 4).

2.5.3.1 *Nocturnal penile tumescence and rigidity (NPTR)*

The nocturnal penile tumescence and rigidity 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 or more (10).

2.5.3.2 *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 (11). This response indicates a functional, but not necessarily normal, erection, as the erection may co-exist with arterial insufficiency or veno-occlusive dysfunction (12). A positive test shows that a patient will respond to the intracavernous injection programme. The test is inconclusive as a diagnostic procedure and Duplex ultrasound of the penile arteries should be requested.

2.5.3.3 *Duplex ultrasound of penile arteries*

A peak systolic blood flow higher than 30 cm/s and a resistance index higher than 0.8 are generally considered normal (11). Further vascular investigation is unnecessary when a Duplex examination is normal.

2.5.3.4 *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 (13).

2.5.3.5 *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.

2.5.3.6 *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. Success rates are high (*see* EAU Guidelines on Penile Curvature).

2.5.4 ***Patient education – consultation and referrals***

The consultation with the patient should include a discussion of the expectations and needs of both the patient and his partner. It should also review both the patient's and partner's understanding of ED and results of the

diagnostic tests, and provide a rational selection of treatment options. Patient and partner education are an essential part of ED management (14,15).

Table 3: Indications for specific diagnostic tests

Primary erectile disorder (not caused by organic disease or psychogenic disorder)
Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery
Patients with penile deformities that might require surgical correction, e.g. Peyronie's disease, congenital curvature
Patients with complex psychiatric or psychosexual disorders
Patients with complex endocrine disorders
Specific tests may be indicated at the request of the patient or his partner
Medicolegal reasons, e.g. implantation of penile prosthesis, sexual abuse

Table 4: Specific diagnostic tests

Nocturnal penile tumescence and rigidity (NTPR) using Rigiscan®
Vascular studies
- Intracavernous vasoactive drug injection
- Duplex ultrasound of the cavernous arteries
- Dynamic infusion cavernosometry or cavernosography (DICC)
- Internal pudendal arteriography
Neurological studies, e.g. bulbocavernosus reflex latency, nerve conduction studies
Endocrinological studies
Specialised psychodiagnostic evaluation

*2.5.5 **Guidelines for the diagnosis of ED***

	LE	GR
Clinical use of validated questionnaire related to ED may help to assess all sexual function domains and the effect of a specific treatment modality	3	B
Physical examination is needed in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED	4	B
Routine laboratory tests, including glucid-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

*2.5.6 **References***

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3. TREATMENT OF ERECTILE DYSFUNCTION

3.1 Treatment options

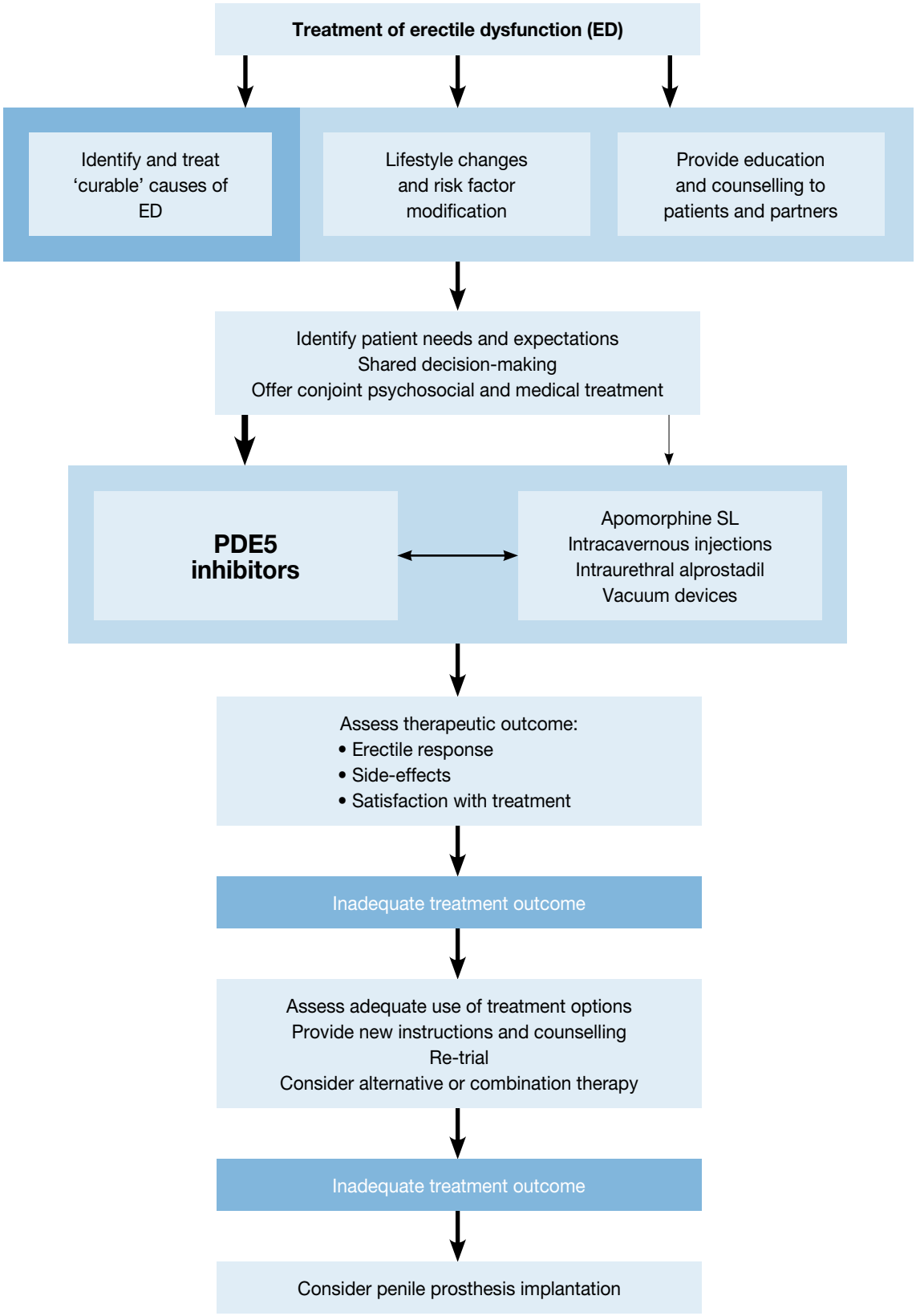
The primary goal in the management strategy of a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. Erectile dysfunction may be associated with modifiable or reversible factors, including lifestyle or drug-related factors. These 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, hyperprolactinaemia), which can be potentially cured with specific treatment.

Most men with ED will be treated with treatment 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 counsel patients properly with ED, physicians must be fully informed of all treatment options.

The assessment of treatment options must consider the effects on patient and partner satisfaction and other QoL factors as well as efficacy and safety. A treatment algorithm for ED is given in Figure 3.

Figure 3: Treatment algorithm for ED



PDE5 inhibitor = phosphodiesterase type 5 inhibitor.

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 ED treatment.

The potential benefits of lifestyle changes may be particularly important in individuals with ED and specific comorbid cardiovascular or metabolic diseases, 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).

Although further studies are needed to make clear the role of lifestyle changes in the 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 PDE5 inhibitors may be enhanced when other comorbidities or risk factors are aggressively managed (6). However, these results have yet to be confirmed in well-controlled, long-term studies. Because 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 (RP)

Use of pro-erectile drugs following RP is very important in achieving erectile function following surgery. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED.

Historically, the treatment options for post-operative ED included intracavernous injections (7), urethral microsuppository (8), vacuum device therapy (9), and penile implants (10). 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 post-operative patients (*see* Sections 3.8 and 3.9).

The management of post-RP ED has been revolutionised by the advent of PDE5 inhibitors, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. At present, PDE5 inhibitors are the first-line choice of oral pharmacotherapy for post-RP ED in patients who have undergone a nerve-sparing (NS) surgical approach. The choice of PDE5 inhibitors as first-line treatment is controversial because the experience (surgical volume) of the surgeon is a key factor in preserving post-operative erectile function in addition to patient age and NS technique (11-13). In fact, PDE5 inhibitors are most effective in patients who have undergone a rigorous NS procedure, which is more commonly performed by the largest-volume surgeons (12,13).

The early use of a high dose of sildenafil after RP is associated with the preservation of smooth muscle within the human corpora cavernosa (14). Daily sildenafil also resulted in a greater return of spontaneous normal erectile function post RP compared to placebo following bilateral nerve-sparing RP (NSRP) in patients who were fully potent before surgery (15,16). The response rate to sildenafil treatment for ED after RP in different trials ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP (15-18).

The effectiveness of both tadalafil and vardenafil as on-demand treatment has also been evaluated in post-RP ED:

- A large multicentre trial in Europe and USA studied tadalafil in patients with ED following a bilateral NS procedure. Erectile function was improved in 71% of patients treated with tadalafil 20 mg versus 24% treated with placebo, while the rate of successful intercourse attempts was 52% with tadalafil 20 mg versus 26% with placebo (19).
- Similarly, vardenafil has been tested in patients treated with ED following either a unilateral or bilateral NS procedure in a multicentre, prospective, placebo-controlled, randomised North American study (20). Following bilateral NSRP, erectile function improved by 71% and 60% with vardenafil, 20 mg and 10 mg, 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 (21).

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 PDE5 inhibitors in post-RP ED (22). Patients who do not respond to oral PDE5 inhibitors after NSRP should be treated with prophylactic intracorporeal alprostadil (23). A penile prosthesis remains a very satisfactory approach for patients who do not respond to either oral or intracavernous pharmacotherapy or to a vacuum device (24).

3.4 'Curable' causes of ED

3.4.1 ***Hormonal causes***

An endocrinologist's advice is essential 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 (25). Testosterone replacement is contraindicated in men with a history of prostate carcinoma or with symptoms of prostatism. Before initiating testosterone replacement, a digital rectal examination (DRE) and serum PSA test should be performed. Patients given androgen therapy should be monitored for clinical response and the development of hepatic or prostatic disease.

There is no contraindication for testosterone therapy in men with coronary artery disease who have been properly diagnosed with hypogonadism and/or ED. However, the haematocrit level should be monitored and a dose adjustment of testosterone may be necessary, especially in congestive heart failure.

Hormonal treatment is not always effective in the management of ED associated with hypogonadism (26).

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 (27). The lesion must be demonstrated by Duplex ultrasound and confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by DICC (9,10). Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results (28).

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 takes time and has had variable results (29).

3.5 First-line therapy

3.5.1 ***Oral pharmacotherapy***

The PDE5 enzyme hydrolyses cyclic guanosine monophosphate (cGMP) in the cavernosum tissue of the penis. Inhibition of PDE5 results in increased arterial blood flow leading to smooth muscle relaxation, vasodilatation, and penile erection (30).

Three potent selective PDE5 inhibitors have been approved by the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) for treatment of ED. They are not initiators of erection and require sexual stimulation to facilitate an erection.

3.5.1.1 Sildenafil

Sildenafil, launched in 1998, was the first PDE5 inhibitor available on the market. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration. Sildenafil is effective from 30 to 60 min after administration. Its efficacy is reduced after a heavy, fatty meal due to prolonged absorption. It is administered in 25, 50 and 100 mg doses. 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 (31). The pharmacokinetic data of sildenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to placebo (32).

After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of men taking 25, 50 and 100 mg of sildenafil, respectively, compared to 25% of men taking placebo (33). Sildenafil statistically improved patient scores in IIEF, sexual encounter profile 2 (SEP2), 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 diabetic patients, 66.6% reported improved erections (GAQ) and 63% successful intercourse attempts compared to 28.6% and 33% of men taking placebo, respectively (34).

3.5.1.2 Tadalafil

Tadalafil, licensed for the treatment of ED as of February 2003, is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h (35) and is not affected by food. It is administered in 10 and 20 mg doses. 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 5. Adverse events (Table 6) are generally mild in nature, self-limited by continuous use. The drop-out rate due to adverse events is similar to placebo (36).

In pre-marketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of men taking 10 mg and 20 mg of tadalafil compared to 35% of men in the control placebo group (36). Tadalafil statistically improved patient scores in IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. These results were confirmed in post-marketing studies (37).

Tadalafil also improved erections in difficult-to-treat subgroups. In diabetic patients, 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 (38).

3.5.1.3 Vardenafil

Vardenafil, commercially available as of March 2003, is effective from 30 min after administration. Its effect is reduced by a heavy, fatty meal (> 57% fat). It is administered in 5, 10 and 20 mg doses. 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, though this does not necessarily mean greater clinical efficacy (39). Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use, with a drop-out rate similar to placebo (40).

After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively, compared with 30% of men taking placebo (41). Vardenafil statistically improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy was confirmed in post-marketing studies (42).

Vardenafil improved erections in difficult-to-treat subgroups. In diabetic patients, 72% reported improved erections (i.e. improved GAQ) compared to 13% of patients taking placebo and the final IIEF-EF score was 19 compared to 12.6 for placebo (43).

3.5.1.4 Choice or preference between the different PDE5 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, 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 PDE5 inhibitors improves or prevents significantly the intracavernous structure alterations due to age, diabetes, or surgical damage (44-50).

In humans, a randomised study (n = 145) showed that daily tadalafil led to a significantly higher IIEF-EF score and higher completion of successful intercourse attempts compared to on-demand tadalafil (51). Two major double-blind, randomised studies, using daily 5 and 10 mg tadalafil for 12 weeks (n = 268) (52) and daily 2.5 and 5 mg tadalafil for 24 weeks (n = 286) (53), showed that daily dosing was well tolerated and significantly improved erectile function. However, these studies lacked an on-demand treatment arm. An open-label extension was carried out of 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 (54). Tadafil, 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 of wash-out, erectile function was not maintained after discontinuation of therapy in most patients (about 75%).

A double-blind, placebo-controlled, multicentre, parallel-group study was conducted in 236 men with mild-to-moderate ED randomised to receive once-daily vardenafil 10 mg plus on-demand placebo for 12 or 24 weeks, or once-daily placebo plus on-demand vardenafil 10 mg for 24 weeks, followed by 4 weeks of wash-out (55). Despite preclinical evidence, the results suggested that once-daily dosing of vardenafil 10 mg 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, cross-over studies with limited patient numbers) showed that chronic, but not on-demand, tadalafil treatment improved endothelial function with sustained effect after its discontinuation (56,57). This was confirmed in another study of chronic sildenafil in men with type 2 diabetes (58).

Recently, in the first double-blind, placebo-controlled study, enrolling 298 men with diabetes and ED for 12 weeks, once-daily tadalafil 2.5 mg and 5 mg was efficacious and well tolerated. This regimen provides an alternative to on-demand treatment for some diabetic men (59).

However, when patients have the choice, it seems that they prefer on-demand rather than continuous therapy (60).

Table 5: Summary of the key pharmacokinetic data for the three PDE5 inhibitors used to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg
Cmax	560 µg/L	378 µg/L	18.7 µg/L
Tmax	0.8-1 h	2 h	0.9 h
T1/2	2.6-3.7 h	17.5 h	3.9 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L
Protein binding	96%	94%	94%
Bioavailability	41%	NA	15%

Cmax: maximal concentration, Tmax: time-to-maximum plasma concentration; T1/2: plasma elimination half-time; AUC: area under curve or serum concentration time curve.

** Fasted state, higher recommended dose. Data adapted from EMEA statements on product characteristics.*

Table 6: Common adverse events of the three PDE5 inhibitors used to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%		< 2%
Back pain		6.5%	
Myalgia		5.7%	

** Adapted from EMEA statements on product characteristics.*

Sildenafil: http://www.emea.europa.eu/humandocs/Humans/EPAR/viagra/viagra.htm
Tadalafil: http://www.emea.europa.eu/humandocs/Humans/EPAR/cialis/cialis.htm
Vardenafil: http://www.emea.europa.eu/humandocs/Humans/EPAR/levitra/levitra.htm

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 PDE5 inhibitors, 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 PDE5 inhibitors had an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina (61,62). In fact, they may 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 totally contraindicated with PDE5 inhibitors

Organic nitrates (e.g. nitroglycerine, isosorbide mononitrate, isosorbide dinitrate) and other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate ('poppers' used for recreation), are absolute contraindications with the use of PDE5 inhibitors. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5 inhibitors depends upon the PDE5 inhibitor and nitrate used.

If a PDE5 inhibitor is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) was used (half-life, 4 h), and for at least 48 h if tadalafil was used (half-life, 17.5 h).

If a patient develops angina while taking a PDE5 inhibitor, other agents may be given instead of nitroglycerine until the appropriate time has passed. If nitroglycerine must be re-introduced following administration of a PDE5 inhibitor, 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 PDE5 inhibitors with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, beta-blockers, diuretics) may result in small additive drops in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5 inhibitor is not made worse by a background of antihypertensive medication, even when the patient is taking several

antihypertensive agents.

3.5.1.6.4 Alpha-blocker interactions
All PDE5 inhibitors show some interaction with alpha-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling currently advises that 50 or 100 mg of sildenafil should not be taken within 4 h following treatment with an alpha-blocker. This restriction does not apply to 25 mg dose of sildenafil.
- In the USA, vardenafil is absolutely contraindicated with alpha-blockers.
- Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension (63).
- Tadalafil is contraindicated in patients taking alpha-blockers, except for tamsulosin, 0.4 mg (64).

These interactions are more pronounced when PDE5 inhibitors are given to healthy volunteers not previously taking alpha-blockers. Further research is needed into the interaction between other PDE5 inhibitors and other alpha-blockers (e.g. alfuzosin, once-daily), or mixed alpha-/beta-blockers (e.g. carvedilol, labetalol).

3.5.1.6.5 Dosage adjustment
Drugs that inhibit the CYP34A pathway will inhibit the metabolic breakdown of PDE5 inhibitors. They include ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (ritonavir, saquinavir). Such agents may increase blood levels of PDE5 inhibitors, so that lower doses of PDE5 inhibitors are necessary.

However, other agents, such as rifampin, phenobarbital, phenytoin, and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5 inhibitors, so that higher doses of PDE5 inhibitors 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 PDE5 inhibitor are either incorrect drug use or inefficacy of the drug. The management of a non-responder depends upon identifying the underlying cause.

3.5.1.7.1 Check that the patient has been using a licensed medication
There is a very large 'black market' in PDE5 inhibitors. 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 a patient fails to use his medication correctly is inadequate counselling from his 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: PDE5 inhibitors depend for their action upon the release of nitric oxide (NO) by the parasympathetic nerves of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work.

Not enough time between taking the medication and intercourse attempt: Oral PDE5 inhibitors take different times to reach maximal plasma concentrations (65-67). 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 (68-70), 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.

Food may affect drug absorption: sildenafil's absorption can be delayed by a meal (65), while varenafil's absorption can be delayed by a fatty meal (71). Tadalafil's absorption is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse (67).

Too much time between taking medication and intercourse attempt: It is also 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 about 6-8 h following ingestion of the medication, though

responses following this time period are well recognised. Tadalafil had a longer half-life of about 17.5 h, so the window of efficacy is much longer at about 36 h.

Insufficient dose: For financial reasons, some physicians may prescribe only the lower doses of a medication. It is important to check that the patient has had an adequate trial of the maximal dose of the drug. Data suggests an adequate trial involves at least six attempts with a particular drug (72).

Benefit of education for a non-responding patient: Data from uncontrolled studies suggests patient education can help salvage an apparent non-responder to a PDE5 inhibitor. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function was effectively restored following re-administration of the relevant PDE5 inhibitor (73-76).

One study (74) went further, and in those patients who still did not respond to the PDE5 inhibitor, 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 a number of changes that may improve the efficacy of the medication, though the evidence supporting these interventions is limited.

Modification of associated risk factors: ED is typically a symptom of an underlying condition, such as diabetes, hypertension, dyslipidaemia, etc. Limited evidence suggests that, in a hypogonadal patient, normalisation of the serum testosterone might improve the patient's response to a PDE5 inhibitor (77). So far, modification of other risk factors, such as diabetic control, hypertension and dyslipidaemia, has not been shown to be effective in improving response to a PDE5 inhibitor.

Change the PDE5 inhibitor: A randomised trial suggested vardenafil might benefit non-responders to sildenafil (78), but the results are considered to overstate the benefits of switching PDE5 inhibitors because of poor study design. However, a randomised, open-label, crossover trial comparing sildenafil and tadalafil indicated that some patients might respond better to one PDE5 inhibitor than to another (79). 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 PDE5 inhibitor might be helpful.

Regular dosing of PDE5 inhibitor: Two non-randomised trials have suggested that daily dosing with a PDE5 inhibitor might salvage some non-responders to intermittent dosing. In one trial (80), some men benefited from regular dosing with either vardenafil or tadalafil, while in the other trial (75) daily dosing with tadalafil salvaged some men who had failed to respond to intermittent dosing with a PDE5 inhibitor.

Currently, there are no randomised trials to support this intervention. Although tadalafil is licensed for daily dosing at a dose of 2.5 mg and 5 mg, neither sildenafil nor vardenafil are licensed for use in this way.

Introduction of an alternative therapeutic modality: If drug treatment fails, then the patient should be offered an alternative therapy, with intracavernosal injection therapy of with a vacuum erection device. Intraurethral therapy is usually ineffective in these patients.

3.5.1.8 Apomorphine sublingual

Apomorphine is a centrally acting dopamine agonist that improves erectile function by enhancing the natural central erectile signals that normally occur during sexual stimulation (81,82). It is administered sublingually on demand in 2 or 3 mg doses. Apomorphine has been approved for ED treatment in several countries but not in the USA.

Efficacy rates (erections sufficient for intercourse) range from 28.5% to 55% (83-85). Due to rapid absorption, 71% of erections are achieved within 20 min. The most common adverse events are nausea (7%), headache (6.8%) and dizziness (4.4%). These events are generally mild in nature and self-limited (85). Severe events, such as syncope, are extremely rare (< 0.2%) (86).

Apomorphine is not contraindicated in patients taking nitrates or antihypertensive drugs (of all classes) and it does not affect vital signs (87,88). There was no marked improvement in sexual desire, but a slight improvement in orgasmic function was noticed.

Comparative studies clearly show that apomorphine is associated with significantly lower efficacy and satisfaction rates than sildenafil (89-91). The most significant strength of apomorphine is its safety profile (92). Even in pre-marketing studies, apomorphine significantly improves erectile function, intercourse, and overall satisfaction domains of the IIEF compared to placebo.

Its use is limited to patients with mild-to-moderate ED or psychogenic causes of sexual dysfunction due to reduced efficacy rates. It may also be a first-line treatment in patients with certain contraindications for the use of PDE5 inhibitors, e.g. nitrates.

3.5.1.9 Other oral agents

Several other drugs have been used in the treatment of ED with various mechanisms of action (93), but today there is no place for these drugs in the treatment of ED.

- Yohimbine is a centrally and peripherally active alpha-2 adrenergic antagonist used as an aphrodisiac for almost a century.
- Delequamine is a more specific and selective alpha-2 adrenergic antagonist than yohimbine.
- Trazodone is a serotonin reuptake inhibitor (antidepressant) associated with prolonged erections and priapism. It is also a non-selective alpha-adrenergic antagonist in the corporal smooth muscle cells.
- L-arginine is a nitric oxide donor and nalmefene/naltrexone is an opioid-receptor antagonist.
- Red Korea ginseng is a formulation with an unknown mechanism of action (though it may possibly act as a nitric oxide donor).
- Limaprost is an alprostadil derivative for oral use.
- An oral formulation of phentolamine (non-selective alpha-adrenergic antagonist) has undergone phase III clinical trials (94).

Randomised trials have shown that yohimbine and trazodone have a similar efficacy to placebo in patients with organic causes of ED (95,96). Oral phentolamine had efficacy rates (erections sufficient for intercourse) of about 50% (94), but possible carcinogenesis in animal models stopped further development. Efficacy data on Red Korea ginseng suggested it might have a role in treatment of ED (97). There are no efficacy data on the other drugs listed above.

3.6 Topical pharmacotherapy

Several vasoactive drugs (2% nitroglycerine, 15-20% papaverine gel, and 2% minoxidil solution or gel) have been used for topical application to the penis. To overcome the poor drug absorption through the thick and dense tunica albuginea, several drug absorption enhancers have been developed for combination with vasoactive drugs (98). The combination (Topiglan™) of alprostadil gel 1% with 5% SEPA® (absorption enhancer) resulted in an erection sufficient for vaginal penetration in 38.9% of patients compared to 6.9% of placebo-treated patients (99). Adverse events include skin and glans erythema, burning sensation, allergic reactions, and side-effects in the partner (hypotension, headache) due to vaginal absorption.

No topical therapy has been approved and currently these agents have no role in treatment of ED.

3.7 Vacuum constriction devices

Vacuum constriction devices (VCD) 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 since 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% (100). Men with a motivated, interested, and understanding partner report the highest satisfaction rates. Long-term use of VCDs decreases to 50-64% after 2 years (101). Most men who discontinue use of VCDs do so within 3 months.

The commonest adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in less than 30% of patients (102). Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 min. Vacuum constriction devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy.

Vacuum constriction devices are generally unacceptable to younger patients. They may be the treatment of choice in well-informed older patients with infrequent sexual intercourses and comorbidities requiring a non-invasive, drug-free management of ED.

3.8 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. Success rate is high (85%) (100). Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago (103).

*3.8.1 **Intracavernous injections***

3.8.1.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) is the first and only drug approved for intracavernous ED treatment (104). It is the more efficacious monotherapy for intracavernous treatment in 5-40 µg doses. 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 more than 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 (105-107).

Complications of intracavernous alprostadil include penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) (108). Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia (109,110). Fibrosis requires temporary discontinuation of the injection programme for several months. 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 (111-113), with most drop outs occurring within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rates (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 (114).

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 (115-117). However, almost one-third of long-term intracavernous injections users who subsequently responded also to sildenafil preferred to continue with an intracavernous injection programme (117,118).

Action to be taken with a prolonged erection

After 4 h of erection, patients are advised to consult their physician to avoid any damage to the intracavernous muscle, which would provoke permanent impotence. A 19-gauge needle is used to aspirate blood and thereby decrease intracavernous pressure. This simple method is usually sufficient to make the penis flaccid. However, if the penis becomes rigid again after this, an intracavernous injection of phenylephrine is required, starting at a dose of 200 µg every 5 min and increasing to 500 µg if necessary. The risk of having a prolonged erection during following subsequent injections cannot be predicted. When this problem occurs, the dose is usually reduced for the next injection.

3.8.1.2 Combination therapy

Combination treatment 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 only 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 (119,120). 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 (121-123). The triple combination regimen of papaverine, phentolamine and alprostadil had the highest efficacy rates, reaching 92%; this combination had similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis was more common (5-10%) when papaverine was used

(depending on total dose). In addition, mild hepatotoxicity has been reported with papaverine (124). Despite high efficacy rates, 5-10% of patients will 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 (125). However, combination therapy was 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.

3.8.1.3 Intraurethral alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved for use in ED (126). A vascular interaction between the urethra and the corpora cavernosa enables drug transfer between these structures (127). Erections sufficient for intercourse were achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 µg) have been used with low consistency rates (127-129). The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy (130).

The most common adverse events are local pain (29-41%) and dizziness (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 (131). Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less invasive, though less efficacious, treatment.

3.9 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. Two types of prosthesis exist: malleable (semi-rigid) and inflatable (two- or three-piece).

Most patients prefer the three-piece inflatable devices due to the more 'natural' erections obtained. However, the two-piece inflatable prosthesis can be a reliable option with fewer mechanical complications and is easier to implant. A semi-rigid prosthesis provides a constantly rigid penis and may be suitable in older patients with infrequent sexual intercourse (132). The inflatable prosthesis is much more expensive. In several countries, patients are reimbursed for the cost of the prosthesis provided the ED has an organic cause and the patient has undergone a complete impotence assessment.

Prosthesis implantation has one of the highest satisfaction rates (70-87%) among treatment options for ED based on appropriate consultation (133-137).

*3.9.1 **Complications***

The two main complications of penile prosthesis implantation are mechanical failures and infection. Several technical modifications of the most commonly used three-piece prosthesis (AMS 700CX/CXM™ and Mentor Alpha I™) resulted in mechanical failure rates of less than 5% at 5-year follow-up (136,137). Careful surgical technique with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduced infections rates to 2-3%. The infection rate may be further reduced to 1% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Mentor Titan™) (138,139). Although diabetes is considered to be one of the main risk factors for infection, this is not supported by current data (132). Infections, as well as erosions, are significantly higher (9%) in patients with spinal cord injuries (9%) (132). Infection requires removal of the prosthesis, antibiotic administration and re-implantation after 6-12 months. However, salvage therapy with removal and re-implantation at the same time, after copious irrigation of the corpora with multi-drug solutions, had an 82% success rate (140).

*3.9.2 **Conclusion***

Penile implants are an attractive solution for patients who do not respond to oral therapy (141).

3.10 Guidelines on the treatment of ED

	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1b	A
Pro-erectile treatments have to be given at the earliest opportunity after radical prostatectomy.	1b	A
When a curable cause of ED is found, the cause must be treated first.	1b	B
PDE5 inhibitors are first-line therapy.	1a	A
Daily administration of PDE5 inhibitors may improve results and restore erectile function.	1b	A

Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5 inhibitors.	3	B
Testosterone replacement restores efficacy in hypogonadic non-responders to PDE5 inhibitors.	1b	B
Apomorphine can be used in mild-to-moderate ED or psychogenic causes or in patients with contraindications for the use of PDE5 inhibitors.	1b	B
A vacuum constriction device can be used in patients with a stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

PDE5 inhibitor = phosphodiesterase type 5 inhibitor; ED = erectile dysfunction.

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4. PREMATURE EJACULATION (PE)

4.1 Introduction

Although PE 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 pre-empting 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 of PE

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 NHSLS 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 (1516).

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 of PE on QoL

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). Sex 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 of PE

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 7: Common factors in different definitions of ED

Time to ejaculation assessed by IELT
Perceived control
Distress
Interpersonal difficulty related to the ejaculatory dysfunction

*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 Guidelines recommendations on the diagnosis of PE

	LE	GR
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.	1a	A
Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials.	2a	B
Patient-reported outcomes (PROs) have the potential to identify men with PE. Further research is needed before PROs can be recommended for clinical use.	3	C
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.	3	C
Routine laboratory or neurophysiological tests are not recommended. They should only be directed by specific findings from history or physical examination.	3	C

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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 Guideline recommendation on the psychological/behavioural treatment of PE

	LE	GR
Psychological/behavioural therapies may be attempted but no clinical data exists supporting prolonged effect.	3	C

4.8.2 ***Topical anaesthetic agents***

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE (8). Several trials (9,10) support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis so delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

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 Guideline recommendations on the topical therapy for PE

	LE	**GR**
Lidocaine-prilocaine cream.	1B	A
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 serontonin 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 serontonin 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, diarrhoea and perspiration; they are usually mild and gradually improve after 2 to 3 weeks (24). Decreased libido, anorgasmia, anejaculation and ED have been also 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%), diarrhoea (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 *Guideline recommendation on the treatment of PE*

	LE	GR
Selective serotonin receptor inhibitors (SSRIs).	1A	A

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 Guidelines recommendation on the use of PDE5 inhibitors for the treatment of PE

	LE	GR
In patients presenting with PE, a trial of PDE5 inhibitors may be attempted.	2B	C

*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.

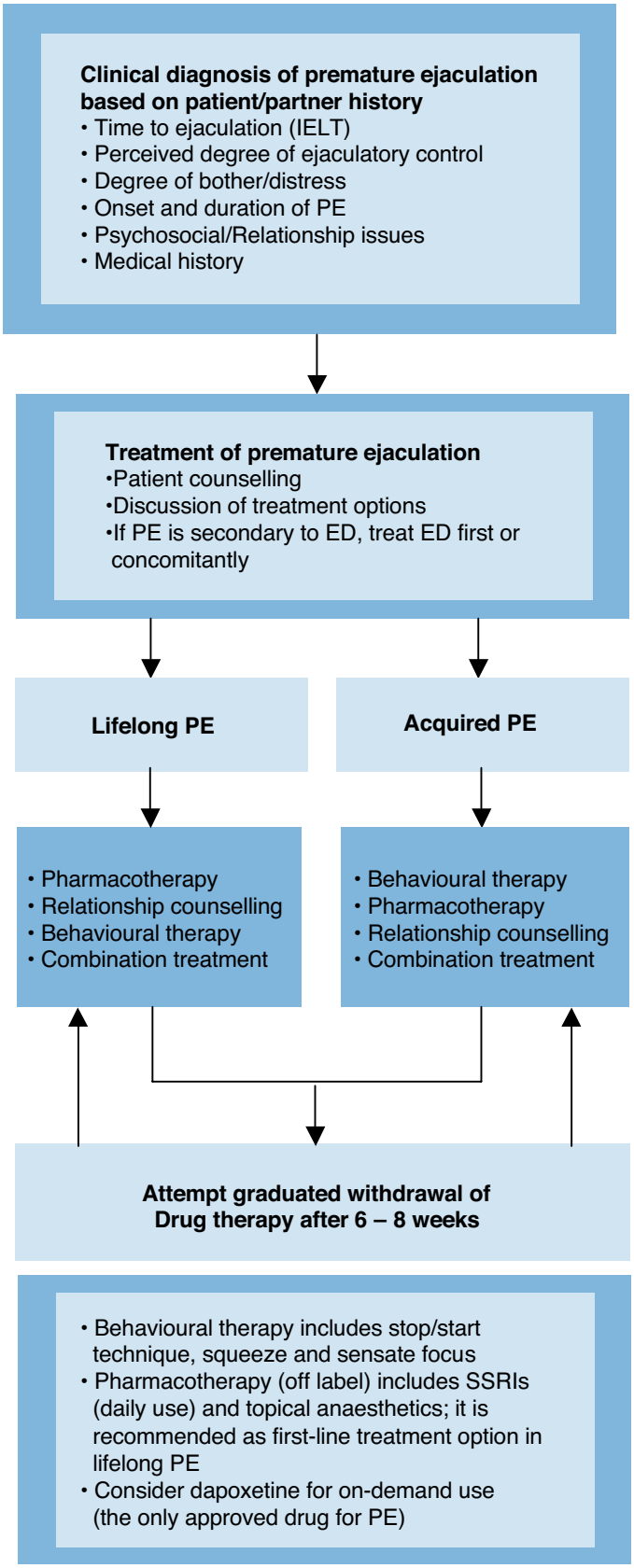
Research suggests that the alpha-1 adrenergic antagonists, terazosin and alfuzosin (45,46), and tramadol (47,48) may have some efficacy in PE. However, further research is needed to investigate their role fully. Currently they are not recommended in clinical practice (49).

*4.8.6 **Guideline recommendations on the treatment of PE***

	LE	GR
ED, other sexual dysfunction or genitourinary infection (e.g. prostatitis) should be treated first.	2a	B
Behavioural techniques have demonstrated benefit in treating PE. However, they are time intensive, require the support of a partner and can be difficult to do.	3	C
Pharmacotherapy is the basis of treatment in lifelong PE.	1a	A
Daily SSRIs are first-line, off-label, pharmacological treatment for PE. The pharmacokinetic profile of SSRIs is not amenable to pm dosing.	1a	A
Dapoxetine, a short-acting SSRI, has already been approved for the on-demand treatment of PE in seven European Countries.	1a	A
Topical anaesthetic agents provide viable alternatives to SSRIs (off-label).	1b	A
Recurrence is likely after treatment cessation.	1b	A
Behavioural therapy may augment pharmacotherapy to enhance relapse prevention.	3	C

ED = erectile dysfunction; PE = premature ejaculation; SSRI = selective serotonin reuptake inhibitor; pm = on-demand adminstration.

Figure 4: Management of PE*



* Adapted from Lue et al. 2004 (49).
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

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5. CONCLUSION

Modern treatment of ED has been revolutionised by the worldwide availability of three PDE5 inhibitors 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 PDE5 inhibitors. 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 fulfil 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
IIEF	International Index for Erectile Function
IIEF-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
PDE5	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 group have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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 Curvature

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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 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, 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 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*

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

**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*

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

**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/).

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. 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 very limited to draw any conclusions (15).

Conclusions on treatment	LE
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.	3
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.	3

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 etiology 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 etiology 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	**LE**
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.	2
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.	3
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).	2
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.	2

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 below* 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).

Sonographic measurement of the plaque's size is inaccurate and operator dependent and it is not recommended in everyday clinical practice (42). Duplex ultrasonography 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).

Guidelines recommendations on the evaluation of Peyronie's disease	**LE**	**GR**
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.	2	B
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).	2	B
Sonographic measurement of the plaque's size is inaccurate and operator dependent. It is not recommended in everyday clinical practice.	3	C
Duplex ultrasonography is required to ascertain vascular parameters associated to erectile dysfunction.	2	B

4.3 Non-operative treatment

Conservative treatment of Peyronie's disease is primarily focused on patients in the early stage of 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, intralesional 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 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

Oral treatments
Vitamin E
Potassium para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Intralesional treatments
Steroids
Verapamil
Clostridial collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shock wave lithotripsy (SWL)
Traction devices
Vacuum devices

*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 paraaminobenzoate (12 g/day for 12 months) improved penile pain significantly, but not penile curvature and penile plaque size (50). In another prospective, randomised, double-blind, placebo-controlled in 103 patients with Peyronie's disease, potassium para-aminobenzoate (4 x 3g/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 size 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 showing that pentoxifylline (400 mg three times daily for 6 months) improved penile curvature and the ultrasonographic appearance 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 (PDE5i)

The rationale for the use of 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 (2.5mg 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 PDEi 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 and 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%) and minor including 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 and 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 60º. 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 (5×10^6 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 (SWL)

The mechanism of action involved in 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 outcome and the remaining had their curvature corrected surgically.

Guidelines recommendations on non-operative treatment for Peyronie's disease	**LE**	**GR**
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.	3	C
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.	1b	B
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b	C
Intralesional treatment with clostridial collagenase showed significant decreases in the deviation angle, plaque width and plaque length.	2b	C
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b	B
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b	B
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b	B
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.	1b	B
Penile traction devices and vacuum devices may reduce penile deformity and increase penile length.	3	C
Recommendations AGAINST		
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.	1b	B
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.	2b	B
Other oral treatments (acetyl esters of carnitine, pentoxifylline) are not recommended.	3	C

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).

During informed consent, the potential aims and risks of surgery should be discussed. Specific issues that should be mentioned during consent 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 suggests 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 on the 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 10º 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 post-operative 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 post-operative 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 draft used, followed by dorsal penile vein (104). In the latter case, a secondary incision for graft harvesting is avoided. Post-operative 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 preferably incision 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 post-operative 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

Autologous grafts
Dermis
Vein grafts
Tunica albuginea
Tunica vaginalis
Temporalis fascia
Buccal mucosa
Allografts
Cadaveric pericardium
Cadaveric fascia lata
Cadaveric dura matter
Cadaveric dermis
Xenografts
Porcine small interstinal submucosa
Bovine pericardium
Porcine dermis
Synthetic grafts
Gore-Tex
Dacron

*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 30°, 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).

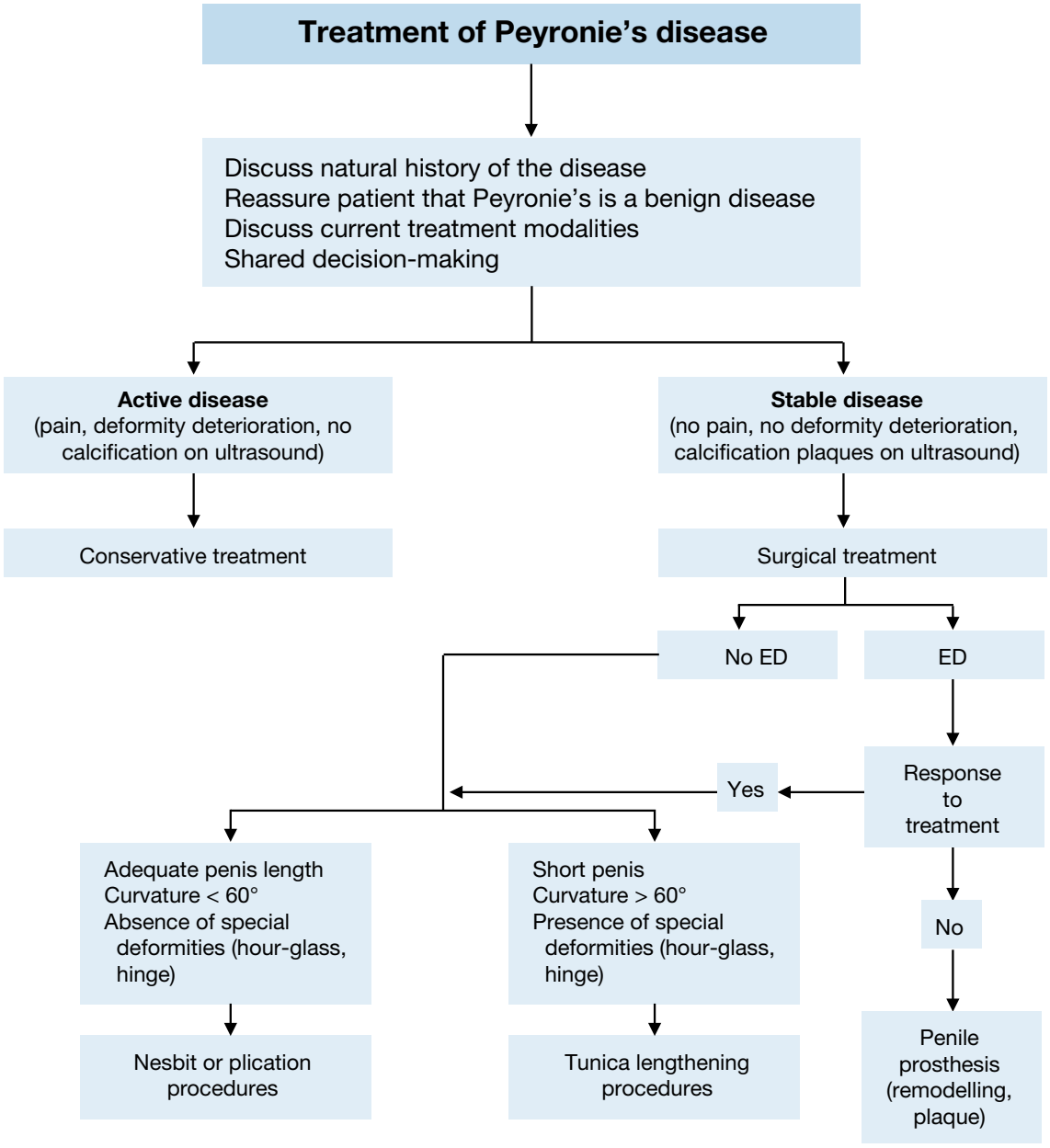
Table 3: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) (108,110-136,138,139)

	Tunical shortening procedures		**Tunical lengthening procedures**
	Nesbit	**Plication**	**Grafts**
Penile shortening	4.7-30.8%	41-90%	0-40%
Penile straightening	79-100%	58-100%	74-100%
Persistent or recurrent curvature	4-26.9%	7.7-10.6%	0-16.7%
Post-operative erectile dysfunction	0-13%	0-22.9%	0-15%
Penile hypoesthesia	2-21%	0-21.4%	0-16.7%
Technical modifications	1	At least 3	Many types of grafts and techniques used

*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 60°, 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 60° 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.

Figure 1: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction.

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).

Guidelines recommendations on surgical treatment for penile curvature	LE	GR
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.	3	C
Penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations must be assessed prior to surgery.	3	C
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 < 60º and absence of special deformities (hour-glass, hinge).	2b	B
Grafting techniques are the preferred treatment option for patients with Peyronie's disease with no adequate penile length, curvature > 60º and presence of special deformities (hour-glass, hinge).	2b	B
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.	2b	B

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6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

EAU	European Association of Urology
EMDA	transdermal electromotive drug administration or electromotive drug administration
SWL	shock wave lithotripsy
GR	grade of recommendation
IIEF	international index of erectile function
LE	level of evidence
MeSH	Medical Subject Headings
PDE5i	Phosphodiesterase type 5 inhibitors

Conflict of interest

All members of the Penile Curvature guidelines writing panel have provided disclosure statements of all relationships they have that may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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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European
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of Urology

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1. METHODOLOGY

1.1 Introduction

The European Association of Urology (EAU) Guideline Panel on Male Infertility has prepared these guidelines to assist urologists and healthcare professionals from related specialities 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 and endocrinologists 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 Medical Subject Headings (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 2010 (previous update) and November 2011 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 (LE)*

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

**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)*

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

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

1.4 Publication history

The EAU Male infertility Guidelines were first published in 2001, followed by full text updates in 2004, 2007 and 2010. For this 2012 publication all sections have been revised and limited changes were implemented. Starting in 2012, the expert panel instigate start a new updating cycle. A quick reference guide presenting the main findings of the Male Infertility Guidelines is also available as well as a number of scientific publications in the EAU journal European Urology. 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.

1.5 Definition

'Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year' World Health Organization (WHO) (5).

1.6 Epidemiology and aetiology

About 15% of couples do not achieve pregnancy within 1 year and seek medical treatment for infertility. Eventually, 5% remain unwillingly childless. 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 (5). Male fertility can be reduced as a result of (5):

- congenital or acquired urogenital abnormalities;
- 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 fertility problems 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-astheno-teratozoospermia (OAT) syndrome. Table 3 summarises the main male infertility-associated factors. Idiopathic male infertility may be explained by several factors, including endocrine disruption as a result of environmental pollution, reactive oxygen species, or genetic abnormalities.

Table 3: Male infertility associated factors and percentage of distribution in10,469 patients

Male infertility associated factor	Distribution %
Idiopathic male infertility	31
Maldescended testes	7.8
Urogenital infection	8.0
Disturbances of semen deposition and sexual factors	5.9
General and systemic disease	3.1
Varicocele	15.6
(Endocrine) Hypogonadism	8.9
Immunological factors	4.5
Obstructions	1.7
Other abnormalities	5.5

1.7 Prognostic factors

Prognostic factors for male infertility are:

- duration of infertility;
- primary or secondary infertility;
- results of semen analysis;
- age and fertility status of female partner.

The cumulative pregnancy rate in infertile couples with 2 years of follow-up and oligozoospermia as the primary cause of infertility is 27% (7). Female age is the most important single variable influencing outcome in assisted reproduction (8). 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.

1.8 Recommendations on epidemiology and aetiology

Recommendations	GR
To categorise infertility, both partners should be investigated simultaneously.	C
In the diagnosis and management of male subfertility, the fertility status of the female partner must also be considered, as this might determine the final outcome (8).	B
The urologist/andrologist should examine any male with fertility problems for urogenital abnormalities. This applies to all males diagnosed with reduced sperm quality. A diagnosis is mandatory to start appropriate therapy (drugs, surgery, assisted reproduction) (5).	C

1.9 References

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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). As important treatment decisions are based on the results of semen analysis, 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% confidence intervals) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6 per ejaculate)	39 (33-46)
Sperm concentration (10^6 per mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6 per mL)	< 1.0
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (µmol/ejaculate)	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≥ 20

PR = progressive; NP = non-progressive; MAR = Mixed antiglobulin reaction.

*2.1.1 **Frequency of semen analysis***

If the results of semen analysis are normal according to WHO criteria, one test should be 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: < 15 million spermatozoa/mL
- asthenozoospermia: < 32% motile spermatozoa
- teratozoospermia: < 4% normal forms.

Quite often, all three anomalies occur simultaneously which is defined as OligoAsthenoTeratozoospermia (OAT). As in azoospermia, in extreme cases of oligozoospermia (< 1 million spermatozoa/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

2.2 Recommendations for investigations in male infertility

Recommendations	GR
According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests.	C
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 (2).	C
Semen analysis must follow the guidelines of the *WHO Laboratory Manual for the Examination and Processing* (5th edn) (1).	B

2.3 References

1. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th edn. WHO, 2010. http://www.who.int/reproductivehealth/publications/infertility/9789241547789/en/index.html
2. World Health Organization. WHO Manual for the Standardised Investigation and Diagnosis of the Infertile Couple. Cambridge: Cambridge University Press, 2000.

3. TESTICULAR DEFICIENCY (SPERMATOGENIC FAILURE)

3.1 Definition

Testicular deficiency as a consequence of spermatogenic failure is caused by conditions other than hypothalamic-pituitary disease and obstructions 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

Factors	Causes
Congenital	Anorchia
	Testicular dysgenesis/cryptorchidism
	Genetic abnormalities (karyotype, Y chromosome deletions)
	Germ cell aplasia, resulting in Sertoli cell only syndrome
	Spermatogenic arrest (maturation arrest)
Acquired	Trauma
	Testicular torsion
	Post-inflammatory forms, particularly mumps orchitis
	Exogenous factors (medications, cytotoxic drugs, irradiation, heat)
	Systemic diseases (liver cirrhosis, renal failure)
	Testicular tumour
	Varicocele
	Surgery that may compromise vascularisation of the testes and subsequently testicular atrophy
Idiopathic	Unknown aetiology
	Unknown pathogenesis

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 toxin(s);
- gonadotoxic medication;
- exposure to radiation or chemical(s);
- 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 minutes and a thorough microscopic examination by phase contrast optics at x200 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 spermatocyte or spermatid blockage is complete. FSH values are within normal range.

However, for an individual patient, FSH levels do not accurately predict the spermatogenesis status (3-5). Preliminary data indicate a stronger correlation between low inhibin B level and spermatogenic damage (6).

3.4.3 ***Testicular biopsy***

Testicular biopsy can be part of an 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 (7-9). Spermatogenesis may be focal, which means that in about 50-60% of men with NOA, spermatozoa can be found and used for ICSI. Most authors therefore recommend taking several testicular samples (10,11). 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 (12,13). However, no clear relationship has been found between FSH, inhibin B or testicular volume and successful sperm harvesting. When there are complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is virtually zero.

Microsurgical testicular sperm extraction may increase retrieval rates, even though comparative studies are not yet available (14-16). After opening the testis, tubules exhibiting larger diameter are excised using micro-scissors or forceps. Then, tubules are minced using mechanical or enzymatic digestion to facilitate sperm search (17). Positive retrievals are reported even in conditions, such as Sertoli cell only syndrome type II (14). Percutaneous Epididymal Sperm Aspiration (PESA) results in lower retrieval rates and does not allow histological examination to detect for instance carcinoma in situ (CIS) and testicular malignancies (18,19). PESA may also result in more tubular and vascular damage than TESE (20).

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) (21-24):

- Birth rates are lower in NOA versus OA (19% vs 28%) (25).
- Fertilisation and implantation rates are significantly lower (26).
- Miscarriage rates are higher in NOA versus OA (11.5% vs 2.5%) (27).

In OA, there were no significant differences in ICSI results between testicular and epididymal sperm (24). Also,

no significant differences have been reported in ICSI results between the use of fresh and frozen-thawed sperm (22,26-28).

3.5 Conclusions and recommendations for testicular deficiency

Conclusions
Impaired spermatogenesis is often associated with elevated FSH concentration.
Testicular biopsy is the best procedure to define the histological diagnosis and the possibility of finding sperm. Spermatozoa should be cryopreserved for use in ICSI.
Spermatozoa are found in about 60% of patients with non-obstructive azoospermia (NOA).
Men who are candidates for sperm retrieval must receive appropriate genetic advice.
For patients with NOA, who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.
Pregnancies and live births are achieved in 30-50% of couples with NOA, when spermatozoa has been found in the testicular biopsy.

Recommendations	GR
Men with non-obstructive azoospermia (NOA) can be offered a testicular sperm extraction with cryopreservation of the spermatozoa to be used for intracytoplasmic sperm injection (28).	B
To increase the chances of positive sperm retrievals in men with NOA, testicular sperm extraction (single, multiple or microsurgical) should be used rather than PESA.	B

3.6 References

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4. GENETIC DISORDERS IN INFERTILITY

4.1 Introduction

All urologists working in andrology must have an understanding of genetic abnormalities in infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with very low sperm counts can be given a reasonable chance of paternity, using in vitro fertilisation (IVF), ICSI and sperm harvesting from the epididymis or the testis in case of azoospermia. However, the sperm of infertile men show an increase in aneuploidy, other genetic abnormalities and DNA damage and carry the risk of passing genetic abnormalities to the next generation. Although there are prospects for screening of sperm (1,2), current routine clinical practice is based on screening peripheral blood samples.

4.2 Chromosomal abnormalities

Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations) (3,4). 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%. For 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 (4). The frequency of chromosomal abnormalities increases as the testicular deficiency becomes more severe. Patients with < 5 million spermatozoa/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population (5). At highest risk are secretory azoospermic men.

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is indicated in azoospermic men and in oligozoospermic men with < 5 million spermatozoa/mL (5). If there is a family history of recurrent abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

*4.2.1 **Sperm chromosomal abnormalities***

Sperm can be examined for chromosomal normality using multicolour fluorescent *in situ* hybridisation (FISH). Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis (3,6-10) and is also seen in men with translocations (11).

FISH analysis of spermatozoa is a research investigation. It should be used to assess spermatozoa from men with defined andrological conditions (6). Techniques are needed to separate populations of genetically abnormal sperm from normal sperm or to safely screen individual spermatozoa before IVF and ICSI.

*4.2.2 **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 (3,12). Adult men with Klinefelter's syndrome have small firm testicles devoid of germ cells. The phenotype varies from a normally virilised man to a man 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 (13). 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 sperm should be considered (14). Based on sperm FISH studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidies (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI (15).

The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism (16-18) and in 1.36-25% of men with somatic karyotype 47,XXY (19-22). In azoospermic patients, TESE or (MicroTESE) 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 (PDG) and the conception of one 47,XXY fetus has been reported (12). However, a study of ICSI combined with PDG in 113 embryos reported a significant fall in the rate of normal embryos for couples with Klinefelter's syndrome in 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, pre-implantation diagnosis or amniocentesis and karyotype analysis should be strongly advised.

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. All men

with Klinefelter's syndrome who undergo testicular biopsy procedures for sperm retrieval need long-term endocrine follow-up.

*4.2.3 **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 fetus. As with Klinefelter's syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring.

When IVF/ICSI is carried out for men with translocations, preimplantation genetic diagnosis or amniocentesis and karyotype analysis should be used. Embryos with known unbalanced translocation should probably not be implanted.

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. The predominant form is an X-linked recessive disorder caused by a mutation in the KALIG-1 gene on Xp22.3 (23). A number of newly identified autosomal gene mutations can also cause Kallmann syndrome (24). 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 renal abnormalities.

Since spermatogenesis can be relatively easily induced by hormonal treatment (25), genetic screening prior to therapy is strongly adviced. Treatment with gonadotrophins allows natural conception in most cases, even in 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 i.e. 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 (26).The phenotypic features of complete androgen insensitivity syndrome (CAIS) 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 later phenotype is also termed Reifenstein syndrome. In the above mentioned severe forms of androgen resistances there is no risk of transmission since affected men cannot generate their own biological children using the current technologies. Patients with mild AIS 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, only a few mutations have been reported in infertile men (26-30).

*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 especially pre-meiotic genes are over-represented on the X chromosome compared with autosomal chromosomes (31,32). Nevertheless, up to now only two genes, USP26 and TAF7L, have been screened in relatively small study populations and neither of them appear relevant for male infertility (33,34).

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 by Tiepolo and Zuffardi in 1976 (35). The first cases of Y microdeletions and male infertility were reported in 1992 (36), and many case series have subsequently been published. Microdeletions have been found in three non-overlapping regions, AZFa+b+c, of the Y chromosome (37). Several years after the discovery of the three AZF regions and with knowledge of the precise structure of the Y chromosome in Yq11, it was realised that the AZFb and AZFc regions overlap and that there was no AZFd region (38). 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 (39). In each AFZ region, there are a number of candidate genes, but their function in spermatogenesis remains largely unknown (40).

Since deletions occur in block (i.e. removing more than one gene), it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and thus it is unclear if they are all participating in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region. These studies suggested that the USP9Y gene is not essential for spermatogenesis and is most likely to be a 'fine tuner' of sperm production (41).

A new type of Yq deletions, known as 'gr/gr deletion' has been described in the AZFc region (42). This deletion removes half of the AZFc region gene content and affects the dosage of multicopy genes mapping inside this region (e.g. DAZ, CDY1, BPY2).

*4.4.2 **Clinical implications of Y microdeletions***

The clinical significance of Yq deletions have been debated for a long time because of the large variability found in deletion frequencies and reports of Yq deletions in 'fertile' men. More than 10 years of clinical research has found the following about Y deletions:

- They are not found in normospermic men, proving there is clearly a 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 of spermatozoa/mL (approximately 0.7%).
- AZFc deletions are most common (approximately 65-70%), followed by deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are extremely 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 arrest. Complete removal of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Classical AZF deletions do not confer a risk for cryptorchidism or testicular cancer (39).

The specificity and genotype/phenotype correlation reported above means that Y deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval (39). In the case of gr/gr deletion, there is no such strict genotype/phenotype correlation. This type of partial AZFc deletion can also be found in normozoospermic men, although at a significantly lower frequency (0.5-1%) than in men with abnormal spermatogenesis (3-5%). In the largest Caucasian study population (> 1000 men), gr/gr deletion carriers were 7-fold more likely to develop oligozoospermia (44). The phenotypic expression may vary in different ethnic groups, depending on the Y chromosome background (45,46). An overall risk of 2.4-fold for reduced sperm production in gr/gr deletion carriers has recently been reported by a meta-analysis that included only studies free from methodological and selection bias (47). There has also been a report of gr/gr deletion as a potential risk factor for testicular germ cell tumours (48). However, this data needs further confirmation in an ethnically and geographically matched case-control study setting.

After conception, any Y deletions are transmitted automatically to a male offspring, and genetic counselling is therefore mandatory. In most cases, father and son have the same microdeletion (49-52), but occasionally the son has a larger microdeletion (53). It has been proposed that partial AZFc deletions (gr/gr and b2/b3) may predispose to complete AZFc deletion in the next generation (54). There is a substantial variation in the son's phenotype and the extent of spermatogenic failure (still in the range of azoo/oligozoospermia) cannot be predicted entirely, 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 chromosome (55,56), 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%) (57). There is data to support the association of Yq microdeletions with an overall Y chromosomal instability, which leads to the formation of 45,X0 cell lines (58,59). Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal (39,60). This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortions 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 cryoconservation of spermatozoa at a young age can be considered. However, there has only been a single report (48) of an enhanced risk for testicular germ cell

tumours in carriers of gr/gr deletion. Thus, it is only necessary to consider introducing preventive measures (e.g. testis ultrasound) in the sons of gr/gr deletion carriers if confirmatory studies are published.

4.4.2.1 Testing for Y microdeletions

Indications for AZF deletions screening are based on sperm count and include azoospermia and severe oligozoospermia (< 5 million spermatozoa/mL). Thanks to the European Academy of Andrology (EAA) guidelines (60) 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 (60). The primers consist of two markers for each region and control markers from the Yp and X chromosome. 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 Y chromosome: 'gr/gr' deletion

A new type of Yq deletions, known as the gr/gr deletion, has been described in the AZFc region (42). This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. There is an almost 8-fold higher risk of developing oligozoospermia (OR = 7.9, 95% CI: 1.8-33.8; $p < 0.001$) in gr/gr deletion carriers in the largest Caucasian study population published to date (43). The frequency of gr/gr deletion in oligozoospermic patients is about 4%. According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production (61,62).

However, 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). The routine screening for gr/gr deletion is a still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations.

4.4.2.3 Conclusions

Testing for microdeletions is not necessary in men with obstructive azoospermia when ICSI is used because spermatogenesis should be normal.
Men with severely damaged spermatogenesis (with < 5 million spermatozoa/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*).
If complete AZFa or AZFb microdeletions are detected, microtesticular sperm extraction is not worth doing because it is extremely unlikely that any sperm will be found.
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 TCGTs is needed.
If a man with microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.
A son who inherits a microdeletion will have abnormal spermatogenesis because complete AZF deletions are not reported in normozoospermic men.

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 6: Less common inherited disorders associated with infertility and other alterations to phenotype

Disorder	Phenotype	Genetic basis
Prader-Willi syndrome	Obesity, mental retardation	Deletion of 15q12 on paternally inherited chromosome
Bardet-Biedle syndrome	Obesity, mental retardation, retinitis pigmentosa, polydactyly	Autosomal recessive 16q21
Cerebellar ataxia and hyogonadotrophic hypogonadism	Eunuchoidism, disturbances of gait and speech	Autosomal recessive
Noonan's syndrome	Short stature, webbed neck, cardiac and pulmonary abnormalities, cryptorchidism	Autosomal dominant
Myotonic dystrophy	Muscle wasting, cataract, testicular atrophy	Autosomal dominant 19q13.3
Dominant polycystic kidney disease	Renal cysts, obstruction from epididymal cysts	Autosomal dominant 16p13.3 and 4q
5-alpha reductase deficiency	Perineal or scrotal hypospadias, vaginal pouch, immature female phenotype	Autosomal recessive

4.5 Cystic fibrosis mutations and male infertility

Cystic fibrosis 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. This gene is located on the short arm of chromosome 7. 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 approximately 2% of men with OA attending a clinic in Edinburgh (63). 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 of < 1.5 mL and pH less than 7.0.

Approximately 1,500 mutations are listed on the CFTR database (http://www.genet.sickkids.on.ca/cftr/). Many series of men with CBAVD tested for varying numbers of mutations have been published. In general, the more mutations tested for, the higher the percentage of men found to have them. In a review of published series of 449 men with CBAVD, the Delta F508 mutation was detected in 244 men, the R117H mutation in 54 men and the W1282X mutation in 37; 63 other mutations were found in 1 to 9 men, but not all mutations were tested for in all case series (64).

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, as many have a very low prevalence in a particular population. Testing is usually restricted to the most common mutations in a particular community.

Mutations may be found in both copies of the CFTR gene; however, in most men with CBAVD, mutation is found in only one copy. In some of these supposedly heterozygous cases, there may be an unknown second mutation, but there is also another mechanism. In two-thirds of men with CBAVD, a DNA variant (the fifth allele) can be detected in a non-coding region of CFTR (65). Consequently, since the 5T-tract variant is now considered a mild CFTR mutation rather than a polymorphism, it should be analysed in each CAVD patient.

Men with CBAVD often have mild clinical stigmata of CF (e.g. history of chest infections). Children born after ICSI, where the father has CBAVD and is either hetero- or homozygous, must be followed up.

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, the couple must consider very carefully whether to proceed with ICSI using the husband's sperm, as the risk of a having a baby with CF will be 25% if the man is heterozygous and 50% if the man is homozygous. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is about 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 (66) and probably has a different genetic causation. 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. Nevertheless, men with unilateral absence of the vas deferens and CF mutations may have the same underlying genetic diseases as men with true CBAVD. Men with bilateral absence of vas deferens and renal abnormalities do not have CFTR gene abnormalities (67).

Men who have unilateral absence of the vas and normal kidneys or bilateral absence or bilateral abnormality, should be tested for CF mutations. If the results are negative and renal anatomy has not been defined, an abdominal ultrasound should be undertaken. 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.

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, 68, 69, and references therein). The introduction of new analytical approaches is likely to provide major advancement in this field (70,71).

ICSI 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 fetal 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 fertilised. However, fetal abnormality statistics from ICSI centres do not indicate any increase in congenital malformations compared with the general population.

On the other hand, ICSI babies have a higher risk of *de novo* sex chromosomal aberrations (about a 3-fold increase compared with natural conceptions) and paternally inherited structural abnormalities (72-74).

Indications for ICSI are constantly being extended to include fertilisation with immature sperm forms, and it is therefore particularly important to continue to monitor fetal abnormality rates, using detailed subgroup analysis according to the father's clinical and molecular diagnosis.

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, to a lesser extent, conception after IVF/ICSI, and with an increase in early pregnancy loss (75,76). DNA damage may improve after varicocele ligation (77,78).

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. CF mutations), there is up to a 50% chance of the child developing a clinical condition and dying early after a number of years of morbidity. Many clinicians and infertility clinic personnel may consider it is 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

Conclusions
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.
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.

Recommendations	GR
Standard karyotype analysis should be offered to all men with damaged spermatogenesis (< 10 million spermatozoa/mL) who are seeking fertility treatment by in vitro fertilisation/intracytoplasmic sperm injection (ICSI) (2).	B
Men with Klinefelter's syndrome might require androgen replacement therapy as they get older.	B
All men with Klinefelter's syndrome who undergo testicular biopsy procedures for sperm retrieval need long-term endocrine follow-up.	B
For men with severely damaged spermatogenesis (< 5 million spermatozoa/mL), testing for Yq microdeletions is strongly advised (39,60).	B
When a man has structural abnormalities of the vas deferens (bilateral absence of vas deferens, unilateral absence of the vas), it is important to test him and his partner for CF gene mutations (64).	A
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 (1).	A

4.11 References

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5. OBSTRUCTIVE AZOOSPERMIA

5.1 Definition

Obstructive azoospermia (OA) is the inability to detect both 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.

Table 7: Classification of OA, on the basis of ductal obstruction due to congenital and acquired causes

Conditions	Congenital	Acquired
Epididymal obstruction	Idiopathic epididymal obstruction	Post-infective (epididymitis) Post-surgical (epididymal cysts)
Vas deferens obstruction	Congenital absence of vas deferens	Post-vasectomy Post-surgical (hernia, scrotal surgery)
Ejaculatory duct obstruction	Prostatic cysts (Müllerian cysts)	Post-surgical (bladder neck surgery) Post-infective

5.2 Classification

*5.2.1 **Intratesticular obstruction***

Intratesticular obstruction occurs in 15% of OA (1). Congenital forms (dysjunction between rete testis and efferent ductules) are less common than acquired forms, i.e. post-inflammatory or post-traumatic obstructions. Acquired forms are often associated with an obstruction of epididymis and vas deferens.

*5.2.2 **Epididymal obstruction***

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men with a serum FSH 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 above* Chapter 4: Genetic disorders in infertility). Other congenital forms of obstruction are rare, e.g. disjunction between efferent ductules and the corpus epididymis, agenesis/atresia 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 below* Chapter 11: Male accessory gland infections). Acute or chronic traumas can result in epididymal damage (9).

Azoospermia caused by surgery may occur after epididymal surgery, e.g. 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 vaso-vasostomy, 5-10% have epididymal blockage as a result of tubule rupture, making epididymo-vasostomy mandatory (*see below* Chapter 10: Male contraception). Vasal obstruction may also occur after herniotomy (13). Polypropylene mesh herniorrhaphy appears to be able to induce a fibroblastic response able to 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 above* Chapter 4: Genetic disorders in infertility). 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 about 1-3% of OA (1) and is classified as either cystic or post-inflammatory.

Cystic obstructions are usually congenital (i.e. Müllerian 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 Müllerian duct anomalies, 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 urethro-prostatitis (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 of 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: Investigations).

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 traumas;
- chronic sinopulmonary infections.

5.3.2 ***Clinical examination***

Clinical examination should follow suggestions for investigation of the infertile man. The following findings indicate OA:

- at least one testis with a volume > 15 ml, although a smaller testicular 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 above* Chapter 2: Investigations). Azoospermia means the inability to detect spermatozoa after centrifugation at x400 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 3000 G for 15 minutes. The pellet must be examined for spermatozoa.

Ejaculatory duct obstruction or CBAVD is suggested by a semen volume of less than 1.5 mL, acid pH and a low fructose level. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation, as 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). Follicle-stimulating hormone 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, absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g. non-homogenous testicular architecture and microcalcifications) and associated carcinoma *in situ* 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 (anterior-posterior diameter 15 mm) (21) and roundish, 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. Müllerian duct cysts or urogenital sinus/ejaculatory duct cysts (20) and ejaculatory duct calcifications (25) are other known anomalies in obstructive azoospermia. Transrectal ultrasound 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 at the same time.

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 given in Table 8 (27).

Table 8: Scoring system for testicular biopsies (Johnsen score)*

Score	Histological criteria
10	Full spermatogenesis
9	Slightly impaired spermatogenesis, many late spermatids, disorganised epithelium
8	< 5 spermatozoa per tubule, few late spermatids
7	No spermatozoa, no late spermatids, many early spermatids
6	No spermatozoa, no late spermatids, few early spermatids
5	No spermatozoa or spermatids, many spermatocytes
4	No spermatozoa or spermatids, few spermatocytes
3	Spermatogonia only
2	No germinal cells, Sertoli cells only
1	No seminiferous epithelium

** From Johnsen, 1970 (27).*

5.4 Treatment

*5.4.1 **Intratesticular obstruction***

At this level seminal duct recanalisation is impossible. Both Testicular Sperm Extraction (TESE) or Microsurgical Epididymal Sperm Aspiration (MESA) allow sperm retrieval in nearly all OA patients. TESE and MESA are therefore recommended. The spermatozoa retrieved may be used immediately for ICSI, or may be cryopreserved.

*5.4.2 **Epididymal obstruction***

Microsurgical epididymal sperm aspiration (MESA) (28) is indicated in men with CBAVD. TESA 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 epididymo-vasostomy is recommended, with the preferred technique being microsurgical intussusception epididymo-vasostomy (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 pre-operative and operative findings (e.g. concomitant abnormal testicular histology, absence of sperm in the spermatic fluid on sectioning the small epididymal tubules, wide fibrosis of the epididymis).

*5.4.3 **Proximal vas obstruction***

Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (*see* Chapter 10: Male contraception). Vaso-vasostomy is also required in rare cases of proximal vasal obstructions (iatrogenic, post-traumatic, post-inflammatory). The absence of spermatozoa in the intraoperative vas deferens fluid may suggest the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas has a thick 'toothpaste' appearance. Microsurgical vaso-epididymostomy 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 vas deferences 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 cross-over vaso-vasostomy or vaso-epididymostomy.

*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). Intra-operative 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 ducts, seminal vesicles and vasa (causing poor sperm motility, acid semen 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.
Results of reconstructive microsurgery depend on the cause and location of the obstruction and the surgeon's expertise. Standardised procedures include vaso-vasostomy and epididymo-vasostomy.
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.

Recommendation	GR
In azoospermia caused by epididymal obstruction, a scrotal exploration with microsurgical epididymal sperm aspiration and cryopreservation of the spermatozoa should be carried out, together with a microsurgical reconstruction (35).	B

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6. VARICOCELE

6.1 Introduction

Varicocele is a common abnormality (*see* Chapter 2: Investigations) with the following andrological implications:

- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- 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 valsalva manoeuvre, but can be shown by special tests (Doppler ultrasound studies) (3);
- grade 1: palpable during valsalva 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 can 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 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 the varicocele improves a couples' chance of conception (7). This meta-analysis was criticised for including several heterogenous studies, men with normal semen analysis and men with a subclinical varicocele (8). In 3 randomised controlled studies varicocele repair in men with a subclinical varicocele was found to be ineffective (9-11). Also, studies of men with a varicocele and normal semen analysis showed no clear benefit of treatment over observation (12,13).

The duration of the infertility also seems of importance: in a recent study it was shown that couples with an infertility duration of more than 2 years had a significant higher pregnancy rate 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 4 RCTs on varicocelectomy in men with a clinical varicocele, oligospermia and otherwise unexplained infertility a trend in favour of surgical correction was observed (15). The combined odds ratio was 2.23 (95% confidence interval [CI], 0.86-5.78; p=0.091), indicating that varicocelectomy is 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). While 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

Treatment	Ref.	Recurrence/ persistence %	Complication rates
Antegrade sclerotherapy	18	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema
Retrograde sclerotherapy	19	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation
Retrograde embolisation	20,21	3.8-10	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
Open operation			
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and gangrene of testicle, scrotal haematoma, post-operative hydrocele
Inguinal approach	22	13.3	Possibility of missing out a branch of testicular vein
High ligation	23	29	5-10% incidence of hydrocele (< 1%)
Microsurgical inguinal or subinguinal	24,25	0.8-4	Post-operative hydrocele arterial injury, scrotal haematoma
Laparoscopy	26,27	3-7	Injury to testicular artery and lymph vessels, intestinal, vascular and nerve damage, pulmonary embolism, peritonitis, bleeding, post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum), pneumoscrotum, wound infection

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 over-treatment.
Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility. Further RCTs are needed to confirm that this subgroup of infertile couples will benefit from treatment.

Recommendations	GR
Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination (9,10).	B
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).	A
Varicocele repair should be considered in case of a clinical varicocele, oligospermia, duration of infertility of at least 2 years and otherwise unexplained infertility in the couple.	B

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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 given in Table 10.

Table 10: Symptoms and signs of hypogonadism debuting before and after completion of puberty*

Affected organ/function	Before completed puberty	After completed puberty
Larynx	No voice mutation	No voice mutation
Hair	Horizontal pubic hairline Straight frontal hairline Diminished beard growth	Diminished secondary body hair
Skin	Absent sebum production Lack of acne Pallor Skin wrinkling	Decreased sebum production Lack of acne Pallor Skin wrinkling
Bones	Eunuchoid tall stature Osteoporosis	Osteoporosis
Bone marrow	Mild anaemia	Mild anaemia
Muscles	Underdeveloped	Hypotrophy
Prostate	Underdeveloped	Hypotrophy
Penis	Infantile	No change of size
Testes	Possibly maldescended testes Small volume	Decrease of testicular volume
Spermatogenesis	Not initiated	Involuted
Libido and potency	Not developed	Loss

**Modified from Nieschlag et al. (1998) (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 gonadotrophin-releasing hormone (GnRH) and/or gonadotrophin (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: Genetic disorders in infertility).

Table 11: Disorders with male hypogonadism*

Primary (hypergonadotropic) hypogonadism (testicular failure)*
Anorchia
Maldescended testes
Klinefelter's syndrome
Y chromosome microdeletions
Numerical and structural chromosomal anomalies
Trauma, testicular torsion, orchitis
Iatrogenic (surgery, medications, irradiation, cytostatic drugs)
Exogenous factors (toxins, heat, occupational hazards)
Systemic diseases (liver cirrhosis, renal failure)
Testicular tumour
Varicocele
Idiopathic
Secondary (hypogonadotropic) hypogonadism (secondary testicular failure)
Congenital o Idiopathic hypogonadotrophic hypogonadism o Normosmic o Iposmic/anosmic (Kallmann syndrome)

Acquired (tumours in the following regions) o Dyencephalon (craniopharyngiomas, meningiomas) o Hypothalamus or pituitary
Empty sella
Granulomatous illnesses
Fractures of the skull base
Ischaemic or haemorrhagic lesions in hypothalamic area
Hyperprolactinaemia
Drugs/anabolic steroids, radiotherapy
Target organ resistance to androgens
Testicular feminisation
Reifenstein's syndrome

7.2 Hypogonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Idiopathic hypogonadotrophic hypogonadism (IHH) is characterised by low levels of gonadotrophins and sex steroid in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis (2). Idiopathic HH may be an isolated condition or may be associated with anosmia/hyposmia (Kallmann syndrome). Genetic factors causing a deficit of gonadotrophins may act at the hypothalamic or pituitary level. Mutations in candidate genes (X-linked or autosomal) can be found in about 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, and by tumours. A suspected tumour requires imaging (CT or MR) of the sella region and a complete endocrine work-up.

The 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 (drug, hormones, tumours), the therapy of choice depends on whether the goal is to achieve normal androgen levels or to achieve fertility.

Normal androgen levels and subsequent development of secondary sex characteristics (in cases of onset of hypogonadism before puberty) and eugonadal state can be achieved by androgen replacement alone. However, the stimulation of sperm production requires treatment with human chorionic gonadotrophin (hCG) combined with recombinant FSH or urinary FSH or human menopausal gonadotropins (HMG). In the rare cases of 'fertile eunuchs', who have sufficient production of FSH but not LH, treatment with hCG alone may be sufficient to stimulate sperm production and to achieve normal testosterone levels (5).

If hypogonadotrophic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is therapy with 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 are associated in men with hypogonadotrophic hypogonadism (Table 11, *see also* Chapter 4: Genetic disorders in infertility). Most conditions listed in Table 11 only affect the reproductive function of the testis so that only the FSH level is elevated. However, it has been reported that men with infertility problems 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 testis occurs after treatment with GnRH analogues or surgical castration for prostatic cancer (10).

The 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 concentration of the serum concentration of sex hormone binding globulin (SHBG). Based on levels of total testosterone 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 am. The existing guidelines for androgen replacement are based on mainly 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. If the serum total testosterone level is between 8 and 12 nmol / L, testosterone supplementation is based on the presence of symptoms.

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 as near as possible to physiological concentrations (11-13).

7.4 Conclusion and recommendation for hypogonadism

Conclusion
It is generally agreed that patients with primary or secondary hypogonadism associated with hypoandrogenism should receive testosterone substitution therapy.

Recommendation	GR
Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism (4).	A

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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 hypothalamo-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 three-fold higher incidence of cryptorchidism compared to African-Americans. Even between Caucasians, there are significant differences in the risk of cryptorchidism, e.g. 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 more than 3,000 boys weighing > 2500 g and 21% in premature boys weighing < 2500 g. 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 > 2500 g and < 2500 g 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-Müllerian hormone regulates the 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, while other gene families, e.g. 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 anti-androgenic 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 pre-

operative testicular location and testicular 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] former "CIS" of the testis. In 5-10% of testicular cancers, there is a history of cryptorchidism (17). The risk of a germ cell tumour 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 preformed 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 does 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 gonadotrophin or GnRH has been used widely in the past to treat cryptorchidism. However, although 15-20% of retained testes descend during hormonal treatment, one-fifth of these re-ascend 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 early treatment (during the first 2 years of life) has a beneficial effect on preserving future fertility (20), while 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. The results clearly indicate that early surgery has a beneficial effect on testicular growth. Because testicular volume is an approximate indirect measure of spermatogenic activity, 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 intratubular germ cell neoplasia of unclassified type [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 males with non-palpable testes, the post-operative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged ochidopexy has been reported in up to 40% of patients (19).

8.7 Conclusions and recommendations for cryptorchidism

Conclusions
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and germ cell tumours.
Whether early surgical intervention can prevent germ cell loss is still debatable, but in a randomised study it improved testicular growth in boys treated at the age of 9 months compared to those aged 3 years at the time of orchidopexy.
Paternity in men with unilateral cryptorchidism in almost equal to that in men without cryptorchidism.
Bilateral cryptorchidism significantly reduces the likelihood of paternity.

Recommendations	GR
Hormonal treatment of cryptorchidism should be abolished because of the risk of germ cell apoptosis and subsequent reduction of sperm production.	B
Early orchidopexy (6-12 months of age) might be beneficial for testicular development in adulthood.	B
If undescended testes are corrected in adulthood, testicular biopsy for detection of intratubular germ cell neoplasia of unclassified type [ITGCNU; former “CIS] is recommended at the time of orchidopexy (17).	B

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9. IDIOPATHIC MALE INFERTILITY

9.1 Introduction

No demonstrable cause of male infertility, other than idiopathic OAT syndrome, 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/human menopausal gonadotrophin, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Follicle-stimulating hormone (3) and anti-oestrogens in combination with testosterone (4) might be beneficial in a selection of patients (3,4). A Cochrane analysis showed that men taking oral antioxidants had an associated statistically significant increase in live birth rate (pooled odds ratio (OR) = 4.85; 95% CI: 1.92-12.24; p = 0.0008; I(2) = 0%) when compared with men taking the control. No studies reported harmful side effects from the antioxidant therapy used. The evidence suggests that antioxidant supplementation in subfertile males may improve the outcomes of live birth and pregnancy rate for subfertile couples undergoing ART cycles. Further head-to-head comparisons are necessary to identify the superiority of one antioxidant over another (5).

Recommendation	GR
Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism (1).	A

9.3 References

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10. MALE CONTRACEPTION

10.1 Introduction

'Male contribution to contraception' is a more accurate phrase than 'male contraception', as 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 gonadotrophins and testosterone substitution to maintain male sexual function and bone mineralisation 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 progestin has resulted 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). 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 (9).

10.2.1 ***Surgical techniques***

Various techniques are available for vasectomy. The least invasive approach is the no-scalpel vasectomy (10), which is also associated with a low rate of complications (11). The most effective occlusion technique is cauterisation of the lumen of the vas deferens and fascial interposition (12-14). 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 (17).

Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases (15). The potential long-term complications (e.g. chronic testicular pain) (16) 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 pre-operatively that, although rare, long-term re-canalisation 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 (18).

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).
- Vascetomy 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 (vaso-vasostomy or vaso-epididymostomy), and whether reversal was unilateral or bilateral. However, there have been no randomised controlled trials comparing macrosurgery (loops) and microsurgery. Microsurgical techniques with the help of magnification and smaller suture materials should be used (20).

10.3.1 ***Length of time since vasectomy***

Vaso-vasostomy 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%, respectively, for 3-8 years, 79% and 44%, respectively, for 9-14 years, and 71% and 30%, respectively, for > 15 years (21).

10.3.2 ***Epididymo-vasostomy***

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, epididymo-vasostomy is needed to reverse the vasectomy (*see above* Chapter 5: Obstructive azoospermia) (22).

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 (23,24). 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
The most cost-effective approach to treatment of post-vasectomy infertility is microsurgical reversal. This procedure is also associated with the highest chance of pregnancy.
Pregnancy is still achievable after successful vasectomy reversal.
MESA/TESE/PESA (25) and ICSI should be reserved for failed vasectomy reversal surgery.
All available data indicate vasectomy is not associated with any serious, long-term, side effects (15).
Fascial interposition and cauterisation appears to be the most effective vasectomy technique (12-14).

Recommendations	**GR**
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.	C
Methods of male contraception other than vasectomy are associated with high failure rates or are still experimental (e.g. hormonal approach).	B
Microsurgical vasectomy reversal is a low-risk and (cost-) effective method of restoring fertility.	B

For couples wanting to achieve pregnancy, sperm aspiration together with ICSI is a second-line option for selected cases and in those with failed vaso-vasostomy.	B

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11. MALE ACCESSORY GLAND INFECTIONS

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.

11.2 Urethritis

Infectious, sexually acquired urethritis is caused by various pathogens, most often *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Neisseria gonorrhoea* (4). Non-infectious causes of urethritis include irritations as a result of allergic reactions, trauma and manipulations. Urethral discharge and bladder voiding problems are the predominant symptoms of acute urethritis.

11.2.1 ***Diagnosis and treatment***

Diagnosis is based on the analysis of urethral smear and first-voided urine (VB1). Pathognomonic evidence is > 4 granulocytes per microscopic high-power field (×1000) in an urethral smear, or 15 granulocytes per microscopic field (×400) in the smear of the sediment of 3 mL VB1, is pathognomonic (4). In urethritis, defined by inflammatory discharge, semen analysis for disorders of male fertility is not possible because the anterior urethra is full of infectious and inflammatory material that hampers any useful analysis (5).

The impact of urethritis on semen quality and fertility has not been proven because the ejaculate is contaminated with inflammatory material from the urethra.

It is still debated whether infection with sexually transmitted micro-organisms has a negative effect on sperm function (1,6,7). Male fertility can be impaired by urethral strictures, ejaculatory disturbances (2), or the development of obstruction (8). Obstruction can develop as either a normal urethral stricture or a lesion in the posterior urethra in the area of the verumontanum, both of which can lead to ejaculatory disturbances and central obstruction of the seminal pathway (2).

The Centers for Disease Control and Prevention in Atlanta, GA, USA have published guidelines to standardise the treatment of sexually transmitted diseases (9). Because the aetiology of acute urethritis is usually unknown at the time of diagnosis, empirical therapy is used against potential pathogens. A single dose of a fluoroquinolone is given, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections.

11.3 Prostatitis

Prostatitis is the most common urological diagnosis in men < 50 years of age (10). Traditionally, prostatitis has been classified into four clinical entities:

- acute bacterial prostatitis (abp) and prostatic abscess as a sequela/complication of abp;
- chronic bacterial prostatitis (cbp);
- non- or abacterial prostatitis (nbp);
- prostatodynia.

To improve the definition and understanding of prostatitis, a classification system has been proposed by the National Institutes of Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (10) (Table 12).

Table 12: NIH/NIDDK classification of prostatitis syndrome*

New NIH category	Clinical entity	Description
I	ABP	Acute infection of the prostate gland
II	CBP	Recurrent infection of the prostate
III	Chronic abacterial prostatitis/CPPS	No demonstrable infection
IIIA	Inflammatory CPPS	White cells in semen, expressed prostatic secretions or post-prostatic massage urine
IIIB	Non-inflammatory CPPS	No white cells in semen, expressed prostatic secretions or post-prostatic massage urine
IV	Asymptomatic inflammatory prostatitis	No subjective symptoms. Inflammation detected either by prostate biopsy or by the presence of white cells in expressed prostatic secretions or semen during evaluation for other disorders

** Adapted from Wagenlehner et al. (10).*
ABP = acute bacterial prostatitis; CBP = chronic bacterial prostatitis; CPPS = chronic pelvic pain syndrome.

11.3.1 ***Microbiology***

ABP (NIH I), CBP (NIH II) and, more significantly, prostatic abscesses are clinically relevant but uncommon diseases. The most common causes of bacterial prostatitis are Gram-negative bacteria, mainly strains of *Escherichia coli* (11). The role of Gram-positive bacteria in bacterial prostatitis is controversial. Although enterococci can cause bacterial prostatitis and associated recurrent urinary tract infection (UTI), the importance of other Gram-positive bacteria in chronic prostatitis is doubtful (11), as is that of *C. trachomatis* and *Mycoplasma*, particularly *U. urealyticum* (11-15). Hidden bacteria may be aetiologically involved in patients with chronic idiopathic prostatitis after exclusion of typical bacterial infection (16). Detection of bacteria by molecular techniques has not been evaluated definitively.

11.3.2 ***Diagnosis***

Symptoms must be evaluated using standardised scores, especially the NIH symptom score (17). Other investigative procedures include laboratory diagnosis of CBP using the four-specimen test for bacterial localisation (10,11), which measures sequential quantitative bacteriological cultures of the urethra, bladder urine and prostatic secretions, both in expressed prostatic excretion (EPS) and urine after prostatic massage (12).

Simplified techniques compare bacterial and leukocyte counts in the urine before and after prostatic massage (18). Screening of bladder voiding and imaging analysis of the prostate gland must be integrated.

The key to diagnosis is the demonstration of leukocytes in EPS, urine after prostatic massage and/or ejaculate to differentiate between inflammatory and non-inflammatory CPPS.

11.3.3 ***Ejaculate analysis***

An ejaculate analysis (*see* Chapter 2: Investigations) 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 CPPS (NIH IIa vs NIH IIIb).

11.3.4 ***Microbiological findings***

After exclusion of urethritis and bladder infection, > 10^6 peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be made for common urinary tract pathogens, particularly Gram-negative bacteria.

A concentration of > 10^3 cfu/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia. Various micro-organisms 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 micro-organisms in semen and the frequency of isolation of different strains (19). The ideal diagnostic test for *C. trachomatis* in semen has not yet been established (14). 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 (14).

Ureaplasma urealyticum is pathogenic only in high concentrations (> 10^3 cfu/mL ejaculate). No more than about 10% of samples analysed for ureaplasma exceed this concentration (20). Normal colonisation of the urethra hampers the clarification of mycoplasma-associated urogenital infections, using samples such as the ejaculate (15).

11.3.5 ***White blood cells***

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial (21). 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 (7). Earlier findings have shown that elevated leukocyte numbers are not a natural cause of male infertility (22).
According to WHO classification, leukocytospermia is defined as > 10^6 WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis (23,24). Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH IIIb).

11.3.6 ***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 (25-27).

11.3.7 ***Seminal plasma alterations***

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate (1,28,29), 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 (30-32), but no correlations have been found. The prostate is the main site of origin of IL-6 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process (33). However, elevated cytokine levels do not depend on the number of leukocytes in EPS (34).

11.3.8 ***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 (20,35).

11.3.9 ***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 NBP (36,37). However, except for suspected chlamydial infections (38), only a history of vasectomy is predictive of sperm antibody formation (39).

11.3.10 ***Reactive oxygen species***

Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers (40). However, their biological significance in prostatitis remains unclear (1).

11.3.11 ***Therapy***

Treatment of chronic prostatitis is usually targeted at relieving symptoms (10,41). 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 micro-organisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g. leukocytes) and secretory parameters;
- improvement of sperm parameters to counteract fertility impairment (42).

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 CBP (NIH II) has provided symptomatic relief, eradication of microorganisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. The use of alpha-blockers for symptom relief is controversial. Although antibiotics might improve sperm quality (42), there is no evidence that treatment of chronic prostatitis increases the probability of conception (1,43).

11.4 Orchitis and epididymo-orchitis

11.4.1 ***Introduction***

Orchitis is an inflammatory lesion of the testis associated with a predominantly WBC exudate inside and outside the seminiferous tubules, which potentially results in tubular sclerosis. The inflammation causes pain and swelling. Chronic inflammatory alterations in the seminiferous tubules disrupt the normal process

of spermatogenesis and alter sperm number and quality (44). Orchitis might also be an important cause of spermatogenetic arrest (45), which might be reversible in most cases. Testicular atrophy can develop as a result of tubular sclerosis (45).

11.4.2 ***Diagnosis***

Epididymo-orchitis usually presents with unilateral scrotal pain (46). Diagnosis is based on past medical history and palpation. Ultrasonography usually indicates a swollen, enlarged testis. The sonographic features of the tissue do not allow any differential diagnosis (47).

11.4.3 ***Ejaculate analysis***

Ejaculate analysis, including leukocyte analysis, indicates persistent inflammatory activity. In many cases, especially in acute epididymo-orchitis, transiently decreased sperm counts and reduced forward motility occur (44,46). Obstructive azoospermia caused by complete obstruction is a rare complication. Mumps orchitis can result in bilateral testicular atrophy (45) and non-obstructive azoospermia. When granulomatous orchitis is suspected, sperm-bound autoantibodies occur.

11.4.4 ***Therapy***

Only therapy of acute bacterial epididymo-orchitis and of specific granulomatous orchitis is standardised (45) (Table 13). Several regimens improve the inflammatory lesion. Unfortunately, corticosteroids and non-steroidal anti-inflammatory agents (e.g. diclofenac, indomethacin, acetylsalicylic acid) have not been evaluated for their andrological outcome (47). In mumps orchitis, systemic therapy with interferon α-2b prevents testicular atrophy and azoospermia (50). In idiopathic granulomatous orchitis, surgical removal of the testis is the therapy of choice.

Table 13: Treatment of epididymo-orchitis

Condition and pathogen	**Treatment**
Acute bacterial epididymo-orchitis	
N. gonorrhoeae	Tetracyclines
C. trachomatis	Tetracyclines
E. coli, Enterobacteriaceae	Fluoroquinolones
Mumps orchitis	Interferon α-2b
Non-specific chronic epididymo-orchitis	Steroidal and non-steroidal inflammatory agents
Granulomatous (idiopathic) orchitis	Semi-castration
Specific orchitis	According to therapy of underlying diseases

11.5 Epididymitis

11.5.1 ***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 *N. gonorrhoea* (51,52). Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTI 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 (52).

11.5.2 ***Diagnosis***

In acute epididymitis, inflammation and swelling usually start in the tail of the epididymis and can spread to involve the rest of the epididymis and testicular tissue (46). Although men with epididymitis caused by sexually transmitted micro-organisms always have a history of sexual activity, exposure could have occurred several months before onset. The microbial aetiology of epididymitis is usually easy to determine by Gram-stained examination of both a urethral smear for urethritis and of a mid-stream urine specimen for Gram-negative bacteriuria (51,52). Intracellular Gram-negative diplococci on the smear indicate the presence of *N. gonorrhoea*. Only WBCs on urethral smear indicate non-gonorrhoeal urethritis; *C. trachomatis* will be isolated in about two-thirds of these patients (53).

11.5.3 ***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

(46,48,51). Ipsilateral low-grade orchitis (54,55) might be the cause of this slight impairment in sperm quality (Table 14) (56).

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: Obstructive azoospermia). The extent of azoospermia after epididymitis is unclear.

Table 14: Acute epididymitis and impact on sperm parameters.

Authors	Negative influence			
	Density	**Motility**	**Morphology**	**Comment**
Ludwig & Haselberger (57)	+	+	+	Pyospermia in 19 of 22 cases
Berger *et al*. (51)		+		
Weidner *et al*. (47)	+	+	+	Azoospermia in 3 of 70 men
Haidl (58)		+		Chronic infections; macrophages elevated
Cooper *et al*. (59)				Decrease in epididymal markers: α-glucosidase, L-carnitine

11.5.4 ***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. gonorrhoea* or *C. trachomatis* must be told to refer their sexual partners for evaluation and treatment (60).

11.6 Conclusions and recommendations for male accessory gland infections

Conclusions
Urethritis and prostatitis are not associated clearly with male infertility.
Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations, and cannot reverse functional deficits and anatomical dysfunction.

Recommendations	**GR**
In most cases, the aetiology of acute urethritis is unknown at the time of diagnosis; empirical therapy is therefore suggested using a single dose of a fluoroquinolone, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections (9).	B
Antibiotic therapy of (chronic) bacterial prostatitis has been shown to provide symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions (61-64).	B
Although antibiotic procedures for MAGI might provide improvement in sperm quality, therapy does not necessarily enhance the probability of conception (1,43).	B
Patients with epididymitis that is known or suspected to be caused by *N.* gonorrhoea or *C. trachomatis* must be instructed to refer their sexual partners for evaluation and treatment (60).	B

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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 always preceded by CIS, and untreated germ cell neoplasia of unclassified type ([ITGCNU] former CIS) 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, seen on ultrasound, can be associated with germ cell tumours and CIS of the testis.

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: Semen cryopreservation). 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 $\geq$ 3 cycles of chemotherapy and in patients who have received 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). Even the risk of low libido and erectile dysfunction is 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 testicular microlithiasis (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 a 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 and those with a history of TGCT, and contralateral TM (21).

12.4 Recommendations for germ cell malignancy and testicular microcalcification

Recommendations	GR
It is important to encourage and educate patients with TM about self-examination, as this might result in early detection of TGCT.	B
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, and men with a history of TGCT and contralateral TM (21).	B
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.	B
Testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic computed tomography is not justified for men with isolated TM without associated risk factors (e.g. infertility, cryptorchidism, testicular cancer, atrophic testis) (15).	B
Men with TGCT are at increased risk of developing hypogonadism and sexual dysfunction and should therefore be followed up (10,11).	B

TGCT = testicular germ cell tumour; TM = testicular microlithiasis

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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 and is caused by failure of emission of semen from the seminal vesicles, the prostate and the 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).

Table 15: Aetiology of anejaculation

Neurogenic	**Drug-related**
Spinal cord injury	Antihypertensives
Cauda equina lesion	Antipsychotics
Retroperitoneal lymphadenectomy	Antidepressants
Aortoiliac or horseshoe-kidney surgery	Alcohol
Colorectal surgery	
Multiple sclerosis	
Parkinson's disease	
Autonomic neuropathy (diabetes mellitus)	

13.2.2 ***Anorgasmia***

Anorgasmia is the inability to reach orgasm and can give rise to anejaculation. Anorgasmia is often a primary condition and its cause is usually psychological. Some patients report sporadic events of nocturnal emission or of ejaculation occurring 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 (1). 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 or organic, e.g. incomplete spinal cord lesion (3), iatrogenic penile nerve damage (4), or pharmacological, e.g. antidepressants, antihypertensives, antipsychotics (5).

13.2.4 ***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 bulbo-urethral glands. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence (Table 16).

Table 16: Aetiology of retrograde ejaculation

Neurogenic	**Pharmacological**
Spinal cord injury	Antihypertensives
Cauda equina lesions	α1-adrenoceptor antagonists
Multiple sclerosis	Antipsychotics
Autonomic neuropathy (juvenile diabetes)	Antidepressants
Retroperitoneal lymphadenectomy	**Bladder neck incompetence**
Sympathectomy	Congenital defects/dysfunction of hemitrigone
Colorectal and anal surgery	Bladder extrophy
Urethral	Bladder neck resection
Ectopic ureterocele	Prostatectomy
Urethral stricture	
Urethral valves or verumontaneum hyperplasia	
Congenital dopamine β-hydroxylase deficiency	

13.2.5 ***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.

13.2.6 ***Premature ejaculation***

Premature ejaculation is the inability to control ejaculation for a sufficient length of time during vaginal penetration. Although a universally accepted definition of sufficient length of time does not exist, some patients are unable to delay ejaculation beyond a few coital thrusts, or even after vaginal penetration. Premature ejaculation may be strictly organic (e.g. prostatitis-related) or psychogenic, primary or acquired, partner-related or non-selective, and can be associated with erectile dysfunction. Premature ejaculation does not impair fertility, provided intravaginal ejaculation occurs. For more extensive discussion on this topic, the EAU Male Sexual Dysfunction guidelines should be consulted.

13.2.7 ***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.

13.3 Diagnosis

Diagnostic management includes the following recommended procedures.

13.3.1 ***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, primary or acquired disorder), as well as to psychosexual aspects (education, features of affective relationship, pre-existent psychological trauma, previous psychological therapy).

13.3.2 ***Physical examination***

Genital and rectal examinations are conducted, including evaluation of the prostate, bulbo-cavernosus 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 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 is also suggested (8).

13.3.5 Optional diagnostic work-up

This diagnostic workup can include:

- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;
- video-cystometry;
- 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 retrieving spermatozoa for use in assisted reproduction techniques (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 ejaculations, tamsulosin can be administered during antidepressant treatment (9). Treatment should be given for urogenital infections (i.e. in cases of painful ejaculation) (8). Dapoxetin, a selective serotonin re-uptake inhibitor (SSRI) has been introduced for the therapy of premature ejaculation (PE) (10), since 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 (PE)***

Premature ejaculation can be treated with the selective SSRI dapoxetine, topical anaesthetic agents to increase intravaginal ejaculation latency time, behavioural therapy and/or psychotherapy. Off-label use of SSRIs (e.g. paroxetine, 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 17). Alternatively, the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure (11).

Table 17: Drug therapy for retrograde ejaculation

Drug	Dosage regimen	Ref.
Ephedrine sulphate	10-15 mg four times daily	12
Midodrin	5 mg three times daily	13
Brompheniramine maleate	8 mg twice daily	14
Imipramine	25-75 mg three times daily	15
Desipramine	50 mg every second day	16

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 alkalinised (pH 7.2-7.8) and osmolarity must be 200-300 mOsmol/kg. The patient is asked to have intercourse or to masturbate. Within 10 minutes after ejaculation, urine must be voided and centrifuged, and the pellet resuspended in 0.5 mL Tyrode's or Ham's F-10 medium, and immediately inseminated (17). Alternatively, a catheter can be applied to the bladder and 10-50 mL Tyrode's or Ham's F-10 medium instilled into the bladder. The patient must ejaculate, and a second catheterisation is carried out immediately to retrieve spermatozoa. The latter treatment minimises contact between spermatozoa and urine (18). If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo *in vitro* reproductive procedures (i.e. ICSI) with fresh orcryopreserved spermatozoa.

13.6.3 ***Anejaculation***

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy or psychosexual therapy in anorgasmic men is not very effective. In all these cases, and in men who have a spinal cord injury, vibrostimulation (i.e. the 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, electro-ejaculation is the therapy of choice (20). Electro-ejaculation

involves electric 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 electro-ejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens (22) (*see* Chapter 5 Obstructive azoospermia) or seminal tract washout (23).

When sperm cannot be retrieved, epididymal obstruction or testicular failure must be suspected. 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 autosomic nerve preservation (24), respectively.

13.7 Conclusion and recommendations for disorders of ejaculation

Conclusion
Ejaculation disorders can be treated using a wide range of drugs and physical stimulation, with a high level of efficacy.

Recommendations	**GR**
Aetiological treatments for ejaculatory disorders should be offered before sperm collection and ART is performed.	B
Premature ejaculation can be treated successfully with either topical anaesthetic creams or SSRIs (22).	A
In men with spinal cord injury, vibrostimulation and electro-ejaculation are effective methods of sperm retrieval.	B

13.8 References

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14. SEMEN CRYOPRESERVATION

14.1 Definition

Cryopreservation is the storage of biological material at subzero temperatures [e.g. -80°C 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, testicular and ovarian tissue and early embryos.

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 testical in a man with testicular malignancy, before vasectomy).
- 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, multiple sclerosis).

- For men with paraplegia when sperm have been obtained by electro-ejaculation or obtained by using penile vibratory stimulation.
- For men with psychogenic anejaculation, after sperm have been obtained either by electro-ejaculation or a sperm retrieval procedure.
- After gonadotrophin treatment has induced spermatogenesis in men with hypogonadotrophic hypogonadism.
- For men with NOA, the chance of finding sperm using micro-TESE is approximately 60-70%. Cryopreservation can be used to separate sperm collection from ICSI, thus avoiding unnecessary hyperstimulation of the female partner. It can also be used to avoid repeated sperm retrieval procedures.
- In any situation where 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 and a quarantine period of 3-6 months reduces the risk of transmission of infection from sperm donors; in most countries, fresh sperm are no longer used.

14.4 Precautions and techniques

14.4.1 ***Freezing and thawing process***

The cryopreservation techniques currently used are not yet optimal as 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 that 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 micro-organisms 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 albumen. After freezing, the tissues are immersed in liquid nitrogen.

Several techniques have been developed to try to reduce damage caused by freezing and thawing, including:

- Rapid method (9,10): sample is held in the vapour phase for 10 minutes before being plunged into liquid nitrogen.
- Slow method (11): sample is gradually cooled in the vapour phase for approximately 40 minutes.
- 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 increased storage time and repeated freezing and thawing. The maximum viable storage time for human sperm is not known. Many laboratory or regulatory authorities apply a storage time limit of up to 10 years (12). However, longer storage times are 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 very small numbers of sperm***

Standard cryopreservation in straws is an efficient way of storing large number of sperm (e.g. for a donor insemination programme). However, in micro-TESE, very few sperm might be obtained, and the choice is either to freeze testicular tissue and find sperm after thawing the tissue, or to freeze very small numbers of sperm. If sperm are frozen in straws, it can be very 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 accept samples for storage only from patients whose semen samples have been tested for infection and confirmed as safe. Donor samples should be tested for viral (hepatitis B and C, human immunodeficiency virus [HIV]) and sexually transmitted (*C. trachomatis*, gonorrhoea, syphilis) infections.

Until the test results are known, samples must be stored in an individual quarantine vessel (15)

(http://www.hfea.gov.uk/docs/8th_Code_of_Practice(2).pdf) [acces date December 2011]. Some laboratories use the additional safeguard of double-wrapping the straws before freezing, although this is more costly and can interfere with the freezing process, thus reducing sample quality upon thawing. Some centres carry out cytomegalovirus (CMV) testing and store CMV-negative and CMV-positive samples separately.

Considerable ethical issues surround the storage of samples before cancer chemotherapy for a man who is hepatitis-virus- or HIV-positive. Very 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, as sperm-washing techniques fail in about 5%.

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. The level of precaution depends on the cost and resources available to the laboratory, but if possible the following safeguards should be in place:

- All in-use storage vessels should be fitted with an alarm system that is activated by rising temperature or liquid nitrogen leakage.
- The alarm system should alert a laboratory staff member, according to a 24-h, 365-day rota.
- Ideally, there should be a spare storage container, in which samples can be transferred following a vessel failure.

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.

It is best to obtain instructions from the owner of the sample at the time of, or very shortly after storage, about what to do with the sample in the event of death or untraceability. In some countries, owners are legally required to provide instructions/consent. Choices available for the owner of the sample depend on the laws of the country, might not be appropriate in all situations, and include:

- a request that the sample should be destroyed;
- use of the sample by their wife or partner;
- use of the sample in research;
- donation of the sample to help another infertile couple.

14.5 Biological aspects

Cryopreservation induces deterioration of the seminal 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 Conclusions and recommendations for semen cryopreservation

Conclusions
The purpose of sperm cryopreservation is to enable future ART procedures.
Cryopreservation techniques are not optimal, and future efforts are needed to improve the outcome of sperm banking.
Cryopreservation should be offered and explained in patients with specific diseases, or before a patient undergoes surgery, chemotherapy or radiotherapy that might damage his reproductive integrity.
If testicular biopsies are indicated, sperm cryopreservation is strongly advised.

Recommendations	GR
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.	B
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.	C
Consent for cryopreservation should include a record of the man's wishes for his samples if he dies or is otherwise untraceable.	C
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.	C

14.7 References

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15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ABP	acute bacterial prostatitis
ART	assisted reproduction techniques
CAIS	complete androgen insensitivity syndrome
CBAVD	congenital bilateral absence of the vas deferens
CBP	chronic bacterial prostatitis
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CIS	carcinoma *in situ*
CMV	cytomegalovirus
CPPS	chronic pelvic pain syndrome
EAA	European Academy of Andrology
EPS	espressed prostatic excretion
FISH	(multicolour) fluorescent *in situ* hybridisation
FSH	follicle-stimulating hormone
GnRH	gonadotrophin-releasing hormone
GR	grade of recommendation
GREAT	G-protein-coupled receptor affecting testis descent
hCG	human chorionic gonadotrophin
HIV	human immunodeficiency virus
ICSI	intracytoplasmic sperm injection
IHH	idiopathic hypogonadotrophic hypogonadism
IL-6	interleukin-6
ITGCNU	intratubular germ cell neoplasia of unclassified type
IVF	in vitro fertilisation
LE	level of evidence
LH	luteinising hormone
MAGI	male accessory gland infection
MAR	mixed antiglobulin reaction
MESA	microsurgical epididymal sperm aspiration
NBP	non- or abacterial prostatitis
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NOA	non-obstructive azoospermia
OA	obstructive azoospermia
OAT	oligo-astheno-teratozoospermia [syndrome]
PE	premature ejaculation
PGD	preimplantation genetic diagnosis
SHBG	sex hormone binding globulin
SSRIs	selective serotonin reuptake inhibitors
TDS	testicular dysgenesis syndrome
TEFNA	testicular fine-needle aspiration
TESE	testicular sperm extraction
TGCT	testicular germ cell tumour
TM	testicular microlithiasis
TRUS	transurethral ultrasound
TURED	transurethral resection of the ejaculatory ducts
UTI	urinary tract infection
WBC	white blood cell
VB1	first-voided urine
WHO	World Health Organization

Conflict of interest

All members of the Male Infertility guidelines writing panel have provided disclosure statements of all relationships they have that may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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 Hypogonadism

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European
Association
of Urology

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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 diagnosis and treatment of male hypogonadism. This guideline aims 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

1. Nieschlag E, Behre HM (eds). *Andrology: male reproductive health and dysfunction*. 3rd edn. Heidelberg: Springer, 2010.

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 guideline 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*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.

3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	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*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

** 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 being 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

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. http://www.cebm.net/index.aspx?o=1025 [Access date January 2012]
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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 estradiol by aromatase, present in fatty tissue, the prostate and bone. Estradiol 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.

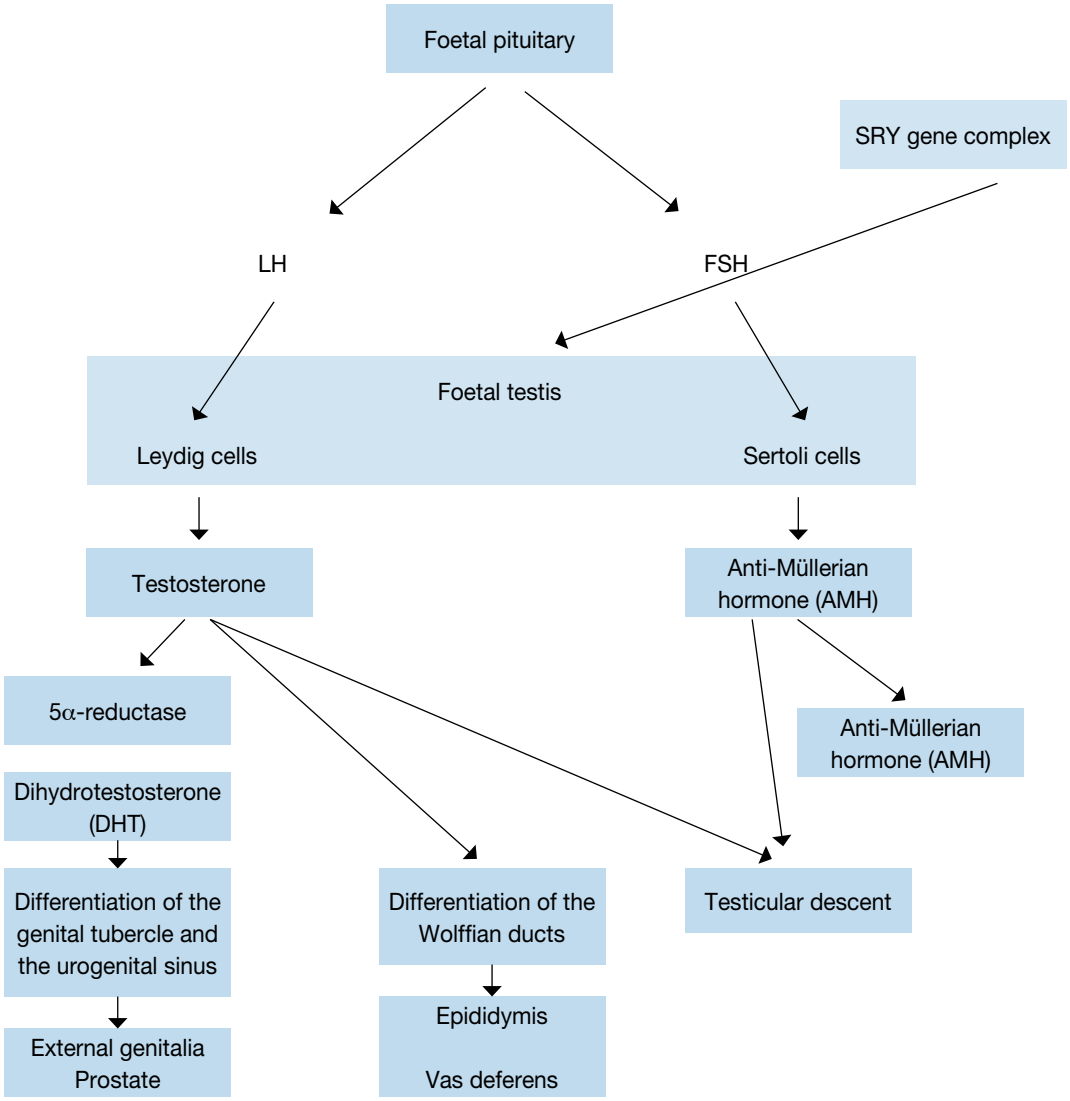
3.4 The androgen receptor

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.

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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 hypogonadotropic hypogonadism* (IHH) (formerly termed idiopathic hypogonadotropic hypogonadism, IHH).
- *Kallmann syndrome* (hypogonadotropic hypogonadism with anosmia, genetically determined, prevalence one in 10,000).

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 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 per 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 recently named late-onset hypogonadism (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 this guideline. 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

Disease	Causes for deficiency
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced.
Isolated hypogonadotropic hypogonadism (IHH) (formerly termed idiopathic hypogonadotropic hypogonadism, IHH)	GnRH deficiency.
Kallmann syndrome (hypogonadotropic hypogonadism with anosmia (prevalence 1 in 10,000)	GnRH deficiency and anosmia, genetically determined.
Secondary GnRH deficiency	Medication, drugs, toxins, systemic diseases.
Hypopituitarism	Radiotherapy, trauma, infections, hemochromatosis and vascular insufficiency or congenital.
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases from the pituitary or pituitary stalk.
Prader-Willi syndrome (PWS) (formerly Prader-Labhart-Willi syndrome) (prevalence 1 in 10,000 individuals)	Congenital disturbance of GnRH secretion.
Congenital adrenal hypoplasia with hypogonadotropic hypogonadism (prevalence 1 in 12,500 individuals)	X-chromosomal recessive disease, in the majority of patients caused by mutations in the DAX1 gene.
Pasqualini syndrome	Isolated LH deficiency.

Table 4: Forms of primary hypogonadism

Disease	Causes of deficiency
Maldescended or ectopic testes	Failure of testicular descent, 85% idiopathic.
Orchitis	Viral or unspecific orchitis.
Acquired anorchia	Traumatic, tumour, torsion, inflammation, iatrogenic, surgical removal.
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases.
(Idiopathic) testicular atrophy	Male infertility (Idiopathic or specific causes).
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Intrauterine torsion is the most probable cause.
46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)	Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20-desmolase defect, 17β-hydroxsteroid dehydrogenase defect).
Gonadal dysgenesis (synonym ‘streak gonads’)	XY gonadal dysgenesis can be caused by mutations in different genes.
46,XX male syndrome (prevalence of 1 in 10,000-20,000)	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.
47,XYY syndrome (prevalence of 1 in 2,000)	Caused by non-disjunction in paternal meiosis.
Noonan syndrome (prevalence of 1 in 1,000 to 1 in 5,000)	Genetic origin.
Inactivating LH receptor mutations, Leydig cell hypoplasia (prevalence of 1 in 1,000,000 to 1 in 20,000)	Leydig cells are unable to develop due to the mutation (19).

Recommendation	LE	GR
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.	1b	B

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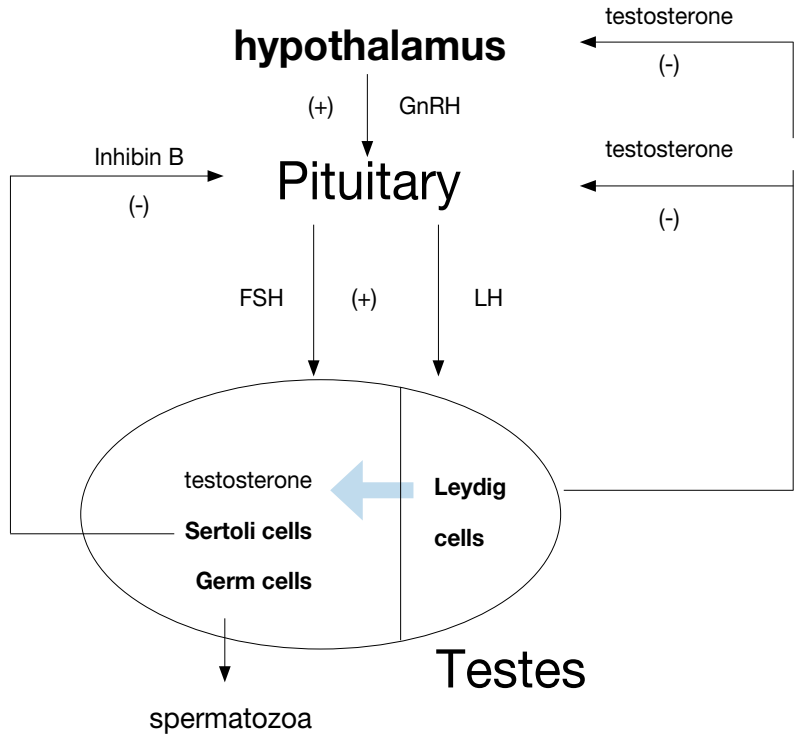
Figure 2: The hypothalamic-pituitary-testes axis



FSH = follicle-stimulating hormone; GnRH = Gonadotrohin-relasing hormone; LH = luteinizing hormone.

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).

Table 5: Clinical symptoms and signs suggestive for androgen deficiency

Delayed puberty
Small testes
Male-factor infertility
Decreased body hair
Gynaecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Reduced sexual desire and sexual activity
Erectile dysfunction
Diminished nocturnal erections
Hot flushes
Changes in mood, fatigue and anger
Sleep disturbances
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Diminished cognitive function

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 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 T 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 marihuana, 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) and a structural examination of the penis as well as a digital rectal examination 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.

Recommendations	**LE**	**GR**
The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism (Table 5) (1-7).	3	C
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).	1	A
Currently available diagnostic instruments (questionnaires) are not reliable as case-finding tools (10), as they have not been validated.	3	C
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).	2	B
LH serum levels should be analysed to differentiate between primary, secondary, and late-onset hypogonadism.		

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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 amenorrhoea 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

Small testes
Cryptorchidism
Gynaecomastia
High voice
Unclosed epiphyses
Linear growth into adulthood
Eunuchoid habitus
Sparse body hair / facial hair
Infertility
Low bone mass
Sarcopenia
Reduced sexual desire / activity

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 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

Loss of libido
Erectile dysfunction
Sarcopenia
Low bone mass
Depressive thoughts
Fatigue
Loss of body hair
Hot flushes
Loss of vigour

Recommendations	LE	GR
Screening of testosterone deficiency is only recommended in adult men with consistent and preferably multiple signs and symptoms listed in Table 7.	3	C
Adult men with established severe hypogonadism should be screened for concomitant osteoporosis.	2	B

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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

Delayed puberty (idiopathic, Kallmann syndrome)
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low bone mass in hypogonadism
Adult men with consistent and preferably multiple signs and symptoms of hypogonadism (listed in Table 7)
Hypopituitarism
Testicular dysgenesis and hypogonadism

Table 9: Contraindications against testosterone treatment

Prostate cancer
PSA > 4 ng/mL
Male breast cancer
Severe sleep apnoea
Male infertility
Haematocrit > 50%
Severe lower urinary tract symptoms due to benign prostatic hyperplasia

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 recent 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 recent randomised trial, while benefits in relation to the cognitive spectrum have been reported in studies with a lower impact (12,13).

Conclusion	**LE**
Benefits including a reduction in BMI and waist size and improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT.	2a

Recommendations	LE	GR
Testosterone replacement therapy is recommended in patients with:		
A decline in muscle mass and strength	1b	A
Reduced bone mineral density at the lumbar spine	1a	A
Decreased libido and erection	3	B

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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 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

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 h	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range (1) Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side effects.	Possible fluctuation of testosterone levels (5,6).
Testosterone enanthate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side effects.	Possible fluctuation of testosterone levels (5,6).
Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side effects (7).
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation.	Skin irritation at the site of application and risk of interpersonal transfer (8,9).
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation (10,11).
Buccal testosterone	Buccal tablet; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone.	Irritation and pain at the site of application (10,11).
Subdermal depots	Subdermal implant every 5-7 months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants (1,12,13).

Recommendations	LE	GR
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.	1a	A
Short-acting preparations may be preferred to long-acting depot administration when starting the initial treatment.	3	B
hCG treatment can only be recommended for hypogonadal patients with simultaneous fertility treatment.	1b	B

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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 recent 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	LE
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	LE	GR
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

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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 recent 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.

Recommendations	LE	GR
The response to treatment should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.	4	C
In men with an abnormal BMD, BMD measurements should be repeated 6 and 12 months after the start of TRT and thereafter annually.	4	C
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.	4	C
Prostate health should be assessed by digital rectal examination (DRE) and PSA before the start of TRT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually.	4	C
Routine screening of potential cardiovascular side effects is not indicated in men receiving TRT.	1B	A
Men with cardiovascular co-morbidity should be assessed by a cardiologist before TRT is initiated and there should be close cardiovascular monitoring during TRT.	3	C

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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 hypogonadotropic 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 group 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 kept on file in the European Association of Urology Central Office database. 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 Urological Infections

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European Association of Urology

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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. There are only limited data from Europe. 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 clear. 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 and communities of Europe mirrors the global increase in resistant strains. There is a clear association between antibiotic use and the level of resistance on both individual and community levels (8). Multi-resistant microbial strains such as well known meticillin-resistant *Staphylococcus aureus* (MRSA) are found in an increasing number of patients. The presence of extended-spectrum β-lactamase producing *E. coli* (ESBL) showing resistance to most antibiotics, except for the carbapenem class, is steadily increasing in the population (9). Particularly troublesome is the increasing resistance to broad-spectrum antibiotics such as fluoroquinolones and cephalosorines. The microbes are harboured in the faecal reservoir and become a threat for urological patients in general, and men undergoing prostate biopsy in particular. The most important risk factors for this colonisation are recurrent infections and exposure to these antibiotics (10). Aggravating the situation is the observation of co-resistance to alternative antibiotics such as gentamicin (10).
A strong grip on this threatening development is thus required. With few new antibiotics in the development chain, prudent use of antibiotics is the only option to delay the development of resistance (8). The urological community has a responsibility to engage in evidence-based practices regarding the use of antimicrobial agents. It is also essential to consider the local microbial environment and resistance pattern as well as each individual patient's risk factor for harbouring resistant strains.

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 misuse and 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 ($\geq 10^5$ cfu/mL) in the context of pyelonephritis in pregnancy (11). 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:

- $\geq 10^3$ cfu/mL of uropathogens in a mid-stream sample of urine (MSU) in acute uncomplicated cystitis in women.
- $\geq 10^4$ cfu/mL of uropathogens in an MSU in acute uncomplicated pyelonephritis in women.
- $\geq 10^5$ cfu/mL of uropathogens in an MSU in women, or $\geq 10^4$ 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 $\geq$ 24 h apart, show bacteriuria of $\geq 10^5$ 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) (12,13), or the National Committee for Clinical Laboratory Standards (NCCLS) (14). 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) (15). The aim of grading recommendations (GR) is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

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

**Modified from Sackett et al. (15).*

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 (16-18).

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*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

**Modified from Sackett et al. (15).*

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 (19). A second updated version was included in the EAU guidelines 2006. The EAU/ICUD textbook on Urogenital Infections (20) has become the book of reference for the Guidelines and the recent update 2011. This version included an improved classification of UTI, a chapter on Fournier's gangrene and the updates following a systematic review of the literature on uncomplicated UTI and antibiotic prophylaxis in urological surgery. Guidelines on special conditions of the urogenital tract have also been published elsewhere (21-23).

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/).

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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.

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 Level of infection

The symptoms, as presented in the Appendix 16.1, focus on the level of infection, defined as:

- urethritis (UR);
- cystitis (CY);
- pyelonephritis (PN);
- sepsis (US).

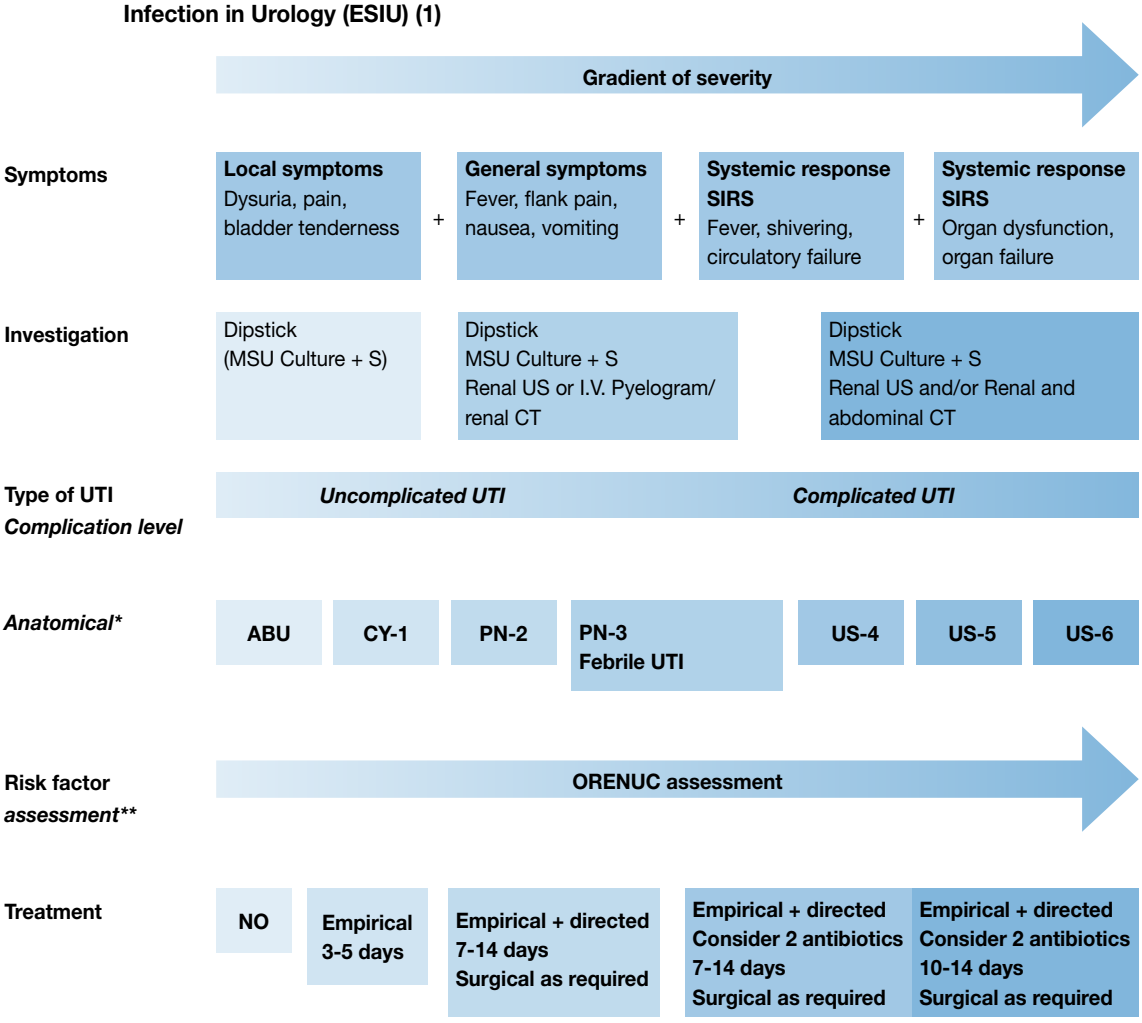
Urethritis being poorly understood is for the time being not included in the algorithm and treatment strategy of pure UTI. The male genital infections prostatitis and epididymitis are also not included.

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: Traditional and improved classification of UTI as proposed by the EAU European Section of Infection in Urology (ESIU) (1)



** see Figure 2.2*
*** see Table 2.1*

Table 2.1: Host risk factors in UTI

Type	Category of risk factor	Examples of risk factors
O	No known/associated RF	- Healthy premenopausal women
R	RF of recurrent UTI, but no risk of severe outcome	- Sexual behaviour and contraceptive devices - Hormonal deficiency in post menopause - Secretory type of certain blood groups - Controlled diabetes mellitus
E	Extra-urogenital RF, with risk or more severe outcome	- Pregnancy - Male gender - Badly controlled diabetes mellitus - Relevant immunosuppression* - Connective tissue diseases* - Prematurity, new-born
N	Nephropathic disease, with risk of more severe outcome	- Relevant renal insufficiency* - Polycystic nephropathy

U	Urological RF, with risk or more severe outcome, which can be resolved during therapy	- Ureteral obstruction (i.e. stone, stricture) - Transient short-term urinary tract catheter - Asymptomatic Bacteriuria** - Controlled neurogenic bladder dysfunction - Urological surgery
C	Permanent urinary Catheter and non resolvable urological RF, with risk of more severe outcome	- Long-term urinary tract catheter treatment - Non resolvable urinary obstruction - Badly controlled neurogenic bladder

*RF = Risk Factor; * = not well defined; ** = usually in combination with other RF (i.e. pregnancy, urological internvention).*

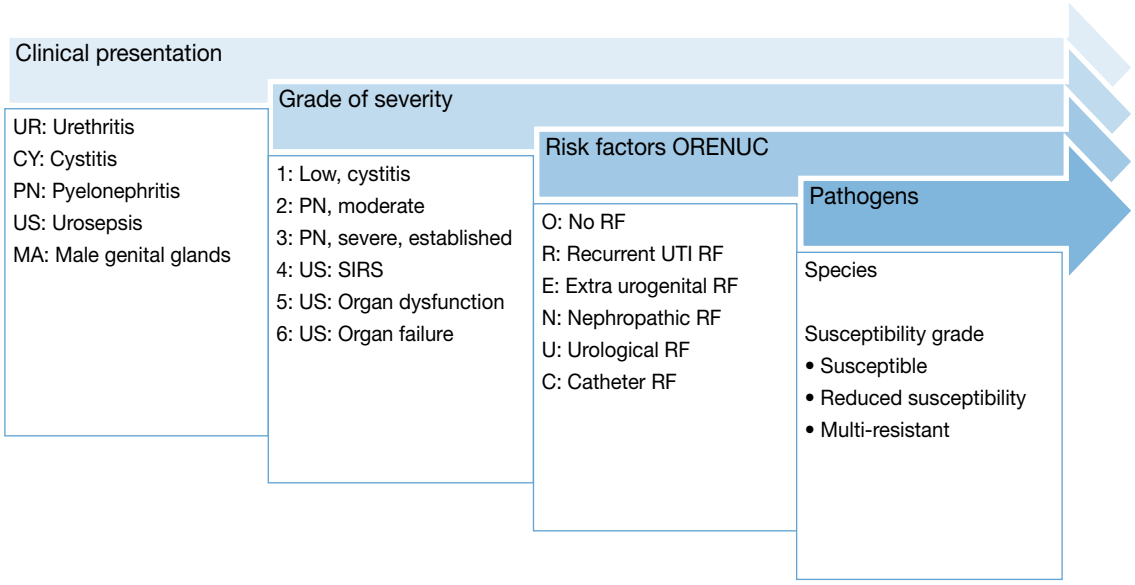
2.4 Pathogens

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.

Figure 2.2: Additive parameters of UTI classification and severity assessment



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 pneumonia* (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.

2.6 Reference

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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***

3.3.1.1 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).

3.3.1.2 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 aetiological 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

Antibiotics	Daily dose	Duration of therapy
Fosfomycin trometamol°	3 g SD	1 day
Nitrofurantoin	50 mg q6h	7 days
Nitrofurantoin macrocrystal	100 mg bid	5-7 days
Pivmecillinam*	400 mg bid	3 days
Pivmecillinam*	200 mg bid	7 days
Alternatives		
Ciprofloxacin	250 mg bid	3 days
Levofloxacin	250 mg qd	3 days
Norfloxacin	400 mg bid	3 days
Ofloxacin	200 mg bid	3 days
Cefpodoxime proxetil	100 mg bid	3 days
*If local resistance pattern is known (*E. coli *resistance < 20%)*		
Trimethoprim-sulphamethoxazole	160/800mg bid	3 days
Trimethoprim	200 mg bid	5 days

°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 ≥ 10^4 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:

	LE	**GR**
a parenteral fluoroquinolone, in communities with *E. coli* fluoroquinolone-resistance rates < 10%.	1b	B
a third-generation cephalosporin, in communities with ESBL-producing *E. coli* resistance rates < 10%.	1b	B
an aminopenicillin plus a β-lactamase-inhibitor in cases of known susceptible Gram-positive pathogens.	4	B
an aminoglycoside or carbapenem in communities with fluoroquinolone and/or ESBL-producing *E. coli* resistance rates > 10%.	1b	B

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			
Antibiotics	Daily dose	Duration of therapy	Reference
Ciprofloxacin[1]	500-750 mg bid	7-10 days	(21)
Levofloxacin[1]	250-500 mg qd	7-10 days	(27)
Levofloxacin	750 mg qd	5 days	(22,23)
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones):			
Cefpodoxime proxetil	200 mg bid	10 days	(25)
Ceftibuten	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-amoxiclav[2,3]	0.5/0.125 g tid	14 days	

[1]lower dose studied, but higher dose recommended by experts.
[2]not studied as monotherapy for acute uncomplicated pyelonephritis.
[3]mainly 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.		
Antibiotics	Daily dose	Reference
Ciprofloxacin	400 mg bid	(21)
Levofloxacin[1]	250-500 mg qd	(27)
Levofloxacin	750 mg qd	(22)
Alternatives:		
Cefotaxime[2]	2 g tid	
Ceftriaxone[1,4]	1-2 g qd	(28)
Ceftazidime[2]	1-2 g tid	(29)
Cefepime[1,4]	1-2 g bid	(30)
Co-amoxiclav[2,3]	1.5 g tid	
Piperacillin/tazobactam[1,4]	2.5-4.5 g tid	(31)
Gentamicin[2]	5 mg/kg qd	
Amikacin[2]	15 mg/kg qd	
Ertapenem[4]	1 g qd	(28)
Imipenem/cilastatin[4]	0.5/0.5 g tid	(31)
Meropenem[4]	1 g tid	(29)
Doripenem[4]	0.5 g tid	(32)

[1]lower dose studied, but higher dose recommended by experts.
[2]not studied as monotherapy in acute uncomplicated pyelonephritis.
[3]mainly for Gram-positive pathogens.
[4]same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).

*3.4.3 **Follow-up***

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C).

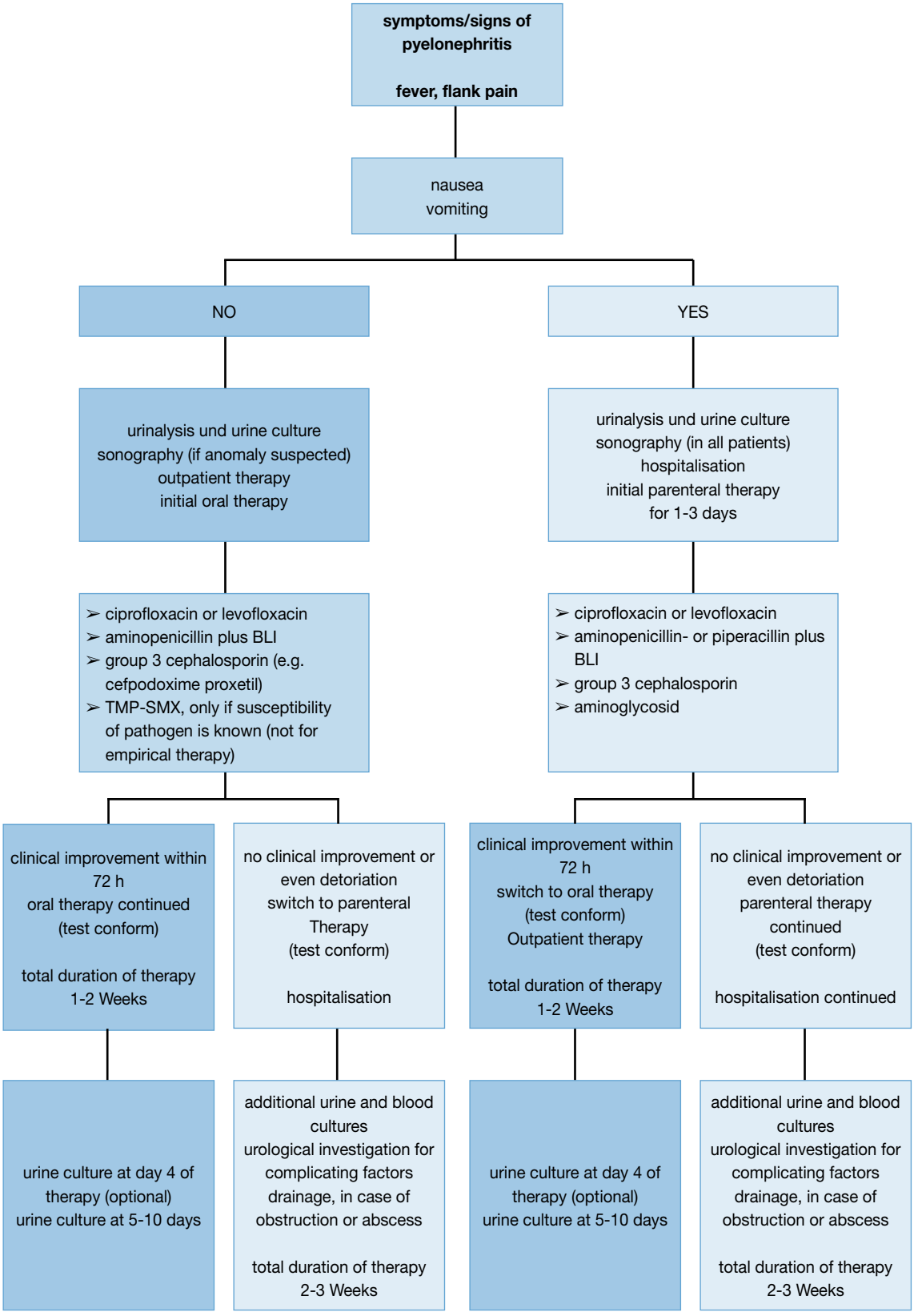
In women whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal ultrasound, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

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.

Figure 3.1: Clinical management of acute pyelonephritis



BLI = β-lactamase inhibitor; TMP = trimethoprim; SMX = sulphamethoxazole.

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)

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg once daily	0-0.2
TMP-SMX 40/200 mg thrice weekly	0.1
Trimethoprim 100 mg once daily	0-1.5**
Nitrofurantoin 50 mg once daily	0-0.6
Nitrofurantoin 100 mg once daily	0-0.7
Cefaclor 250 mg once daily	0.0
Cephalexin 125 mg once daily	0.1
Cephalexin 250 mg once daily	0.2
Norfloxacin 200 mg once daily	0.0
Ciprofloxacin 125 mg once daily	0.0
Fosfomycin 3 g every 10 days	0.14

**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)

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg	0.30
TMP-SMX 80/400 mg	0.00
Nitrofurantoin 50 or 100 mg	0.10
Cephalexin 250 mg	0.03
Ciprofloxacin 125 mg	0.00
Norfloxacin 200 mg	0.00
Ofloxacin 100 mg	0.06

**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 proanthocyanindin 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 are common during pregnancy. Most women acquire bacteriuria before pregnancy, and 20-40% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy.

3.6.1 ***Definition of significant bacteriuria***

- in an asymptomatic pregnant woman, bacteriuria is considered significant if two consecutive voided urine specimens grow $\geq 10^5$ cfu/mL of the same bacterial species on quantitative culture; or a single catheterised specimen grows $\geq 10^5$ cfu/mL of a uropathogen (17) (LE: 2a, GR: A).
- in a pregnant woman with symptoms compatible with UTI, bacteriuria is considered significant if a voided or catheterised urine specimen grows $\geq 10^3$ cfu/mL of a uropathogen (LE: 4, GR: B).

3.6.2 ***Screening***

Pregnant women should be screened for bacteriuria during the first trimester (42) (LE: 1a, GR: A).

3.6.3 ***Treatment of asymptomatic bacteriuria***

Asymptomatic bacteriuria detected in pregnancy should be eradicated with antimicrobial therapy (42) (LE: 1a, GR: A). Recommended antibiotic regimens are shown in Table 3.5.

Table 3.5: Treatment regimens for asymptomatic bacteriuria and cystitis in pregnancy (44)

Antibiotics	Duration of therapy	Comments
Nitrofurantoin (Macrobid®) 100 mg	q12 h, 3-5 days	Avoid in G6PD deficiency
Amoxicillin 500 mg	q8 h, 3-5 days	Increasing resistance
Co-amoxicillin/clavulanate 500 mg	q12 h, 3-5 days	
Cephalexin (Keflex®) 500 mg	q8 h, 3-5 days	Increasing resistance
Fosfomycin 3 g	Single dose	
Trimethoprim-sulfamethoxazole	q12 h, 3-5 days	Avoid trimethoprim in first trimester/term and sulfamethoxazole in third trimester/term

G6PD = glucose-6-phosphate dehydrogenase

3.6.4 *Duration of therapy*

Short courses of antimicrobial therapy (3 days) should be considered for the treatment of asymptomatic bacteriuria and cystitis in pregnancy (43) (LE: 1a, GR: A).

3.6.5 *Follow-up*

Urine cultures should be obtained soon after completion of therapy for asymptomatic bacteriuria and symptomatic UTI in pregnancy (LE: 4, GR: A).

3.6.6 *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 (44) (LE: 2b, GR: B).

3.6.7 *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 (45) (LE: 1b, GR: A). Recommended antibiotic regimens are shown in Table 3.6 (46).

Table 3.6: Treatment regimens for pyelonephritis in pregnancy

Antibiotics	Dose
Ceftriaxone	1-2 g IV or IM q24 h
Aztreonam	1 g IV q8-12 h
Piperacillin-tazobactam	3.375-4.5 g IV q6 h
Cefepime	1 g IV q12 h
Imipenem-cilastatin	500 mg IV q6 h
Ampicillin +	2 g IV q6 h
Gentamicin	3-5 mg/kg/day IV in 3 divided doses

3.6.8 *Complicated UTI*

Prolonged antibiotic therapy (7-10 days) should be considered in this patient population (LE: 4, GR: B). When indicated, ultrasonography or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus (LE: 4, GR: B).

3.7 UTIs in postmenopausal women

3.7.1 *Risk factors*

	Reference	LE
In older institutionalised women, urine catheterisation and functional status deterioration appear to be the most important risk factors associated with UTI.	47	2a
Atrophic vaginitis.	47	2a
Incontinence, cystocele and post-voiding residual urine.	47	2a
UTI before menopause.	47	2a
Non-secretor status of blood group antigens.	47	2a

3.7.2 *Diagnosis*

Diagnosis of UTI in postmenopausal women should always consider the following:

	Reference	LE	GR
History, physical examination and urinalysis, including culture.		4	B
Genitourinary symptoms are not necessarily related to UTI and an indication for antimicrobial treatment.	48	1b	B

3.7.3 ***Treatment***

	Reference	LE	GR
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.	49	1b	C
Treatment of pyelonephritis in postmenopausal women is similar to that in premenopausal women.		4	C
Asymptomatic bacteriuria in elderly women should not be treated with antibiotics.	17	2b	A
Optimal antimicrobials, doses and duration of treatment in elderly women appear to be similar to those recommended for younger postmenopausal women.		4	C
Oestrogen (especially vaginal) can be administered for prevention of UTI, but results are contradictory.	50	1b	C
Alternative methods, such as cranberry and probiotic lactobacilli, can contribute but they are not sufficient to prevent recurrent UTI.	51	1b	C
If complicating factors, such as urinary obstruction and neurogenic bladder, are ruled out, antimicrobial prophylaxis should be carried out as recommended for premenopausal women.		4	C

3.8 Acute uncomplicated UTIs in young men

3.8.1 ***Men with acute uncomplicated UTI***

	Reference	LE	GR
Only a small number of 15-50-year-old men suffer from acute uncomplicated UTI.	52		
Such men should receive, as minimum therapy, a 7-day antibiotic regimen.		4	B

3.8.2 ***Men with UTI and concomitant prostate infection***

	Reference	LE	GR
Most men with febrile UTI have a concomitant infection of the prostate, as measured by transient increases in serum PSA and prostate volume.	53	2a	
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.		4	A
A minimum treatment duration of 2 weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent.	54	2a	B

3.9 Asymptomatic bacteriuria

3.9.1 ***Diagnosis***

	Reference	LE	GR
For women, a count of $\geq 10^5$ cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.	17	2b	B
For men, a count of $\geq 10^3$ cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.	55	2a	B
For men with specimens collected using an external condom catheter, $\geq 10^5$ cfu/mL is an appropriate quantitative diagnostic criterion.	56	2a	B
For patients with indwelling urethral catheters, a count of $\geq 10^5$ cfu/mL is diagnostic of bacteriuria.	17	2b	B
For a urine specimen collected by in and out catheter, a count of ≥ 100 cfu/mL is consistent with bacteriuria.	17	2a	B
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.	17	2b	B

3.9.2 *Screening*

Screening for and treatment of asymptomatic bacteriuria is recommended:

	Reference	LE	GR
For pregnant women.	42	1a	A
Before an invasive genitourinary procedure for which there is a risk of mucosal bleeding.	17	1b	A

Screening for or treatment of asymptomatic bacteriuria is not recommended for:

	Reference	LE	GR
Premenopausal, non-pregnant women	17	1a	A
Postmenopausal women	17	1b	A
Women with diabetes	57	1b	A
Healthy men	58	2b	B
Residents of long-term care facilities	17	1a	A
Patients with an indwelling urethral catheter	17	1b	
Patients with nephrostomy tubes or ureteric stents		4	C
Patients with spinal cord injury	59	2a	B
Patients with candiduria	60	1b	A

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

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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.

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

The presence of an indwelling catheter, stent or splint (urethral, ureteral, renal) or the use of intermittent bladder catheterisation
Post-void residual urine of > 100 mL
An obstructive uropathy of any aetiology, e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumour
Vesicoureteric reflux or other functional abnormalities
Urinary tract modifications, such as an ileal loop or pouch
Chemical or radiation injuries of the uroepithelium
Peri- and postoperative UTI
Renal insufficiency and transplantation, diabetes mellitus and immunodeficiency

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 (LUTSs), are not only caused by UTIs but also by other urological disorders, such as benign prostatic hyperplasia (BPH), 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 mid-stream 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 $\geq 10^5$ cfu/mL of the same microorganism are required. The requirement for pyuria is ≥ 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 *Serratia* sp. and enterococci are the usual strains found in cultures. Enterobacteriaceae predominate (60-75%) (6-8), with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another.

*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, *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 *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 *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 ***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 ***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 **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 **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

Antibiotics recommended for initial empirical treatment
Fluoroquinolones
Aminopenicillin plus a BLI
Cephalosporin (Groups 2 or 3a)
Aminoglycoside
Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases
Fluoroquinolone (if not used for initial therapy)
Ureidopenicillin (piperacillin) plus BLI
Cephalosporin (Group 3b)
Carbapenem
Combination therapy:
- Aminoglycoside + BLI
- Aminoglycoside + fluoroquinolone
Antibiotics not recommended for empirical treatment
Aminopenicillins, e.g. amoxicillin, ampicillin
Trimethoprim-sulphamethoxazole (only if susceptibility of pathogen is known)
Fosfomycin trometamol

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 (7). 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

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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)

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient.
Systematic 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/mm^3 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 inotropic 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***

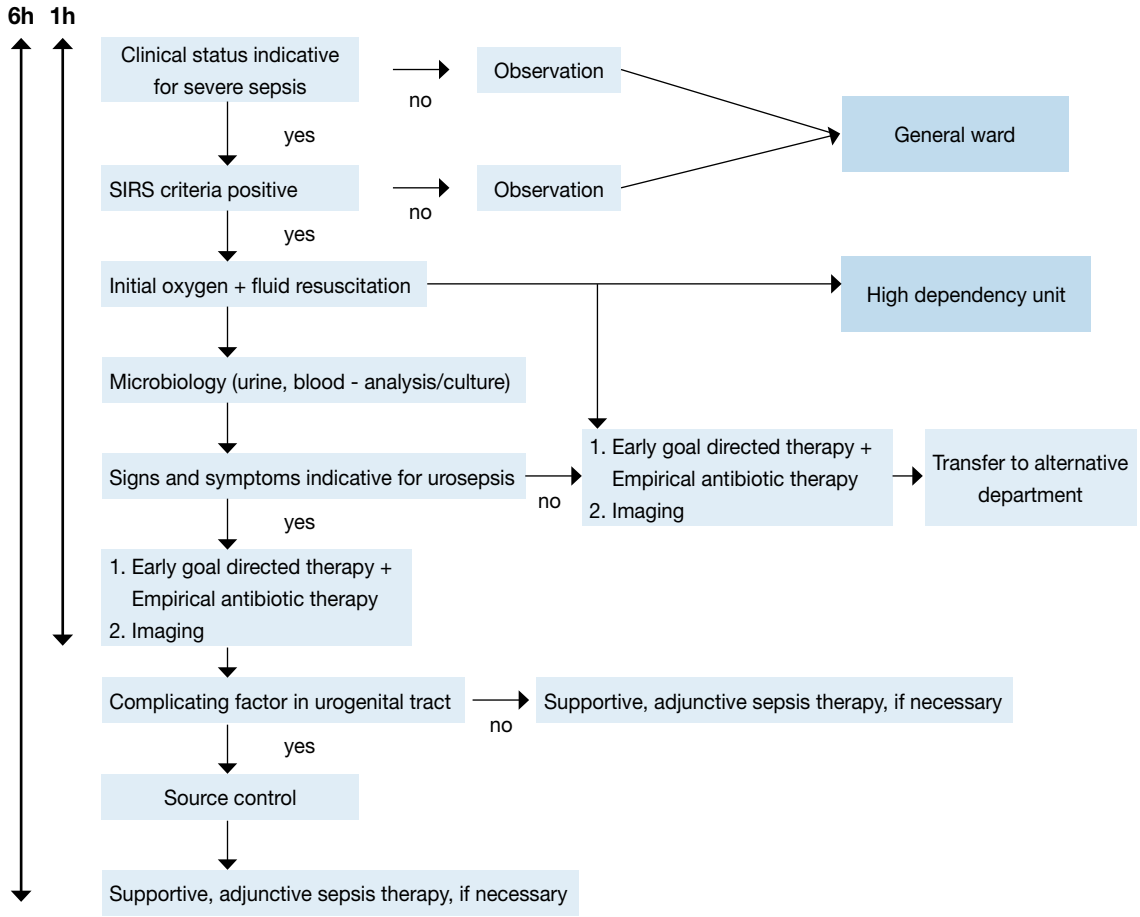
- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.
- Use of urinary catheters coated with antibiotics or silver.

*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

Early goal directed therapy	
Central venous pressure (CVP)	8-12 mmHg
Mean arterial pressure (MAP)	65-90 mmHg
Central venous oxygen (CVO2)	≥ 70%
Haematocrit (HKT)	> 30 %
Urine output	> 40 mL/h

Table 5.3: Levels of therapy in sepsis

Levels of therapy in sepsis	
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 (adrenocorticotropin 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.

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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

Recommendation		GR
General aspects		
1.	Written catheter care protocols are necessary.	B
2.	Health care workers should observe protocols on hand hygiene and the need to use disposable gloves between catheterised patients.	A
Catheter insertion and choice of catheter		
3.	An indwelling catheter should be introduced under antiseptic conditions.	B
4.	Urethral trauma should be minimised by the use of adequate lubricant and the smallest possible catheter calibre.	B
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.	B
6.	Silver alloy catheters significantly reduce the incidence of asymptomatic bacteriuria, but only for < 1 week. There was some evidence of reduced risk for symptomatic UTI. Therefore, they may be useful in some settings.	B
Prevention		
7.	The catheter system should remain closed.	A
8.	The duration of catheterisation should be minimal.	A
9.	Topical antiseptics or antibiotics applied to the catheter, urethra or meatus are not recommended.	A
10.	Benefits from prophylactic antibiotics and antiseptic substances have never been established, therefore, they are not recommended.	A
11.	Removal of the indwelling catheter after non-urological operation before midnight might be beneficial.	B
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.	B
13.	Chronic antibiotic suppressive therapy is generally not recommended.	A
14.	The drainage bag should always be kept below the level of the bladder and the connecting tube.	B
Diagnostics		
15.	Routine urine culture in asymptomatic catheterised patients is not recommended.	B
16.	Urine, and in septic patients, also blood for culture must be taken before any antimicrobial therapy is started.	C
17.	Febrile episodes are only found in < 10% of catheterised patients living in a long-term facility. It is therefore extremely important to rule out other sources of fever.	A
Treatment		
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.	A
19.	In case of asymptomatic candiduria, neither systemic nor local antifungal therapy is indicated, but removal of the catheter or stent should be considered.	A/C
20.	Antimicrobial treatment is recommended only for symptomatic infection.	B
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 > 7 days.	B
22.	For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns.	C
23.	After culture results are available, antibiotic therapy should be adjusted according to pathogen sensitivity.	B

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

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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

Severe UTI	Simple UTI
Fever ≥ 39°C	Mild pyrexia
Persistent vomiting	Good fluid intake
Serious dehydration	Slight dehydration
Poor treatment compliance	Good treatment compliance

7.6.1 ***Severe UTI***

Severe UTI is related to the presence of fever of ≥ 39°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 > 10^4 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 ≥10^5 cfu/mL is considered positive (16) (Table 7.2).

Table 7.2: Criteria for UTI in children

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	≥ 1,000-50,000 cfu/mL	≥ 10^4 cfu/mL with symptoms ≥10^5 cfu/mL without symptoms

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/mm^3 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.

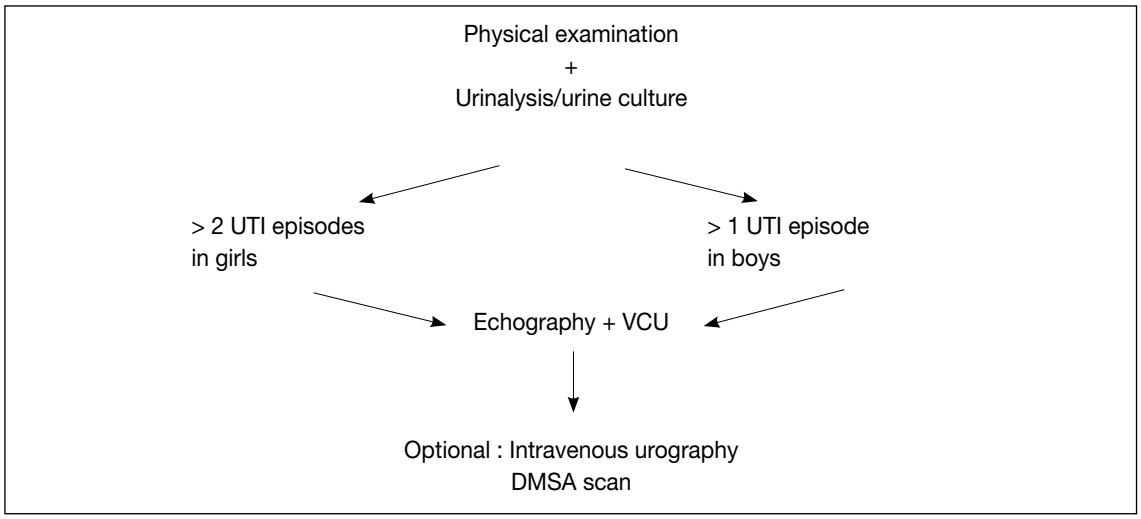
7.7.3.5 Urodynamic evaluation

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



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 amoxycillin/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,

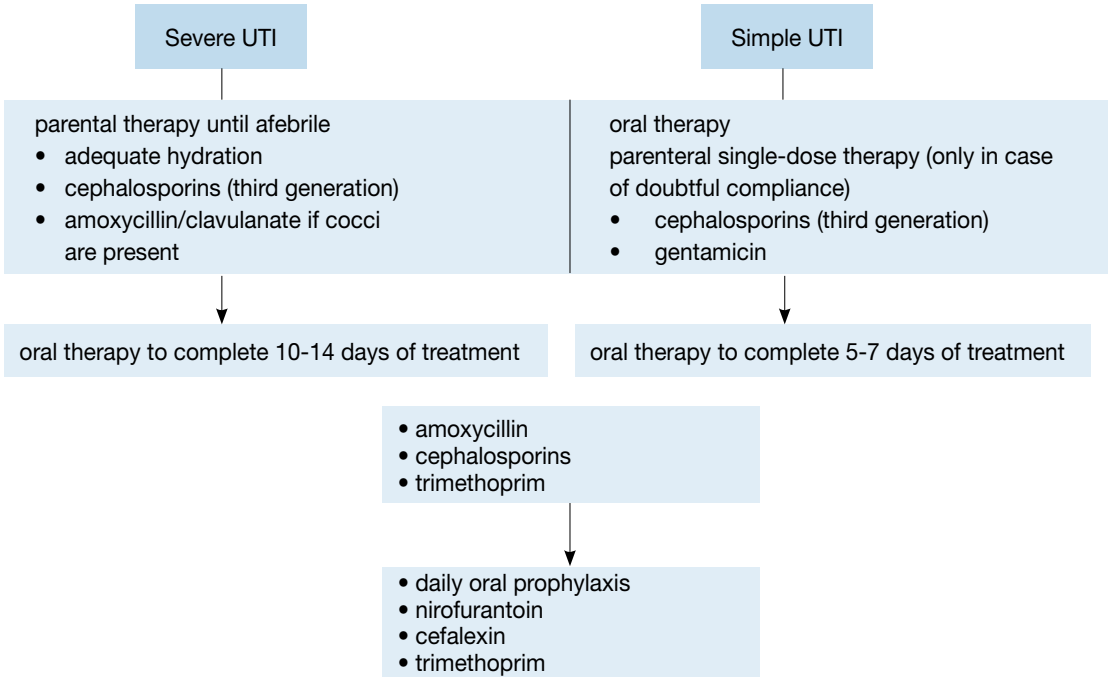
or amoxycillin/clavulanate. However, the indications for TMP are declining in areas with increasing resistance.

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



*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*

Antimicrobial agent	Application	Age	Total dose per day	No. of doses per day
Ampicillin	Intravenous	3-12 months	100-300 mg/kg BW	3
Ampicillin	Intravenous	1-12 years	60-150 (-300) mg/kg BW	3
Amoxycillin	Oral	3 months to 12 years	50-100 mg/kg BW	2-3
Amoxycillin/clavulanate	Intravenous	3 months to 12 years	60-100 mg/kg BW	3
Amoxycillin/clavulanate	Oral	3 months to 12 years	37.5-75 mg/kg BW	2-3
Cephalexin				
Treatment	Oral	3 months to 12 years	50-100 mg/kg BW	3
Prophylaxis	Oral	1-12 years	10 mg/kg BW	1-2
Cefaclor				
Treatment	Oral	3 months to 12 years	50-100 mg/kg BW	3
Prophylaxis	Oral	1-12 years	10 mg/kg BW	1-2
Cefixime	Oral	3 months to 12 years	8-12 mg/kg BW	1-2
Cetriaxone	Intravenous	3 months to 12 years	50-100 mg/kg BW	1
Aztreonam	Intravenous	3 months to 12 years	(50)-100 mg/kg BW	3
Gentamicin Gentamicin	Intravenous Intravenous	3-12 months 1-2 years	5-7.5 mg/kg BW 5 mg/kg BW	1-3 1-3
Trimethoprim				
Treatment	Oral	1-12 years	6 mg/kg BW	2
Prophylaxis	Oral	1-12 years	1-2 mg/kg BW	1
Nitrofurantoin				
Treatment	Oral	1-12 years	3-5 mg/kg BW	2
Prophylaxis	Oral	1-12 years	1 mg/kg BW	1-2

BW = body weight.
** Adapted from ref. 63.*

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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, immunosuppression 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 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 reflux 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 ($\geq 10^5$ 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 kidneys 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

Most antibiotics have a wide therapeutic index. No adjustment of dose is necessary until GFR < 20 mL/min, except antibiotics with nephrotoxic potential, e.g. aminoglycoside.
Drugs removed by dialysis should be administered after dialysis treatment.
Combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic.
Nitrofurantoin and tetracyclines are contraindicated, but not doxycycline.

GFR = glomerular filtration rate.

Table 8.2: Clearance of antibiotics at haemodialysis

Dialysed	Slightly dialysed	Not dialysed
Amoxycillin/ampicillin	Fluoroquinolones*	Amphotericin
Carbenicillin	Co-trimoxazole	Methicillin
Cephalosporins*	Erythromycin	Teicoplanin
Aminoglycosides*	Vancomycin	
Trimethoprim		
Metronidazole		
Aztreonam*		
Fluconazole*		

** Drugs cleared by peritoneal dialysis.*

Table 8.3: Treatment of tuberculosis in renal failure

Rifampicin and isoniazid (INH) not cleared by dialysis. Give pyridoxine.
Ethambutol not dialysed. Reduce dose if GFR < 30 mL/min.
Avoid rifampicin with cyclosporin.

Table 8.4: Recommendations for prevention and treatment of UTI in renal transplanation

Treat infection in recipient before transplantation.
Culture donor tissue sample and perfusate.
Perioperative antibiotic prophylaxis.
6 months low-dose TMP-SMX (co-trimoxazole) (LE: 1b, GR: A).
Empirical treatment of overt infection (quinolone, TMP-SMX for 10-14 days).

TMX = trimethoprim-sulphamethoxazole.

Table 8.5: Drug interactions with cyclosporin and tacrolimus

Rifampicin
Erythromycin
Aminoglycosides
TMP-SMX
Amphotericin B

TMP-SMX = trimethoprim-sulphamethoxazole.

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 immunodeficiencey 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.

8.8 References

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*8.8.1 **Further reading***

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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

- cefixime, 400 mg orally as a single dose, or 400 mg by suspension (200 mg/5 mL)
- ceftriaxone, 1 g intramuscularly (with local anaesthetic) 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. 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:

As first choice of treatment:	**LE**	**GR**
azithromycin, 1 g orally as single dose	1b	A
doxycycline, 100 mg orally twice daily for 7 days	1b	A
As second choice of treatment:		
erythromycin base, 500 mg orally four times daily for 14 days	1b	A
erythromycin ethylsuccinate, 800 mg orally four times daily for 7 days		
ofloxacin, 300 mg orally twice daily for 7 days	1b	A
levofloxacin, 500 mg orally once daily for 7 days		

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 (11). 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.

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10. PROSTATITIS AND CHRONIC PELVIC PAIN SYNDROME

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, a fluoroquinolone or trimethoprim should be given orally for 2 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. Despite the existence of some scientifically valid studies, no specific recommendations have been made until now. This has been because patients with CPPS probably represent a heterogeneous group of diseases and therapeutic outcome is always uncertain.

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 (1). A causative pathogen, however, is detected by routine methods in only 5-10% of cases (2), 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 (3-5).

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 (3-5). The predominant symptoms are pain at various locations and LUTSs (Tables 10.1 and 10.2) (6-8). Chronic bacterial prostatitis is the most frequent cause of recurrent UTI in men (9).

Table 10.1: Localisation of pain in prostatitis and CPPS*

Site of pain	Percentage of patients
Prostate/perineum	46%
Scrotum and/or testes	39%
Penis	6%
Urinary bladder	6%
Lower back	2%

**Adapted from Zermann et al. (6).*

Table 10.2: LUTSs in prostatitis and CPPS*

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. (8).*

10.3.1.1 Symptom questionnaires

Symptoms appear to have the strongest basis for use as a classification parameter in bacterial prostatitis as well as in CPPS (10). Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms (10,11). They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH (USA) (12). 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 differential diagnoses, such as other diseases in the urogenital organs and anorectal disorders. Clinical examination should include evaluation of the pelvic floor musculature.

10.3.3 ***Urine cultures and expressed prostatic secretion***

The most important investigations in the evaluation of the patient with prostatitis are quantitative bacteriological localisation cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey (1) (see Appendix 16.6).

According to the classification developed by the NIDDK/NIH (Table 10.3), the presence of leukocytes in post-massage urine and ejaculate are also included in the definition of inflammatory chronic prostatitis or CPPS (group IIIA) (3). The inclusion of leukocytes in the ejaculate as part of the new consensus CPPS concept allows almost twice as many patients to be reclassified into group IIIA as were formerly included in the category abacterial prostatitis using the earlier Drach's classification (13).

Table 10.3: Classification of prostatitis and CPPS according to NIDDK/NIH (3-5)

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis - CPPS A. Inflammatory CPPS (white cells in semen/EPS/VB3) B. Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine 3 (urine following prostatic massage).

The Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in bacterial prostatitis (Table 10.4) (14). 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).

Table 10.4: Most common pathogens in prostatitis

Aetiologically recognised pathogens*
E. coli
Klebsiella sp.
Prot. mirabilis
Enterococcus faecalis
P. aeruginosa
Organisms of debatable significance
Staphylococci
Streptococci
Corynebacterium sp.
C. trachomatis
U. urealyticum
Myc. hominis

**Adapted from Weidner et al. (2) and Schneider et al. (14).*

There is no correlation between leukocyte and bacterial counts and the severity of symptoms in men with chronic prostatitis/CPPS (17). It has also been shown that culture, leukocyte and antibody status does not predict antibiotic response in this group of prostatitis patients (18). In both studies, however, patients with clearly defined chronic bacterial prostatitis were excluded.

*10.3.4 **Perineal biopsy***

Perineal biopsies may be taken to help in the detection of difficult-to-culture microorganisms, but perineal biopsy should be reserved for research purposes, and cannot be recommended as part of the routine work-up. Bacteria have been cultured from perineal prostate biopsies in 36% of men with CPPS, but these results do not differ from the findings in asymptomatic controls (19).

*10.3.5 **Other tests***

The main parameter for diagnosis of inflammation in the male urogenital tract is increased leukocyte counts in the prostatic fluid, post-prostate massage urine, and seminal fluid.

Prostatic biopsy is not indicated in the routine management of prostatitis/CPPS. However, histological prostatitis is frequently diagnosed in biopsies taken for suspected prostate cancer. If such patients are asymptomatic, they are classified in the new category of asymptomatic prostatitis (type IV) (Table 10.3).

Other inflammatory markers include elevated pH, lactate dehydrogenase (LDH) and immunoglobulins

(20). The cytokines, IL-1β and TNF-α, may be identified in EPS (20) and complement C3, coeruloplasmin or polymorphonuclear (PMN) elastase in the ejaculate. These tests, however, cannot be considered to be part of routine diagnostic work-up (21).

Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate, and dilatation in the seminal vesicles. However, TRUS is not an important classification parameter in prostatitis (22), because it is unreliable for diagnosis.

*10.3.6 **Classification systems***

The purpose of the culture technique described by Meares and Stamey in 1968 was to decide whether bacteriuria originated from the urethra, prostate or bladder. Ten years later, Drach et al. (23) suggested a classification of prostatitis based on the work of Meares and Stamey, in which various types of prostatitis were differentiated according to the number of leukocytes, and positive cultures in EPS and in segmented urine samples, i.e. first voided bladder urine-1 (VB1), mid-stream urine (second voided bladder urine-2, VB2) and urine following prostatic massage (third voided bladder urine-3, VB3). This has been the most widely used classification of prostatitis for almost three decades (Table 10.5), and is still included in the latest WHO classification of diseases (ICD 10) (24).

Table 10.5: Classification of prostatitis according to Drach et al. (23)

Classification	Clinical and laboratory findings
Acute bacterial prostatitis	Clinically significant infection of the prostate
Chronic bacterial prostatitis	Significant inflammation of the prostate Isolation of an aetiologically recognised organism from the prostatic fluid/urine
Chronic abacterial prostatitis	Significant prostatic inflammation Failure to isolate an organism from the prostatic fluid/urine, or isolation of an organism whose aetiological significance is debatable
Prostatodynia	No significant prostatic inflammation Failure to isolate an organism from the prostatic fluid/urine

In 1995, the NIDDK of the NIH (USA) convened a workshop to 'develop a plan which would enable clinicians and research investigators to effectively diagnose, treat, and eventually prevent the prostatitis syndrome' (4). The NIDDK recommended a new classification of the prostatitis syndrome, which has been accepted by the IPCN. The terms abacterial prostatitis and prostatodynia were exchanged for CPPS, with or without inflammation, respectively. Seminal secretion was added to segmented urine and EPS as an additional parameter. A new category (type IV) of asymptomatic prostatitis (histological prostatitis) was added (Table 10.3). This classification is now used as a logical basis for choice of treatment.

*10.3.7 **Diagnostic evaluation***

The content and order of procedures in the diagnostic evaluation of a patient with suspected prostatitis depends on previous examinations undertaken by GPs, the established routines in different hospitals and countries, and the distance from the patient's home to the urologist. A suggested algorithm for diagnostic evaluation is presented in Table 10.6.

Table 10.6: Algorithm for diagnostic urological work-up in prostatitis

Clinical evaluation
Urinalysis and urine culture
Exclude STDs
Micturition chart, uroflowmetry and residual urine
Four-glass test according to Meares and Stamey
Microscopy
Culture
Try antibiotics if signs of inflammation

*10.3.8 **Additional investigations***

The EAU working group believes that guidelines on prostatitis should not contain a set of minimum 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. If suspected, bladder cancer must be excluded by urine cytology and cystoscopy. Ureteric calculus is ruled out by unenhanced spiral CT or intravenous pyelography. Interstitial cystitis is diagnosed by means of a micturition chart, cystoscopy and biopsy. Anorectal examination is carried out whenever indicated.

Microscopic examination of ejaculate is inferior to microscopy of EPS. It is difficult to differentiate between spermatocytes and leukocytes, unless specific methods are applied, e.g. peroxidase staining (25), and the detection rate for positive cultures is significantly reduced (26).

Video-urodynamics and advanced urodynamic examination with measurement of urethral closing pressure are not justified in the routine evaluation of patients with prostatitis, although intriguing results have been obtained in some studies (27).

The measurement of cytokines and biofilms in EPS has research interest only (6,28). Prostate-specific antigen values may be elevated in both symptomatic and asymptomatic prostatitis (29). 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 (30). 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 (31).

10.4 Treatment

10.4.1 ***Antibiotics***

Antibiotics are life-saving in acute bacterial prostatitis, recommended in chronic bacterial prostatitis, and may be tried in inflammatory CPPS.

Acute bacterial prostatitis can be 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, may be administered. For initial therapy, these regimens 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 (32). In less severe cases, a fluoroquinolone may be given orally for 10 days (5) (IVC).

The recommended antibiotics in chronic bacterial prostatitis and inflammatory CPPS (NIH type IIIA), together with their advantages and disadvantages, are listed in Table 10.7 (33). Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties (33) (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 (34). In chronic bacterial prostatitis and in inflammatory CPPS, antibiotics should be given for 2 weeks after initial diagnosis. The patient should then be reassessed and antibiotics continued only if cultures are positive or the patient reports positive effects from the treatment. A total treatment period of 4-6 weeks is recommended. Relatively high doses are needed and oral therapy is preferred (33,34) (LE: 3, GR: B).

The reason for administration of antibiotics in inflammatory CPPS is that there may be a bacterial infection, even though bacteria have not been detected by routine methods (35,36). Furthermore, many clinical studies report a beneficial effect of antibiotics in inflammatory CPPS (37,38) (LE: 2a, GR: B). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given (33,38) (LE: 2b, GR: B).

10.4.2 ***Antibiotics and β-blockers in combination therapy***

Urodynamic studies have shown increased urethral closing pressure in patients with chronic prostatitis (5). A combination treatment of β-blockers and antibiotics is reported to have a higher cure rate than antibiotics alone in inflammatory CPPS (Type IIIA+B) (39) (LE: 1b, GR: B). This is a treatment option that is favoured by many urologists.

However, in a recent randomised, double-blind, placebo-controlled multicentre study, it was shown that neither ciprofloxacin, tamsulozin, nor the combination of ciprofloxacin and tamsulozin was superior to placebo in reducing symptoms in men with moderate to severe symptoms (40) (LE: 1b, GR: B). However, in this study, many patients were included who had already been heavily pre-treated with different drug regimens.

Table 10.7: Antibiotics in chronic bacterial prostatitis*

Antibiotic	Advantages	Disadvantages	Recommendation
Fluoroquinolones	Favourable pharmacokinetics	Depending on the substance:	Recommend
	Excellent penetration into the prostate	Drug interactions	
	Good bioavailability	Phototoxicity	
	Equivalent oral and parenteral pharmacokinetics (depending on the substance)	Central nervous system adverse events	
	Good activity against typical and atypical pathogens and *P. aeruginosa*		
	In general, good safety profile		
Trimethoprim	Good penetration into prostate	No activity against *Pseudomonas*, some enterococci and some Enterobacteriaceae	Consider
	Oral and parenteral forms available		
	Relatively cheap		
	Monitoring unnecessary		
	Active against most relevant pathogens		
Tetracyclines	Cheap	No activity against P. Aeruginosa	Reserve for special indications
	Oral and parenteral forms available	Unreliable activity against coagulase-negative staphylococci, *E. coli*, other Enterobacteriaceae, and enterococci	
	Good activity against *Chlamydia and Mycoplasma*	Contraindicated in renal and liver failure	
		Risk of skin sensitisation	
Macrolides	Reasonably active against Gram-positive bacteria	Minimal supporting data from clinical trials	Reserve for special indications
	Active against Chlamydia	Unreliable activity against Gram-negative bacteria	
	Good penetration into prostate		
	Relatively non-toxic		

**Adapted from Bjerklund Johansen et al. (33).*

10.4.3 ***Other oral medication***

The β-blocker terazosin has been found to be superior to placebo in reducing symptoms for patients with CPPS (41) (LE: 1b, GR: B). Pentosan polysulphate sodium may reduce symptoms and improve quality of life in patients with CPPS (42) (LE: 2a, GR: B). Finasteride will provide some improvement for patients with category IIIA prostatitis (43) (LE: 1b, GR: B).

10.4.4 ***Intraprostatic injection of antibiotics***

This treatment has not been evaluated in controlled trials and should be considered only if oral treatment fails to eradicate the infection (44,45).

10.4.5 ***Surgery***

In acute prostatitis, some patients need bladder drainage, preferably with a suprapubic catheter. A positive effect of TURP and transurethral needle ablation has been observed in patients with severe discomfort (46,47) (LE: 2a, GR: B). Even radical prostatovesiculectomy has been carried out to relieve the pain of chronic prostatitis; the results of which are dubious (48). In general, surgery should be avoided in the treatment of prostatitis patients, except for drainage of prostatic abscesses.

10.4.6 ***Other treatment forms***

Microwave energy delivered from Prostatron 2.0 has an *in vitro* bactericidal effect on laboratory-cultured *E. coli* and *Enterobacter cloacae* (49), and transurethral microwave thermotherapy (TUMT) in inflammatory CPPS has been proven to be superior to sham-treated controls (50) (LE: 1b, GR: B). However, TUMT is still considered an experimental treatment option in patients with a suspected infection.

A number of other medical and physical treatment modalities have been suggested in non-inflammatory CPPS. In this condition, there is no evidence of an infection, therefore, full coverage of this topic lies beyond the scope of this review, and the reader is referred to other publications. It should be recalled, however, that symptoms resolve within 1 year in about 30% of men with CPPS (51) (2).

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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. Azoospermia 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

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12. 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. Concise information and tables that summarise the diagnostic and therapeutic management of STDs in the field of urology allow a synoptic overview and are in agreement with recent international guidelines of other specialities.

Special considerations (i.e. HIV infection, pregnancy, infants, and allergy) and recommended regimens may be looked up here.

12.1 Reference

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13. FOURNIER'S GANGRENE

13.1 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).

13.2 Background

Fournier's gangrene describes an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, perianal 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).

13.3 Clinical presentation

Fournier's gangrene remains rare but its incidence is increasing with an ageing population and higher prevalence of diabetes, together with emergence of multi-resistant pathogens. Typically there is painful swelling of the scrotum or perineum associated with signs of severe sepsis. Examination shows a small necrotic bulla 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.

13.4 Microbiology

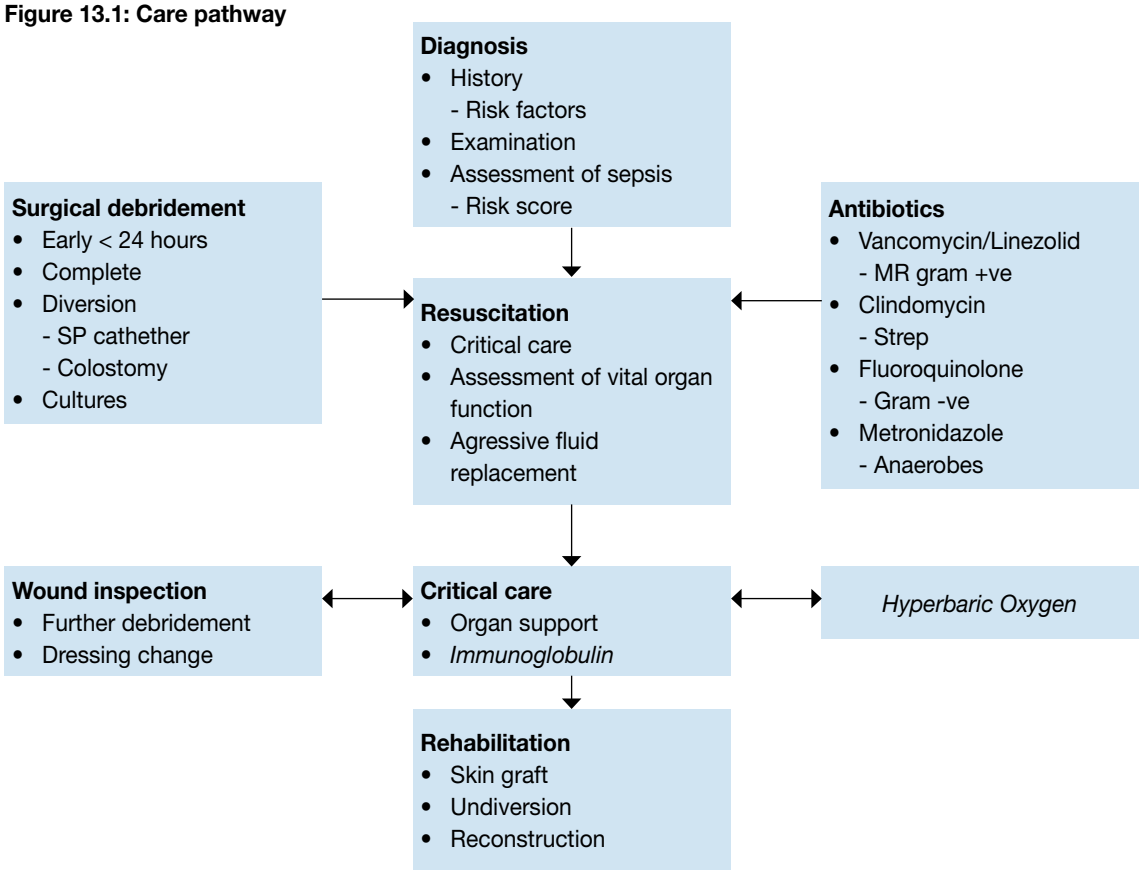
Fournier's gangrene is typically a type 1 necrotising fasciitis that is polymicrobial in origin, including *S. aureus, Streptococcus sp., Klebsiella sp.*, *E. coli* and anaerobic bacteria; involvement of Clostridium sp. is

now less common. These organisms secrete a variety of endotoxins that cause tissue necrosis and severe cardiovascular impairment. Subsequent inflammatory reaction by the host contributes to multi-organ failure and death if untreated.

13.5 Management

It is essential, first, to appreciate that the degree of internal necrosis is much greater than suggested by the external signs, and second, that adequate, repeated surgical debridement is necessary to save the patient's life (LE: 3, GR: B). Recently, severity scoring systems have been devised based on laboratory parameters to aid management, and cross-sectional imaging using CT or MRI can help define para-rectal involvement, which suggests 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: 3/4, 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 (LE: 3, not recommended grade C). With aggressive early surgical management, survival rates are > 70% depending upon patient group and availability of critical care (LE: 3). Following resolution, reconstruction using skin grafts is required.

Figure 13.1: Care pathway



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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 as 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***

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14.2 Urogenital schistosomiasis

More than 100 million people worldwide are affected by bilharziasis, which is caused by Schistosoma heamatobium. 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***

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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. 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/contaminated operations. 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
(The consequences in terms of antibiotic prophylaxis are given in Table 15.5)

Procedure	LE	GR	Remarks
Diagnostic procedures			
Cystoscopy	1b	A	Low frequency of infections Contradictory findings
Urodynamic study	1a	A	Low frequency of infections Contradictory findings
Transrectal core biopsy of prostate	1b	A	High risk of infection Assess carefully risk factors
Diagnostic ureteroscopy	4	C	No available studies
Therapeutic procedures			
TURB	2b	C	Poor data. No concern given to burden of tumor, i.e. size, multiplicity, necrosis
TURP	1a	A	Good documentation
SWL (standard, no risk factors such as the presence of a stent or nephrostomy tube)	1a/1b	A	Low frequency of infections Contradictory findings
Ureteroscopy stone	2b	B	Literature does not distinguish between severity of stone management
Percutaneous stone management	2b	B	High risk of infection
Open and laparoscopic surgery			
Clean operations (no opening of urinary tract)			
Nephrectomy	3	C	SSI poorly documented Catheter-related UTI
Scrotal surgery	3	C	Review studies contradictory
Prosthetic implants	3	B	Limited documentation Regimen not well defined
Clean-contaminated (opening of urinary tract)			
Nephroureterectomy	3	B	Poor documentation
Ureteropelvic junction repair	4	C	No studies detected

Total (radical) prostatectomy	2a	B	No RCT, poor documentation
Partial bladder resection	3	C	No specific RCT studies
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 have 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 9.7% of patients had a healthcare-associated UTI (10). The survey illustrated 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 are some clinical situations, however, that are not easily classified as either prophylaxis or therapy, e.g. patients with long-term indwelling catheters and bacteriuria. These patients must receive antibiotics at the time of surgery, regardless of how they are classified.

There is also a dilemma regarding the definition of infections. The US Centers for Disease Control and Prevention (CDC) have presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications (11). These definitions have also been used in the recent pan-European study on nosocomial UTI (10). Revision of definitions and recommendations are ongoing in some countries (12). 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

Site of infection	Minor	Major
Surgical wound Incision/surgical site infection (SSI)	Superficial wound infection	Deep wound infection Wound rupture (abdominal dehiscence) Deep abdominal or surgical site abscess
UTI or organ-specific infection	Asymptomatic bacteriuria (bacterial colonisation) Symptomatic lower UTI	Febrile UTI Pyelonephritis Renal abscess

Blood stream	Bacteremia without signs of systemic response	SIRS or sepsis with signs of systemic response
Septic embolism Other urogenital sites	Epididymitis (Orchitis)	Acute bacterial prostatitis (type I)
Other sites		Pneumonia

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) 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 (13) into clean, clean-contaminated, contaminated, and 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 (6,14,15).

Table 15.3: Generally accepted risk factors for infectious complications

General risk factors	Special risk factors associated with an increased bacterial load
Older age	Long preoperative hospital stay or recent hospitalisation
Deficient nutritional status	History of recurrent urogenital infections
Impaired immune response	Surgery involving bowel segment
Diabetes mellitus	Colonisation with microorganisms
Smoking	Long-term drainage
Extreme weight	Urinary obstruction
Coexisting infection at a remote site	Urinary stone
Lack of control of risk factors	

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 clearcut 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 (15,16). It is essential to individualise the choice of antibiotic prophylaxis according to each patient's cumulative risk factors (17). Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection (18-20).

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 from 2 h before but not later than 3 h after the start of an intervention (21-23). 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 (24). It is worth noting that a bloodstream infection can develop in less than an hour (21).

*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 between 1 and 2 h before intervention. Administration of the drug several hours before surgery is probably less effective. 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 (25). 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.

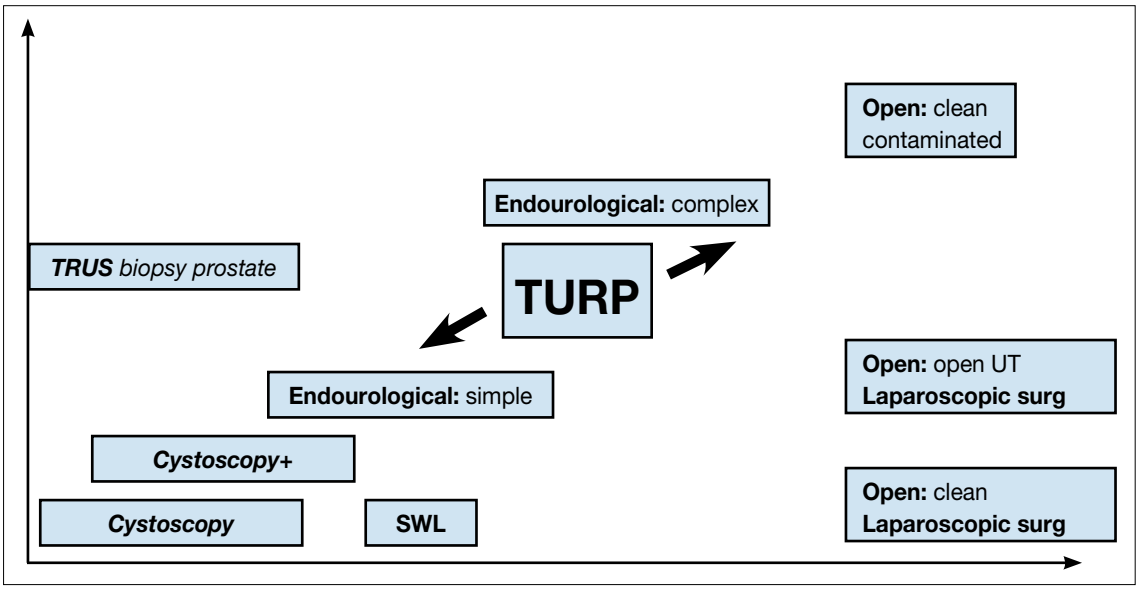
15.6 Prophylactic regimens in defined procedures

The list of major urological diagnostic and therapeutic procedures is given in Table 15.4 and 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 15.6.a and 15.6.b.

Table 15.4: List of urological interventions

Diagnostic procedures
• Fine-needle biopsy of the prostate
• Core-needle biopsy of the prostate
Cystoscopy
• Urodynamic examination
• Radiological diagnostic intervention of the urinary tract
• Ureteroscopy
Deviation procedures
• Insertion of indwelling catheter
• Insertion of suprapubic catheter
• Insertion of nephrostomy tube
• Insertion of ureteric stent
Endourological operations
• Resection of bladder tumour
• Resection of prostate
• Minimal invasive prostatic operation, i.e. microwave thermotherapy
• Ureteroscopy for stone or tumour fulguration
• Percutaneous stone or tumour surgery
SWL
Laparoscopic surgery
• Radical prostatectomy
• Pyeloplasty
• Nephrectomy and nephron-sparing surgery of the kidney
• Other major laparoscopic surgery, including bowel surgery
Open surgery
• Open surgery of the prostate, i.e. enucleation of prostatic adenoma
• Open stone surgery
• Pyeloplasty
• Nephrectomy and nephron-sparing surgery of the kidney
• Nephro-ureterectomy, including bladder resection
• Bladder resection
• Urethroplasty
• Implantation of prosthetic devices
• Urinary diversion procedures using intestinal segments

Figure 15.1: Level of invasiveness and risk of infection in urological procedures (empirical scheme) (5)



The recommendations for antibiotic prophylaxis in standard urological surgery are summarised in Table 15.5 and Appendix 16.4.

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 (26-41) (LE: 1b, GR: A).

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 (42-56) (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 (43,57,58) (LE: 2b, GR: C).

TURP 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 (15,59-61) (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 (62). 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 (63-70) (LE: 2b, GR: B).

SWL 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) (71-79) (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 (80-84) (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 (85-88). In open enucleation of prostatic adenoma, the risk of postoperative infection is particularly high (89) (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 (90-93) (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 (94-97) (LE: 2a, GR: B).

15.5 Recommendations for perioperative antibiotic prophylaxis in urology

Procedure	Pathogens (expected)	Prophylaxis	Antibiotics	Remarks
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes?	All patients	Fluoroquinolones TMP ± SMX Metronidazole?[1]	Single dose effective in low-risk patients. Consider prolonged course in high-risk patients
Cystoscopy Urodynamic examination	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd Generation	Consider in high-risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd generation	Consider in high-risk patients
Endourological surgery and SWL				
SWL	Enterobacteriaceae Enterococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI[a]	
SWL with stent or nephrostomy tube	Enterobacteriaceae Enterococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI[a]	Risk patients

Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones	Consider in risk patients
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones	Short course Length to be determined Intravenous suggested at operation
TURP	Enterobacteriaceae Enterococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Low-risk patients and small-size prostate probably do not require prophylaxis
TUR of bladder tumour	Enterobacteriaceae Enterococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Consider in high-risk patients and large tumours
Open or laparoscopic urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens	No		Consider in high-risk patients Short postoperative catheter requires no treatment
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Single perioperative course
Clean-contaminated/ contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	Cephalosporin 2nd or 3rd generation Metronidazole	As for colonic surgery
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients	Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)	

[1]No evidence for metronidazole in core biopsy of the prostate

[a] = Gram-negative bacteria excluding Pseudomonas aeruginosa

Table 15.6.a: Surgical Wound Classes and risk of wound infection modified for urological procedures. Tentative classification of urological instrumentation and procedures in relation to the different classes. The risk of wound infection as expressed in per cent is that of classical wound infection and not bacteriuria or clinical UTI in urological surgery. (Urogenital infections, EAU/ICUD, 2010, p 674-75)

Category of intervention (risk of surgical wound infection)	Description	Open or laparoscopic urological surgery (Examples)	Endoscopic urological instrumentation and surgery (examples)
Clean (1-4%)	Urogenital tract not entered No evidence of inflammation No break in technique Blunt trauma	Simple nephrectomy Planned scrotal surgery Vasectomy Varicocele surgery	Cystoscopy Urodynamic study TURB (minor, fulguration)* SWL*
Clean-contaminated (4-10%)	*Urogenital tract* entered with no or little (controlled) spillage No major break in technique	Pelvio-ureteric junction repair Nephron-sparing tumour resection Total/radical prostatectomy Bladder surgery and partial cystectomy Incl. Vaginal surgery	TURB (major, necrotic)* TURP* Diagnostic URS* Uncomplicated URS* and PCNL stone management SWL*
	Gastrointestinal tract entered with no or little (controlled) spillage No break in technique	Urine diversion (orthotopic bladder replacement; ileal conduit)	
Contaminated (10-15%)	Spillage of Gastrointestinal content Inflammatory tissue Major break in technique Open, fresh accidental wounds	Urine deviation (colon) and small intestine/spillage Trauma surgery Concomitant gastrointestinal disease	Core prostate biopsy* TURP* Impacted proximal stone management Complicated PCNL
Dirty (15-40%)	Pre-existing infection Perforated viscera at surgery Old traumatic wound	Drainage of abscess Large dirty trauma surgery	Infectious stone surgery

**Detailed description in table 15.6.b*

Table 15.6.b: Tentative list of essential criteria for assessment of surgical wound class/surgical field contamination level of common urological procedures: The estimated risk of infectious complication is related to the surgical class or category (Urogenital infections, EAU/ICUD, 2010, p 674-75)

Operation/ Category	TURB	TURP	Endoscopy Stone	SWL	Prostate biopsy
Clean	Small tumours No history UTI Sterile urine (similar cystoscopy)	-	Distal ureteral stone No history UTI Sterile urine No or minor obstruction No other RF	Standard ureteral or kidney stone No history UTI Sterile urine No or mild obstruction	-
Clean-contaminated	Large tumours History UTI Sterile urine	No history UTI/ UGI Sterile urine No catheter	All ureteral stone History UTI Sterile urine Minor/moderate obstruction No stent Other RF	Standard ureteral or kidney stone History UTI Sterile urine Moderate obstruction Other RF	*Transperineal* Sterile urine No history UTI/UGI
Contamin-ated	Large tumours Necrosis Bacteriuria controlled	History UTI/UGI Catheter prior to surgery Bacteriuria controlled	Proximal impacted stone History UTI Sterile urine or Controlled bacteriuria Moderate obstruction Stent/catheter	Complex stone History UTI Obstruction Bacteriuria controlled Stent or nephrostomy tube	*Transperineal* Sterile urine History UTI/ UGI *Transrectal* No- or history UTI/UGI Sterile urine
Dirty	Clinical infected Emergency	Clinical infected Emergency	Clinical infected Drainage only	Clinical infected Drainage only	*Transrectal* Presence of catheter or bacteriuria

**UTI = urinary tract infection; UGI = urogenital infection (i.e. prostatitis); RF = risk factor.*

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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)

Category	Description	Clinical features	Laboratory investigations
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/mm^3 > 10^3 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/mm^3 > 10^4 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/mm^3 > 10^5 cfu/mL* in women > 10^4 cfu/mL* in men, or in straight catheter urine in women
4	Asymptomatic bacteriuria	No urinary symptoms	> 10 WBC/mm^3 > 10^5 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	< 10^3 cfu/mL*

All pyuria counts refer to unspun urine.
**Uropathogen in MSU culture.*

16.1.1 ***References***

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16.2 Recommendations for antimicrobial therapy in urology

Diagnosis	Most frequent pathogen/species	Initial, empirical antimicrobial therapy	Therapy duration
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 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 Candida: • Fluconazole • Amphotericin B	3-5 days after defervescence or control/elimination of complicating factor
Nosocomial UTI	• *Klebsiella* • *Proteus*		
Pyelonephritis severe acute, complicated	• *Enterobacter* • Other enterobacteria • *(Candida)*		
Prostatitis acute, chronic	• *E. coli* • Other enterobacteria • *Pseudomonas* • Enterococci Chronic: • 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 acylaminopenicillin/BLI • Carbapenem • ± Aminoglycoside	Acute: 2-4 weeks Chronic: 4-6 weeks or longer 3-5 days after defervescence or control/elimination of complicating factor
Epididymitis Ureaplasma: Acute			
Urosepsis			

[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

Antibiotic	GFR (mL/min)			Comments
	Mild 50-20	**Moderate** 20-10	**Severe** < 10	
*Aciclovir	normal dose every 12 h	normal dose every 24 h	50% of normal dose every 24 h	Give post-HD
Aciclovir po	normal	Herpes simplex: normal Herpes zoster: 800 mg Total Dissolved Solids tds	Herpes simplex: 200 mg bid Herpes zoster: 800 mg bd	Give post-HD
Amikacin	5-6 mg/kg 12 h	3-4 mg/kg 24 h HD: 5mg/kg post HD and monitor levels	2 mg/kg 24-48 h	Give post-HD Monitor pre- and 1 h post-dose levels after 3rd dose and adjust dose as required
Amoxicillin po	normal	normal	250 mg 8 h (normal)	Give post-HD
Amphotericin	normal	normal	normal	
(Liposonal + lipid complex)	Amphotericin is highly NEPHROTOXIC. Consider using liposomal/lipid complex amphotericin. Daily monitoring of renal function (GFR) essential.			
Ampicillin IV	normal	250-500 mg 6 h	250 mg 6 h (500 mg 6 h)	Give post-HD
Benzylpenicillin	normal	75%	20-50% Max. 3.6 g/day (1.2 g qds)	Give post-HD Refer to microbiology for dosing in SBE
Caspofungin	normal	normal	normal	
Cefotaxime	normal	normal	1 g stat then 50%	Give post-HD
Cefradine	normal	Normal	250 mg 6 h	Give post-HD
Ceftazidime	1 g 12 h	1 g 24 h	500 mg 24 h (1 g 24 h)	Give post-HD
Ceftriaxone	normal	normal	normal Max. 2 g/day	
Cefuroxime IV	normal	750 mg-1.5 g 12 h	750 mg 24 h (750 mg 12 h)	Give post-HD
Ciproflazin IV + po	normal	50%	50%	
Clarithromycin IV + po	normal	normal	50%	Give post-HD
Clindamycin IV + po	normal	normal	normal	
Co-amoxiclav IV (Augmentin)	normal	1.2 stat then 50% 12 h (1.2 g 12 h)	1.2 stat then 50% 24 h (1.2 g stat then 600 mg 12 h)	Give post-HD
Co-amoxiclav po (Augmentin)	normal	375-625 mg 12 h (375 mg 8 h)	375 mg 12 h (375 mg 8 h)	Give post-HD
*Co-trimoxazole IV	normal	Normal for 3/7 then 50%	50%	Give post-HD

Doxycycline	normal	normal	normal	All other tetracyclines contraindicated in renal impairment
Erythromycin IV + po	normal	normal	normal Max. 1.5 g/day (500 mg qds)	
*Ethambutol	normal	24-36 h	48 h	Give post-HD
	Monitor levels if GFR < 30mL/min (contact Mirco)			
Flucloxacillin IV + po	normal	normal	normal Max. 4 g/day	
Fluconazole	normal	normal	50%	Give post-HD No adjustments in single-dose therapy required
*Flucytosine	50 mg/kg 12 h	50 mg/kg 24 h	50 mg/kg stat then dose according to levels	Give post-HD Levels should be monitored predialysis.
Fusidic acid	normal	normal	normal	
1) Gentamicin ONCE DAILY	**GFR 10-40 mL/min** 3 mg/kg stat (max. 300 mg) Check pre-dose levels 18-24 h after first dose Redose only when level < 1 mg/L		**GFR < 10 mL/min** 2 mg/kg (max. 200 mg) redose according to levels	BOTH METHODS Give post-HD Monitor blood levels:
2) Gentamicin CONVENTIONAL	80 mg 12 h	80 mg 48 h	80 mg 24 h HD: 1-2 mg/kg Post-HD: redose according to levels	Once daily: pre only Conventional: pre and 1 h post level required.
Imipenem	500 mg 8-12 h	250-500 mg bid	Risk of convulsions - use Meropenem: *see below*	Give post-HD
Isoniazid	normal	normal	200-300 mg 24 h	Give post-HD
Itraconazole	normal	normal	normal	
Levoflaxacin	500 mg stat then 250 mg bid**	500 mg stat then 125 mg bid**	500 mg stat then 125 mg od	**Applies if full dose is 500 mg bid If full dose is 500 mg od, five reduced doses daily
Linezolid	normal	normal	normal	Give post-HD
Meropenem	12 h	50% 12 h	50% 24 h	Give post-HD
Metronidazole	normal	normal	12 h (normal)	Give post-HD
Nitrofurantoin	Do **NOT** use in renal impairment			
Penicillin V	normal	normal	normal	Give post-HD
Piperacillin/ Tazobactam (Tazocin)	4.5 g 8 h	4.5 g 12 h	4.5 g 12 h	Give post-HD
Pyrazinamide	normal	normal	normal	
Rifampicin	normal	normal	50-100%	

*Teicoplanin	100% 48 h	100% 72 h	100% 72 h	Dose reduction after day 3 of therapy
Tetracycline	See **Doxycycline**			
Trimethoprim	normal	Normal for 3/7 then 50% 18 h	50% 24 h	Give post-HD
Vancomycin	1 g od Check pre-dose level before 3rd dose	1 g 48 h Check pre-dose level before 2nd dose	1 g stat (or 15 mg/kg, up to max. 2 g). Recheck level after 4-5 days ONLY give subsequent dose when level < 12mg/L	Monitor pre-dose levels and adjust dose as required
Vorinconazole	normal	normal	normal	Give post HD

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 Recommendations for perioperative antibiotic prophylaxis in urology

Procedure	Pathogens (expected)	Prophylaxis	Antibiotics	Remarks
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes?	All patients	Fluoroquinolones TMP ± SMX Metronidazole?[1]	Single dose effective in low-risk patients. Consider prolonged course in high-risk patients
Cystoscopy Urodynamic examination	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd Generation	Consider in high-risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd generation	Consider in high-risk patients
Endourological surgery and SWL				
SWL	Enterobacteriaceae Enterococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI[a]	
SWL with stent or nephrostomy tube	Enterobacteriaceae Enterococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI[a]	Risk patients
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones	Consider in risk patients
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones	Short course Length to be determined Intravenous suggested at operation

TURP	Enterobacteriaceae Enterococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Low-risk patients and small-size prostate probably do not require prophylaxis
TUR of bladder tumour	Enterobacteriaceae Enterococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Consider in high-risk patients and large tumours
Open or laparoscopic urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens	No		Consider in high-risk patients Short postoperative catheter requires no treatment
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Single perioperative course
Clean-contaminated/ contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	Cephalosporin 2nd or 3rd generation Metronidazole	As for colonic surgery
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients	Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)	

[1]No evidence for metronidazole in core biopsy of the prostate.

[a] = gram-negative bacteria excluding Pseudomonas aeruginosa.

16.5 CPSI

from: Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun MA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. The National Institute of Health chronic prostatitis symptom index: development and validation of new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999:162;369-375.

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?

	Yes	No
a. Area between rectum and testicles (perineum)	☐ 1	☐ 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:

	Yes	No
a. Pain or burning during urination?	☐ 1	☐ 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 — 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

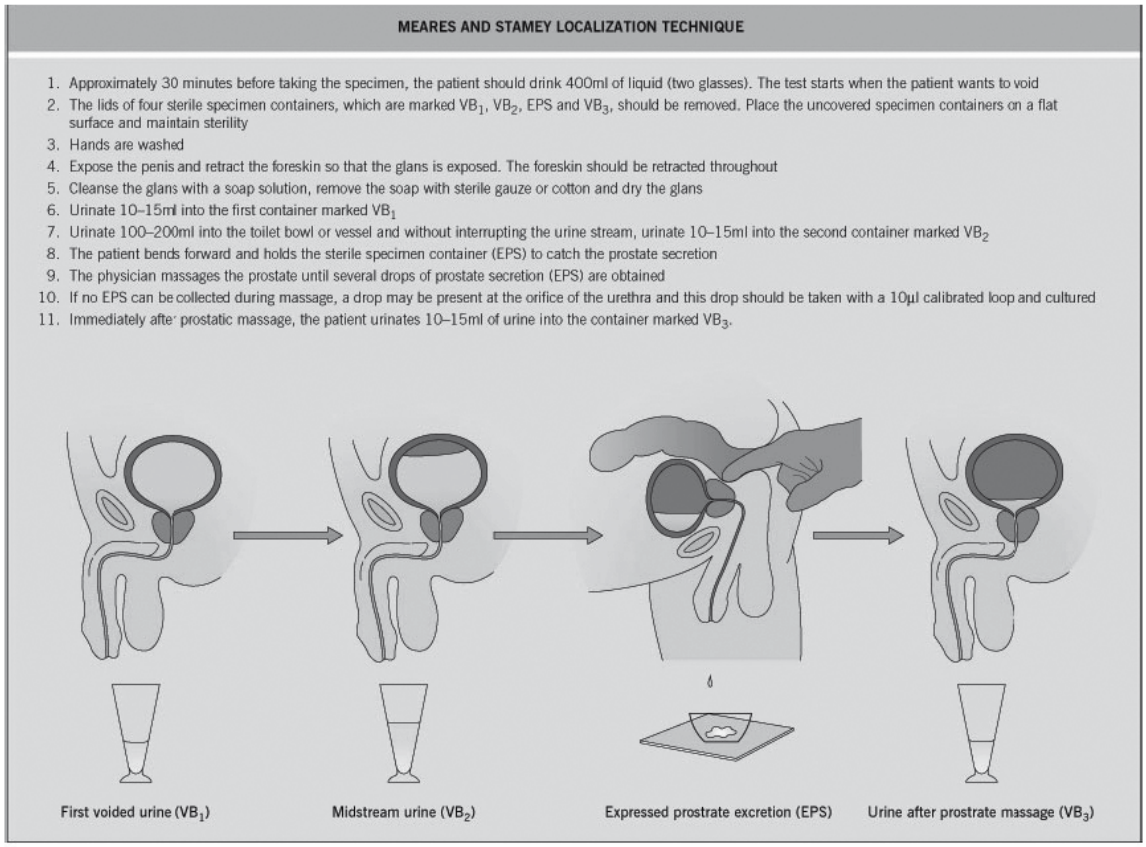
Scoring the NIH-CPSI Prostatitis Symptom Index Domain

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 = _____

16.6 Meares & Stamey localisation technique*



* Naber KG, Weidner W. Prostatitis, epididymitis, orchitis. In: Armstrong D, Cohen J, eds. Infectious Diseases. London: Mosby, Harcourt Publishers Ltd, 1999, pp. 1-58.

16.7 Antibacterial agents

Groups	Agents
Trimethoprim-sulphonamide combinations	Trimethoprim, co-trimoxazole, co-tetroxoprime (trimethoprim plus sulfametrol)
Fluoroquinolones[1,2]	
Group 1	Norfloxacin, pefloxacin
Group 2	Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin
Group 3	Levofloxacin
Group 4	Gatifloxacin, moxifloxacin
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
Tetracyclines	Doxycycline, minocycline, tetracycline
Fosfomycin	Fosfomycin sodium, fosfomycin trometamol3
Nitrofuran[4]	Nitrofurantoin
Penicillins	
Benzylpenicillin	Penicillin G
Phenoxypenicillins	Penicillin V, propicillin, azidocillin
Isoxazolylpenicillins	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin
Aminobenzylpenicillins[5]	Ampicillin, amoxycillin, bacampicillin
Aminopenicillins/BLI[6]	Ampicillin/sulbactam, amoxycillin/clavulanic acid[7]

Acylaminopenicillins	Mezlocillin, piperacillin
±BLI[6]	Piperacillin/tazobactam, sulbactam[6]
Cephalosporins[1]	
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

[1]Classification according to the Paul Ehrlich Society for Chemotherapy (1-3).
[2]Only in adults, except pregnant and lactating women.
[3]Only in acute, uncomplicated cystitis as a single dose.
[4]Contraindicated in renal failure and in newborns.
[5]In cases of resistance, the pathogen is most likely to be a β-lactamase producer.
[6]BLIs can only be used in combination with β-lactam antibiotics.
[7]In solution, storage instability.

16.7.1 ***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.

16.7.1.1 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.

16.7.1.2 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.

16.7.1.3 Isoxazolylpenicillins

Isoxazolylpenicillins are available as parenteral drugs with oxacillin and flucloxacillin, and have a narrow

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.

16.7.2 ***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).

16.7.2.1 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).

16.7.2.2 Group 2 cephalosporins

Compared with Group 1 cephalosporins, Group 2 cephalosporins, e.g. cefuroxime, cefotiame and cefamandole, exhibit markedly improved activity against Gram-negative pathogens and maintain high activity against staphylococci.

16.7.2.3 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.

16.7.2.4 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.

16.7.2.5 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.

16.7.2.6 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 16.7.2: Classification of parenteral cephalosporins (2)

Group	Generic names	Features of the group
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 Cefotiame 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 Ceftizoxime 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	• Spectrum of antibacterial activity similar to that of Group 3a
	Cefoperazone	• Additional activity against P. aeruginosa
Group 4	Cefepime Cefpirome	• Spectrum of antibacterial activity similar to that of Group 3a
Group 5	Cefoxitin	• 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

16.7.3 ***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)

Oral cephalosporins	Drug names
Group 1	Cefalexin Cefadroxil Cefaclor
Group 2	Cefprozil Loracarbef Cefuroxime axetile
Group 3	Cefpodoxime proxetile Cefetamet pivoxile Ceftibuten Cefixime

16.7.3.1 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.

16.7.3.2 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.

16.7.3.3 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.

*16.7.4 **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.

*16.7.5 **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.

*16.7.6 **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 16.7.4).

Table 16.7.4: Classification of fluoroquinolones, as modified according to the Paul Ehrlich Society for Chemotherapy (3)

Generic name	**Trade name* / features of the group**
Group 1	**Indications essentially limited to UTIs in some countries, e.g. Germany**
	Norfloxacin
	Pefloxacin**
Group 2	**Broad indications for systemic use**
	Enoxacin
	Fleroxacin***
	Lomefloxacin
	Ofloxacin
	Ciprofloxacin

Group 3	Improved activity against Gram-positive and atypical pathogens
	Levofloxacin
Group 4	Improved activity against Gram-positive and atypical pathogens and anaerobes
	Gatifloxacin
	Moxifloxacin

** 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.*

16.7.6.1 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.

16.7.6.2 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.

16.7.6.3 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%.

16.7.7 ***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.

16.7.8 ***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.

16.7.9 ***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.

16.7.10 ***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*.

16.7.11 ***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*.

16.7.12 ***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.

16.7.13 ***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.

16.7.14 ***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.

16.7.15 ***References***

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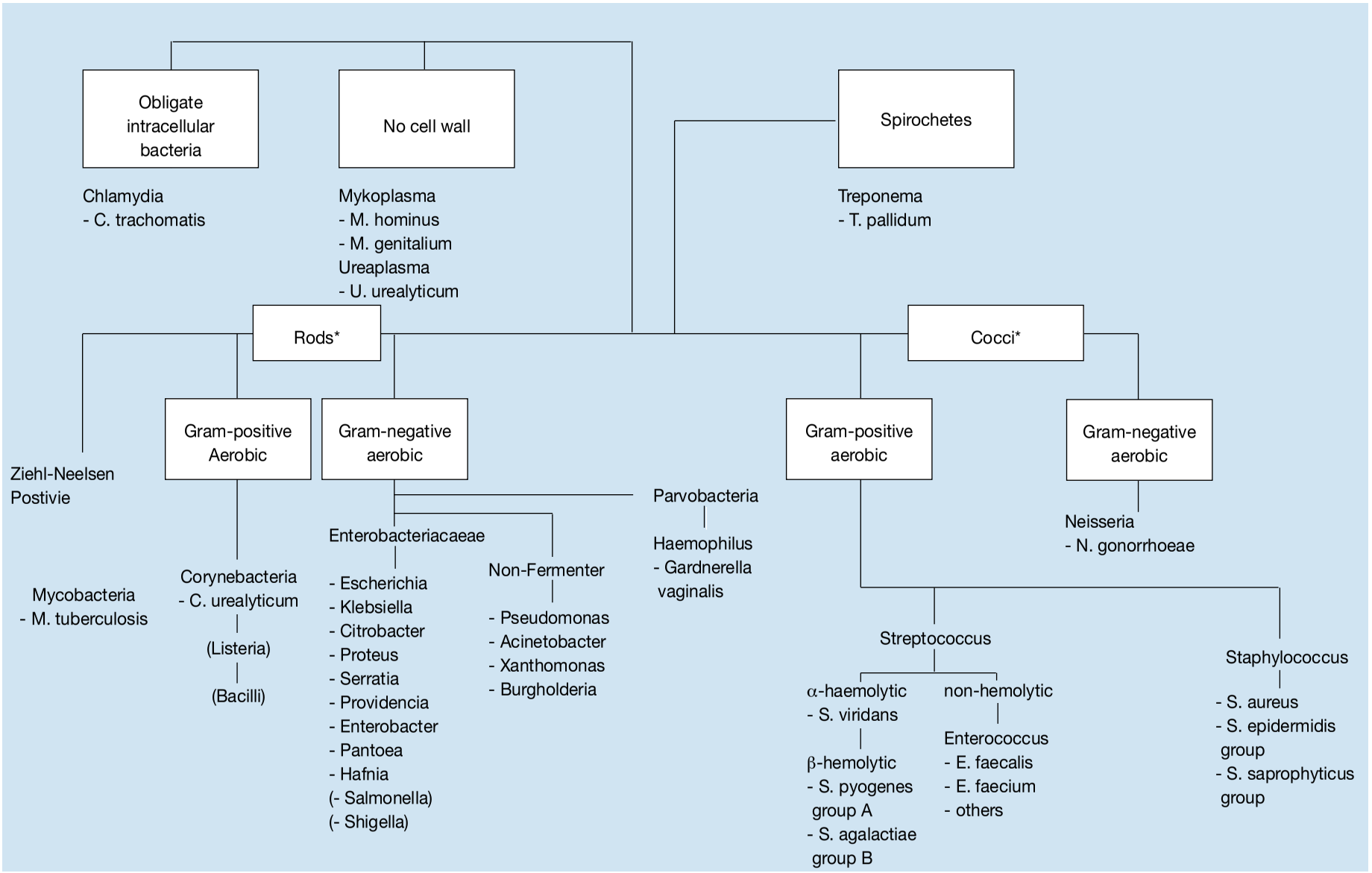
4. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999 Oct;29(4):745-58. http://www.ncbi.nlm.nih.gov/pubmed/10589881

16.8 Relevant bacteria for urological infections



**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	mercaptoacethylglycine
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 cysto-urethography
VUR	vesicoureteric reflux
WBC	white blood cells

Conflict of interest

All members of the Urological Infections guidelines working group have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the EAU Central Office database. This guidelines document was developed with the financial support of the EAU. 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 Urinary Incontinence

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European Association of Urology

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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 being used and the populations being studied. However, there is universal agreement about the importance of the problem, both in terms of human suffering and economic costs.

These new 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 guidance on the clinical problems of UI rather than an exhaustive narrative review. Such a review is already available elsewhere, as provided by the International Consultation on Incontinence (1), and so these Guidelines do not mention topics such as 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 only a little evidence for some issues and a lot of evidence for others. This difference largely reflects the much greater research funding needed to produce the high-quality evidence required for regulatory submissions by the regulated (pharmaceutical) industries and their marketing strategies. The situation regarding published evidence for surgical devices is different, with much more surgical experimentation. However, despite the higher potential for harm, there are far fewer high-quality studies from which to derive clear evidence. There is a high potential for bias in this situation, and so the Panel has deliberately adjusted its expectation for quality evidence, depending on the domain of management being considered, and tried to reflect this in the text.

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 reliable summary of the current state of evidence on clinical topics, complete with references to the original text.
- 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 published 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 is important because it directs the subsequent literature research. For each element, the Panel listed every possible wording variation.

In these Guidelines, four traditional domains of urological practice are presented as separate chapters, namely assessment and diagnosis, conservative management, drug therapy and surgical treatments.

In this first 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 first edition does not review the prevention of UI, the management of fistula, or the special problems of the frail elderly, but these issues will be fully addressed in future editions.

*1.1.2 **Search strategies***

A number of significant narrative reviews and major guidelines and systematic reviews have been produced within the last few years. It was agreed from the start 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 (*see* Number of 'hits', Table 1). 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: Initial list of abstracts

Chapter	Latest 'cut-off' date for search	Number of 'hits'
Assessment and diagnosis	June 2010	1055
Conservative therapy	July 2010	1026
Drug therapy	February 2011	1162
Surgical therapy	May 2011	2191

Each PICO was then assigned to a Panel member, who read the paper 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 review of the literature.

The existing evidence from previous systematic reviews and new evidence were then discussed, for each PICO in turn, at a Panel meeting before the Panel came to its 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, which then leads into the development of an evidence summary. This aims to synthesise the important clinical messages from the available literature and is presented as a series of 'evidence summaries', which follow the standard for levels of evidence used by the EAU (Table 2).

From the evidence summaries, the Panel then produced a series of action-based recommendations 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 guidelines 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 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)*

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

**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, this can be made. 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 economic cost 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)*

Nature of recommendations	GR
Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.	A
Based on well-conducted clinical studies, but without randomised clinical trials.	B
Made despite the absence of directly applicable clinical studies of good quality.	C

**Modified from Sackett et al. (5).*

1.2 Publication history

The complete update in 2009 was largely a synthesis of ICUD and NICE and so was the 2010 edition. In 2011 an addendum was added on the use of drugs, now incorporated in the full text under Chapter 4. This 2012 edition is also partly based on ICUD and NICE but new searches were conducted from June 2008 to present. An addendum to the guidelines is provided on mixed urinary incontinence (see Appendix).

1.3 References

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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 the 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.

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.
- **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 incontinence, associated voiding, and other urinary symptoms. The history should allow the UI to be categorised into stress, urgency or mixed. 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. 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 comorbid conditions, as these may impact on symptoms of UI, or cause it, and details of current medications.

There is little evidence for the necessity to carry out a clinical examination. However, there is wide agreement that clinical examination is essential. In a patient with UI, this should include abdominal examination, to detect an enlarged bladder or other abdominal mass, and perineal and digital examination of the rectum

and/or vagina. Examining the perineum includes an assessment of oestrogen status in women and a careful assessment of any associated genitourinary prolapse. A cough test will often reveal stress incontinence, but only if the bladder contains urine during the examination. Pelvic floor contraction is assessed by means of digital vaginal examination. In men, it is essential to perform a digital examination of the rectum and prostatic assessment.

2.2 Patient questionnaires

Questionnaires may be symptom scores, symptom questionnaires, patient-reported outcome measures (PROMS) or health-related quality of life (HRQoL) measures. Questionnaires are widely used to record patients' symptoms, including their severity and impact on the patient, and have been used to monitor the symptom scores of individual patients or groups of patients over time, e.g. in the context of changes related to treatment. During the last 10 years, many questionnaires have been developed and studied, including ones specifically designed for lower urinary tract symptoms (LUTS), pelvic organ prolapse, faecal incontinence and both condition-specific quality of life (QoL) and generic QoL. The methodology for their development was reviewed in the 4th International Consultation on Incontinence (ICI) 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.

Evidence summary	**LE**
There is no evidence that the use of either questionnaires or PROMs in the assessment of adults with UI has an influence on outcome.	4

*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.

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2.3 Voiding dairies

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 daytime and night-time frequency, urgency, urgency urinary incontinence (UUI) and stress urinary incontinence (SUI) 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.

Any discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency or UI, can be useful in patient management. 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.

*2.3.1 **Questions***

- In adults with UI, what is the reliability, the 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 incontinence.

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 (8,9). 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	**LE**
Voiding diaries of 3-7 days duration are a reliable tool for quantifying mean voided volume, daytime and night-time frequency.	2b
Voiding diaries are sensitive to change and are a reliable measure of outcome.	2b

Recommendations	**GR**
Voiding diaries should be used in urinary incontinence to evaluate co-existing storage and voiding dysfunction in clinical practice and in research.	A
A diary duration of between 3 and 7 days is recommended.	B

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2.4 Urinalysis and urinary tract infection

Urinary incontinence is known to occur more commonly in women with UTIs and is also more likely in the first few days following an acute infection (1). In contrast with symptomatic UTI, asymptomatic bacteriuria appears to have little influence on UI. A study carried out in nursing home residents showed that the severity of UI was unchanged after eradication of bacteriuria (2).

Reagent strip ('dipstick') urinalysis may detect infection, proteinuria, haematuria and glycosuria:

- Nitrite and leucocyte 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 analysis of initial voided and terminal urine samples may be required for 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 on UI of treating UTIs?

*2.4.2 **Evidence***

In both men and women with UI, diagnosis of a UTI by positive leucocytes or nitrites 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 gender, age or aetiology.

Evidence summary	**LE**
There is no evidence that a UTI causes UI.	4
There is no evidence that treating a UTI cures UI.	4
The presence of a symptomatic UTI worsens symptoms of UI.	3
Elderly nursing home patients with established UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	**GR**
Do urinalysis as a part of the initial assessment of a patient with urinary incontinence.	A
In a patient with urinary incontinence, treat a symptomatic urinary tract infection appropriately *(see 'EAU Guidelines on Urological Infections' [5]).*	A
Do not treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.	B

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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.

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 US measurement of PVR is better than measurement using catheterisation.

Several studies have evaluated PVR in different subjects and patients cohorts (7-17). In peri- and post-menopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL (7). A comparison of women with and without LUTS suggested that symptomatic women had a higher incidence of elevated PVR (9). In women with UUI, a PVR > 100 mL was found in 10% of cases (8). Other research has found that a high PVR is associated with pelvic organ prolapse (> stage II), voiding symptoms and an absence of SUI (10,11,13,15). In women with SUI, the mean PVR was 38.5 mL measured by catheterisation and 62.8 mL measured by US, with 15.9% of women having a PVR > 100 mL (8). Overall, women with symptoms of lower urinary tract or pelvic floor dysfunction and pelvic organ prolapse have a higher risk 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 a definition of elevated PVR values (22-25).

There is a lack of evidence to support the routine measurement of PVR in patients with UI (26-30).

Evidence summary	**LE**
Ultrasonography provides an accurate estimate of post-voiding residual.	1b
Lower urinary tract dysfunction is associated with a higher risk of post-voiding residual compared to controls.	2
Elevated post-voiding residual is not a risk factor for poor outcome in the management of SUI.	2

Recommendations	**GR**
Post-voiding residual should be measured by ultrasound.	A
Measure post-voiding residual in patients with urinary incontinence who have voiding dysfunction.	B
Measure post-voiding residual when assessing patients with complicated urinary incontinence.	C
Post-voiding residual should be monitored in patients receiving treatments that may cause or worsen voiding dysfunction.	B

*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.

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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 videourodynamics, 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 videourodynamics 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 a urodynamically measurable phenomenon. Despite these uncertainties, urodynamic testing is still used to establish an uncertain 'diagnosis', to direct decisions about treatment and to provide prognostic information.

*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_{max}) and urodynamic testing?

2.6.2 ***Evidence***

2.6.2.1 Repeatability

Many studies have examined test-retest reliability for a range of urodynamic parameters, including eight studies on cystometry/pressure flow studies (1-8). 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 (9-11).

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 (12-17).

Studies of technical accuracy have included adults with LUTS, with or without UI. The studies used different equipment and lacked standardised techniques (18,19). As with all physiological investigation, results have shown a wide range of variability.

Inter-rater and intra-rater reliability of videourodynamics for the severity and type of SUI is good (20).

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.

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, the National Institute for Health and Clinical Evidence (NICE) reviewed 11 studies (21), which investigated the relationship between clinical diagnosis and urodynamic findings and the diagnostic accuracy of urodynamic measurement, specifically in females. The Panel found no new evidence had been published since 2005 up until July 2011.

There is a consensus that urodynamic tests should aim to reproduce the patient's symptoms. If they do not, the findings are inevitably inconclusive. There is also a consensus that attention to technical and methodological detail during urodynamic testing may increase the accuracy of urodynamics in recording usual bladder behaviour.

In clinical practice, urodynamic testing (cystometry) may help to provide, or confirm, a diagnosis, predict treatment outcome, or facilitate discussion during a consultation.

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 (22).

A few RCTs have investigated the ability of urodynamics to predict treatment decisions or treatment outcomes following conservative management. In 2009, a Cochrane review examined three small RCT studies, two of which were reported as abstracts (23,24). A further RCT, not included in the Cochrane review, also compared patients who underwent urodynamics with those who did not, though they did have urodynamics later in their care (25). Since then, another RCT addressing the same question has been published (26). Patients who underwent urodynamics were more likely to be treated by surgery or drugs or to have a change in their treatment (23). However, urodynamic tests made no difference to the outcomes of conservative treatment, including antimuscarinic therapy (27,28).

2.6.2.4 Does urodynamics influence the outcome of surgery for SUI?

There have been no RCTs specifically addressing this question, though trials are currently underway. Several case series have examined a possible relationship between individual urodynamic parameters and the subsequent success or failure of surgical treatment for SUI. Most were low-quality small studies. Post-hoc analysis of an RCT on surgery for SUI failed to confirm a predictive value for urodynamics, though the success rate for patients with urodynamic SUI exceeded that for women without urodynamic SUI (29).

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 (30-33). A correlation, in itself, was not necessarily predictive.

2.6.2.5 Does urodynamics help to predict complications of surgery?
There have been no RCTs. A large number of case series, or post-hoc analyses of larger studies, have examined the relationship between urodynamic parameters and surgical outcome for SUI. A low Q_{max} or low pressure voiding has been inconsistently associated with post-operative voiding difficulty (34-40). However, the predictive value has rarely been calculated.

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 (41). However pre-operative urodynamics had failed to predict this outcome (29). Other case series, however, have shown a consistent association of poor outcomes with pre-operative DO, though the predictive value was not calculated (42,43).

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 (30,44,45). Pre-operative urgency was resolved in some patients (46,47).

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 incontinence. However, many case series have demonstrated the ability of urodynamics to distinguish between different causes of UI (48-50). The ability of urodynamic testing to predict surgical outcome for post-prostatectomy incontinence is inconsistent (51,52).

Evidence summary	**LE**
Most urodynamic parameters show a high random immediate and short-term test-retest variability of up to 15% in the same subject.	2
Test-retest variability creates an overlap between 'normal' and 'abnormal' populations, which may make it more difficult to categorise urodynamic findings in a particular individua.l	2
Different techniques of measuring urethral function may perform reliably from one test to another, but do not reliably correlate to other tests and to the severity of UI.	3
The accuracy of ambulatory urodynamics remains uncertain.	4
There may be inconsistency between history and urodynamic results.	3
Preliminary urodynamics do not affect the outcome of conservative therapy for UI.	1a
There is limited evidence about whether preliminary urodynamic testing predicts surgical outcomes in adults with UI.	3
There is conflicting low-level evidence that tests suggesting poor urethral function predict surgery failure for SUI in women.	3
There is consistent low-level evidence that pre-operative DO predicts failure of mid-urethral sling surgery in women.	3
There is no evidence about whether preliminary urodynamics predicts outcomes of treatment for UI in men.	4

Recommendations	**GR**
Clinicians carrying out urodynamics in patients with urinary incontinence should: • Ensure that the test replicates patient's symptoms • Interpret results in context of the clinical problem • Check recordings for quality control • Remember there may be physiological variability within the same individual.	C

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.	C
Do not routinely carry out urodynamics when offering conservative treatment for urinary incontinence.	B
Perform urodynamics if the findings may change the choice of surgical treatment.	C
Perform urodynamics prior to surgery for urinary incontinence if there are either symptoms of overactive bladder, a history of previous surgery or a suspicion of voiding difficulty.	C
Do not routinely carry out urethral pressure profilometry.	C

2.6.3 ***Research priority***

Future studies should address whether any urodynamic test influences the choice between treatments or prediction of the outcome of treatment.

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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 (6,7-11).

A few studies have tried to use pad testing to predict the outcome of treatment for UI with variable results (12,13). 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 (14,15). There is good evidence to show that repeat pad testing can detect change following treatment for UI (16-18).

Evidence summary	**LE**
A pad test can diagnose UI accurately, is reproducible and correlates with patients' symptoms.	1b
A pad test cannot differentiate between causes of UI.	4
An office-based pad test requires standardisation of bladder volume and a predefined set of exercises to improve diagnostic accuracy.	1b
A pad weight gain > 1 g in a 1-hour test can be used as a threshold to diagnose UI.	2b
Patient adherence to home pad testing protocols is poor.	1b
A weight gain > 1.3 g in a 24-hour home-based test can be used as a diagnostic threshold for UI.	1b
Home-based pad tests longer than 24 hours provide no additional benefit.	2b
Repeat pad tests can indicate treatment outcome.	1b

Recommendations	**GR**
Use a pad test when quantification of urinary incontinence is required.	C
Use repeat pad test if objective treatment outcome measure is required.	C

2.7.3 ***Research recommendation***

A systematic review of pad testing at home and in the office would clarify its role in routine care.

2.7.4 ***References***

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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.

Ultrasonography and magnetic resonance imaging (MRI) have replaced X-ray imaging as both procedures are safer than X-ray imaging 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***

- Can imaging aid selection of surgical procedure for SUI?
- How accurate is imaging in evaluating the outcome of UI surgery?

*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 pelvic organ prolapse, 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 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).

However, in conclusion, no studies were found which specifically addressed the PICO questions 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).

Evidence summary	LE
Imaging can reliably measure bladder neck and urethral mobility, although there is no evidence of any clinical benefit in patients with UI.	2b
Imaging of the pelvic floor can identify levator ani detachment and hiatus, although there is little evidence of clinical benefit.	2b
Ultrasonography can image mid-urethral slings, although more research is needed into the relationship between sling position and surgical outcome.	2b

Recommendation	GR
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of uncomplicated SUI in women.	A

2.8.3 ***References***

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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 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 that 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 change in an underlying disease has affected a patient's UI.

3.1.1.1 Question

In adults with UI, does correcting an underlying disease or cognitive impairment improve UI or QoL compared to no correction of underlying disease?

3.1.1.2 Evidence

We found only one study that directly addressed the question. The study was a follow-up of an earlier RCT. 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.

Evidence summary	**LE**
Improved diabetic control neither resolves nor improves UI.	3

3.1.1.3 References

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3.1.2 ***Adjustment of medication***

Although UI is listed as an adverse effect in many drug compendiums, e.g. *British National Formulary*, this is mainly due to 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. It is therefore not possible in most cases to be sure that a drug causes incontinence.

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.

3.1.2.1 Question

In adults with UI, does adjustment of medication improve UI or QoL 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 started on 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). Limited evidence from case series and case-control studies suggests that diuretic therapy is not associated with a higher incidence or worsening of UI (2). It is possible that SUI may be worsened by the development of the chronic cough sometimes associated with ACE inhibitors prescribed for heart failure or hypertension.

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, as there has been a decline in the use of oestrogen replacement therapy by post-menopausal women, due to concerns about developing cancer and the association of oestrogen replacement therapy with UI.

Evidence summary	LE
Alpha-blockers used to treat hypertension in women may cause or exacerbate UI, and stopping them may relieve UI.	3
Individuals taking drugs acting on the central nervous system may experience UI as a side effect.	3
Diuretics in elderly patients does not cause or worsen UI.	3
Systemic oestrogen replacement therapy in previously continent women approximately doubles the prevalence of UI at 12 months compared to placebo.	1b
Women with pre-existing UI, who use systemic oestrogen replacement therapy, are 30% more likely to experience worsening UI compared to placebo.	1a

Recommendations	GR
Take a drug history from all patients with urinary incontinence.	A
Inform women with urinary incontinence that begins or worsens after starting systemic oestrogen replacement therapy that it may cause urinary incontinence.	A
Review any new medication associated with the development or worsening of urinary incontinence.	C

3.1.2.3 References

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*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 therapy improve symptoms or QoL in patients with 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 constipation and UI (1). Another study found bowel function improved after successful treatment of voiding problems with sacral nerve stimulation (2). A different study recommended the simultaneous treatment of constipation and urinary disorders in children and adolescents with LUTS.

An observational study comparing women with UI and women with pelvic organ prolapse 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 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.

Evidence summary	LE
There is a consistent association between a history of constipation and the development of UI and pelvic organ prolapse.	3
There is no evidence that treatment of constipation improves UI.	4
Multimodal behavioural therapy improves both constipation and UI in the elderly.	1b
Simultaneous treatment of constipation and urinary incontinence in adolescents is beneficial.	3

Recommendation	GR
For adults with UI, treat co-existing constipation.	C

3.1.3.3 References

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*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, bladder spasm, stone formation, etc.

3.1.4.1 Question

In adults with UI, does urinary containment improve patient outcomes, regarding either urinary symptoms or QoL, compared with 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 (11) evaluated different penile clamps and showed that none completely controlled urine leakage, but penile blood flow was reduced.

Evidence summary	LE
Pads are not effective as a treatment for UI.	1b
Different pads have different advantages and disadvantages.	1b
Intermittent catheterisation carries a lower risk of urinary tract infection and bacteriuria than indwelling catheterisation.	1b
Containment devices are better than no treatment.	4
There is not enough evidence to conclude which containment device is best.	4
Condom catheters are better than indwelling catheters if no residual urine is present.	1b
There is no evidence to compare mechanical devices with other forms of treatment.	4

Recommendations	GR
Offer pads when containment of urinary incontinence is needed.	B
Adapt the choice of pad to the type and severity of urinary incontinence and the patient's needs.	A
Offer catheterisation to manage urinary incontinence when no other treatments can be considered.	B
Offer condom catheters to men with urinary incontinence without significant residual urine.	A
Offer to teach intermittent catheterisation to manage UI associated with retention of urine.	A
Do not routinely offer intravaginal devices as treatment for incontinence.	B
Do not use penile clamps for control of UI in men.	A

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3.2 Lifestyle interventions

Examples of lifestyle factors that may be associated with incontinence include obesity, smoking, level of physical activity and diet. It may therefore be possible to improve UI by beginning lifestyle interventions, such as weight loss, fluid restriction, reduction of caffeine or alcohol intake, limiting heavy activity and stopping smoking.

*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 focussed 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 all adults. 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 bladder training (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).

Evidence summary	**LE**
Reduction of caffeine intake does not improve UI.	2
Reduction in caffeine intake may improve symptoms of urgency and frequency.	2

3.2.1.3 References

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*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 and there is 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).

Evidence summary	**LE**
Female athletes may experience UI during intense physical activity but not during common activities.	3
Strenuous physical activity does not predispose to UI for women later in life.	3
Although moderate exercise is associated with lower rates of UI in middle-aged or older women, there is no evidence that starting moderate exercise improves established UI in women.	2b

3.2.2.3 References

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3.2.3 ***Fluid intake***

It is generally assumed that reduction in total volume of fluid intake may be beneficial for UI. Fluid restriction is a widely used, inexpensive and non-invasive intervention that is easily recommended. 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 are individualised and it is difficult to assess participant adherence to protocol. All available studies are 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 incontinence. An observational study also addressed fluid intake as part of a behavioural regime (4).

Evidence summary	**LE**
There is conflicting evidence on whether fluid modification changes symptoms of urinary incontinence and quality of life.	2

3.2.3.3 References

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3.2.4 ***Obesity and weight loss***

In most developed countries, nearly one-quarter to more than one-third of adult women are 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). Four further RCTs reported a similar benefit beneficial effect on incontinence following surgical weight reduction

programmes (6-9). The largest study was in diabetic women, for whom weight loss was the main lifestyle intervention (9). There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese (10-17). For example, in a longitudinal cohort study, a weight loss of 5-10% was associated with a significant reduction in pad test loss of urine (18).

Evidence summary	**LE**
Obesity is a risk factor for UI in women.	1b
Weight loss (> 5%) in obese women improves UI.	1b

3.4.2.3 References

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*3.2.5 **Smoking***

The role of smoking and the importance of smoking cessation are discussed in the management of almost every disease. 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 versus 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 (2). Other studies involving similar large populations have not shown an association. The effect of smoking cessation on UI was described as uncertain in the latest Cochrane review (5).

Evidence summary	**LE**
There is no consistent evidence that smokers are more likely to suffer from UI.	3
There is some evidence that smoking may be associated with more severe UI, but not mild UI.	3
There is no evidence that smoking cessation will improve the symptoms of UI.	4

Recommendations for lifestyle interventions	**GR**
Encourage obese women suffering from any urinary incontinence to lose weight (> 5%).	A
Advise adults with urinary incontinence that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.	B
Patients with abnormally high or abnormally low fluid intake should be advised to modify their fluid intake appropriately.	C
Counsel female athletes experiencing urinary incontinence with intense physical activity that it will not predispose to urinary incontinence in later life.	C
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.	A

3.2.5.3 References

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3.3 Behavioural therapy/scheduled voiding

Scheduled voiding is a treatment programme designed to gradually increase a person's control over voiding function and urgency and to reduce episodes of incontinence. It is also known as bladder drill, bladder discipline, bladder re-education, or BT. 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.

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.

*3.3.1 **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?

*3.3.2 **Evidence***

There have been four systematic reviews covering the effect of BT compared to standard care (1-4). 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 (5,6). 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(7).

Bladder training has been compared with other treatments for UI in a number of other RCTs. BT alone is as effective in controlling UUI and nocturnal incontinence as oxybutynin, tolterodine and solifenacin (8-13).

Studies have shown that the addition of BT to antimuscarinic therapy gives either no (10,11) or minimal (12) added benefit in terms of improvement of UI compared with antimuscarinic treatment alone. BT combined with antimuscarinic therapy does provide a greater benefit in reducing urinary frequency and nocturia (10,14). BT 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 (15), including in patients previously dissatisfied with the antimuscarinic treatment (16).

Bladder training combined with pelvic floor muscle training (PFMT) is better than standard care for controlling UI in elderly women living in institutions (17). However, BT alone is inferior to a high-intensity programme of PFMT to improve SUI in elderly women (18). BT 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.

Evidence summary	LE
There is limited evidence that supervised bladder training is better than no treatment in women with UUI and mixed urinary incontinence.	1b
The effectiveness of bladder training diminishes after the treatment has ceased.	2
There is inconsistent evidence to show whether bladder training is better than drug therapy.	2
The combination of bladder training with antimuscarinic drugs does not result in greater in improvement of UI but may have other benefits.	2
Bladder training is better than pessary alone.	1b
Timed voiding reduces leakage episodes in cognitively impaired men and women.	1b

For recommendations see page 46.

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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. PFMT 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.

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 ultrasound 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, the role of PFMT in the care of women with SUI was analysed in both direct comparisons and a mixed treatment comparison model, which compared different 'packages' of care (1). 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.

3.4.1.4 Efficacy of PFMT in SUI, UUI and MUI in women

This question has been addressed by one Cochrane systematic review (2), which included six RCTs comparing PFMT to no treatment. Three RCTs evaluated PFMT for mixed urinary incontinence (MUI), while the other three RCTs compared a programme of treatment supervised by a professional versus either self-taught PFMT or unsupervised PFMT. There was 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.

One recent RCT compared interpersonal support and digital vaginal palpation to PFMT and an instruction leaflet, finding superior efficacy for the former group (3). Another recent RCT found that PFMT delivered in a group setting can be as effective as individual treatment (4). 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 (5).

The 4th International Consultation on Incontinence 2009 (6) reviewed studies up to June 2008. This review included the following comparisons:

- vaginal cones: 8 RCTs
- different types of electrical stimulation: 8 RCTs
- BT: 3 RCTs
- different drugs: 4 RCTs
- surgery in which the operation was 'selected' by the surgeon (i.e. inconsistent): 1 RCT.

None of these RCTs were of good quality. In addition, inconsistent reporting of techniques and outcomes makes it difficult to compare studies.

The same review also included comparisons of PFMT with other therapies in women with SUI:

- PFMT versus PFTM + vaginal cones: 2 RCTs
- PFMT versus PFMT + electrical stimulation: 2 small RCTs
- PFMT versus PFMT + biofeedback: 9 RCTs of mixed quality, of which 5 RCTs were clinic-based and 4 RCTs used a home-based biofeedback device. Potential bias was caused by the inconsistent supervision of women between different treatment groups.

There has been one further RCT comparing PFMT + duloxetine versus duloxetine alone versus PFMT alone versus no treatment (6).

These studies, and two additional studies (8,9) were reviewed as part of the 2010 UK Health Technology Appraisal (1), which considered additional data as part of a mixed treatment comparison. The Appraisal resulted in a number of different findings from those based solely on direct comparisons. In conclusion, the Appraisal, using a revised methodology, supported the general principle that greater efficacy was achieved by adding together different types of treatment and increasing intensity.

3.4.1.5 Efficacy of PFMT in childbearing women

The Cochrane review in 2008 (10) reviewed sixteen RCTs in pregnant or post partum women which included PFMT in one arm of the trial. Five of these trials were in post partum women who had developed urinary incontinence. Eight trials reported mixed treatment and prevention groups. Treatment of UI with PFMT in the post partum period inreased the chances of continence at 12 months post partum.

3.4.1.6 Efficacy of PFMT in men with SUI following radical prostatectomy

There has been one systematic review of eleven RCTs. There have been three further RCTs of reasonable quality (11-13). These trials consistently demonstrated improved continence within the first few months after

radical prostatectomy (RP), but not thereafter, suggesting that PFMT speeds the recovery of UI. Two additional RCTs have shown that written instructions alone can achieve the same result (14,15).

3.4.1.7 Preventive value of PFMT in childbearing women and post-RP 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 pregancny and up to 6 months post partum.

Ten RCTs of variable quality compared the preventative effect of PFMT prior to RP 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 (16-24). However, one study was well designed and provided level 2 evidence confirming that pre-operative PFMT speeds recovery of continence post-operatively (25).

PFMT as monotherapy	**LE**
PFMT is better than no treatment for reducing incontinence episodes and improving quality of life in women with SUI, and MUI. There is no evidence that PFMT is better than no treatment in providing a cure.	1
Higher-intensity regimes, or the addition of biofeedback, confer greater benefit, but differences are not sustained long term.	1
A taught/supervised programme of PFMT is more effective than self-taught PFMT.	1
Group-based PFMT is as effective as treatment delivered individually.	1
Short-term benefits of intensive PFMT are not maintained at 15 years' follow-up.	2
PFMT compared with other conservative treatments	**LE**
PFMT results in better reduction in leakage episodes than training using vaginal cones, but no difference in self-reported cure or improvement.	1
PFMT results in fewer incontinence episodes than electrical stimulation.	1
PFMT does not result in measurable improvement in quality of life.	2
PFMT is better than bladder training for improvement of leakage and quality of life, in women with SUI.	2
There is no consistent difference between PFMT and bladder training for women with UUI or MUI.	2
PFMT is as effective as duloxetine in women with SUI and has fewer side effects.	2
PFMT is better tolerated than oxybutynin for UUI.	2
PFMT is better than alpha-blockers for women with SUI.	2
PFMT for UI in childbearing women	**LE**
PFMT commencing in early pregnancy reduces the risk of incontinence in late pregnancy, and up to 6 months post partum.	1
PFMT commencing in the early post partum period improves UI in women for up to 12 months.	1
PFMT for post-prostatectomy incontinence	**LE**
Men undergoing some form of PFMT, before or after radical prostatectomy achieve continence more quickly than non-treated men.	2
There is conflicting evidence on whether the addition of electrical stimulation or biofeedback or supervised training increases the effectiveness of PFMT alone.	2
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.	2
What remains unproven about PFMT	**LE**
There is a lack of evidence about what is the most effective regimen for PFMT.	4
The long-term durability of PFMT, augmented or not by other therapies, remains uncertain in all clinical situations.	4
There is insufficient evidence that adding electrical stimulation or vaginal cones to PFMT alters the efficacy of PFMT alone.	2

3.4.1.8 References

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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 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.

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 complicated by 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
The evidence is inconsistent for whether electrical stimulation alone can improve UI.	2

3.4.2.3 References

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*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 incontinence 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).

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.

Evidence summary	LE
There is no consistent evidence of efficacy of magnetic stimulation for the cure or improvement of UI.	2a
There are no reports of adverse events for magnetic stimulation.	1b

3.4.3.3 References

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*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. 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). 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

Seven studies were reviewed, including two RCTs of PTNS against sham treatment (1,2) and one comparing PTNS to tolterodine in patients with UUI (3). Four relevant case series were also included because they were either extension studies of an RCT population (5-7) or provided data on a large sample. Other studies of PTNS in UUI were excluded because of an inadequate study design (small case series, case series with no follow-up)

or a lack of relevance (series with combination treatment, reviews or studies from which specific results in UUI patients could not be extracted).

The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results allow the conclusion that that PTNS has a benefit in women with UUI not able to tolerate antimuscarinic therapy. However, there is no evidence of benefit for women who do not respond to antimuscarinic therapy. In men there is insufficient data to make a conclusion about efficacy.

Evidence summary	**LE**
There are not enough data to make a conclusion about the effectiveness of PTNS in men.	4
PTNS is effective in women with UUI, who cannot tolerate anticholinergic medication.	2a
PTNS does not give benefit for women with UUI who have not responded to anticholinergic medication.	1b
No serious adverse events have been reported for PTNS in UUI.	2a

Recommendations for behavioural and physical therapies	**GR**
Offer supervised PFMT, lasting at least 3 months, as a first-line therapy to women with stress or mixed urinary incontinence.	A
PFMT programmes should be as intensive as possible.	A
Consider using biofeedback as an adjunct in women with stress urinary incontinence.	A
Offer supervised PFMT to continent women in their first pregnancy to help prevent incontinence in the postnatal period.	A
Offer instruction on pelvic floor exercises to men undergoing radical prostatectomy to speed recovery of urinary incontinence.	B
Offer bladder training as a first-line therapy to adults with urgency urinary incontinence or mixed urinary incontinence.	A
Offer timed voiding to adults with urinary incontinence, who are cognitively impaired.	A
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of urinary incontinence.	A
Do not offer magnetic stimulation for the treatment of urinary incontinence or overactive bladder in adult women.	B
Offer PTNS to women with urgency urinary incontinence who cannot tolerate anticholinergic medication.	A

PFMT = pelvic floor muscle training; PTNS = posterior tibial nerve stimulation.

3.4.4.3 Research priorities

There is a need for well-designed studies of both electrical stimulation and magnetic stimulation in adults with UI.

3.4.4.4 References

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4. DRUG TREATMENT

4.1 Antimuscarinic drugs

Antimuscarinic 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) or extended release (ER) and transdermal.

The evaluation of cure/improvement of UI using oxybutynin and tolterodine IR formulations is made harder by the lack of a standard definition of improvement. Outcome measures vary and are not standardised, and never use 'cure' as a primary outcome. Meta-analysis of the published evidence is therefore not always possible.

There have been many publications of variable quality about the pharmacological treatment of the overactive bladder (OAB), including several systematic reviews and meta-analyses. The systematic reviews, published in 2009 (1), on behalf of the US Agency for Healthcare Research and Quality (AHRQ) and the Oregon Health and Science University (2), have collated together much of the relevant evidence. As well as the studies included in these reviews, the Panel have examined studies published since these reviews up until July 2010.

Dry mouth is the commonest side effect though others include constipation, blurred vision, fatigue and congnitive dysfuction. 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.

*4.1.1 **Immediate-release antimuscarinic agents***

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 been the only available formulation for many years. They 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 safety profile while maintaining efficacy.

4.1.1.1 Question

In adults with UI, are IR formulations of antimuscarinic drugs, and TDS application of oxybutynin, more effective than placebo in reducing UI episodes and achieving continence?

4.1.1.2 Evidence

Four systematic reviews of individual antimuscarinic drugs versus placebo were included by the Panel for this section (1-4).

A systematic review and meta-analysis by Chapple et al. in 2008 (2), which updated previous reviews, showed that oxybutynin IR versus placebo was better for improvement and cure of UUI. In patients receiving oxybutynin IR, 15 mg daily, there were statistically significant improvements compared to placebo. However, the absolute changes in incontinence episodes were small. Treated patients were 3.53 times more likely to achieve complete continence than controls (7-11). Similar changes have been reported for tolterodine IR, 4 mg daily, versus placebo (12-20), although the changes reported for tolterodine IR, 2 mg daily, were smaller

than for the higher dose (15-19). With propiverine IR, a cure of incontinence was 1.8 times more likely than with placebo (21-23). For trospium IR, no cure rates were available (24).

Randomised controlled trials of oxybutynin TDS versus placebo and other oral formulations have shown a significant improvement in the number of incontinence episodes and micturitions per day.

In Staskin et al. oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured (25).

Evidence summary	**LE**
Oxybutynin IR and transdermal, tolterodine IR, and propiverine IR provide a significantly better rate of cure/improvement compared to placebo.	1a
Trospium IR provides significantly better reduction in incontinence episodes than placebo.	1a

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*4.1.2 **Extended-release and longer-acting antimuscarinic agents***

4.1.2.1 Question

In men and women with UUI, do oral extended-release and longer-acting antimuscarinic drugs cure or improve the symptoms of UUI compared with no treatment?

4.1.2.2 Evidence

Most studies included patients with OAB, with a mean age of 55-60 years. Because most patients were women, the results can be generalised to women, but not to men. The reported rates for improvement or cure of UUI were only short term (up to 12 weeks). The evidence reviewed was consistent, indicating that ER formulations of antimuscarinics offer clinically significant short-term cure rates and improvement rates for UUI.

A comprehensive review of antimuscarinic therapy by the AHRQ was published in 2009. The references to individual RCTs included in this review have not been listed separately for this section (1).

Darifenacin
Two RCTs compared darifenacin to placebo, involving 838 patients (681 women). One study included only patients older than 65 years. The second study by Hill et al. found that darifenacin was superior to placebo for cure of UUI. No new data comparing darifenacin with placebo have been published since the AHRQ and Oregon Health and Science University systematic reviews, published in 2009 (1,2).

Fesoterodine
Two randomised trials have been reported since the AHRQ review (4,5). Both trials compared fesoterodine, 8 mg/day, versus tolterodine ER, 4 mg/day, versus placebo. The first study reported higher cure rates with fesoterodine than with placebo, but also higher rates of dry mouth. In the second study, the cure rates were also higher than with placebo, but again with higher rates of dry mouth. These trials are consistent with previous reports showing the effectiveness of fesoterodine compared to no treatment (placebo) described in the AHRQ and Oregon systematic reviews (1-3).

Oxybutynin
None of the identified studies that compared oxybutynin ER with placebo included incontinence as a measured outcome. One study reported that oxybutynin ER produced less cognitive disturbance than placebo (6).

Tolterodine
A study of mostly women (n = 361) compared tolterodine ER, transcutaneous oxybutynin, and placebo (7). Tolterodine ER resulted in a significantly higher chance of cure than placebo. Another study (8) in 337 incontinent men and women calculated the daytime incontinence outcomes in a secondary analysis of data from a previous study of tolterodine ER in OAB with nocturia. The analysis found higher cure rates of UUI using tolterodine ER. These data are consistent with the studies summarised in the AHRQ and Oregon systematic reviews (1,2) showing that tolterodine was effective for improvement of UUI compared to placebo.

Propiverine
We found three RCTs comparing propiverine ER with placebo, all with improvement of UUI as an outcome (9-11). All trials showed propiverine ER had a significant benefit over placebo in terms of improvement (11) and cure (9,10). Adverse effects reported included dry mouth and a prolonged QTc interval (9,10).

Solifenacin
Karram et al. reported a study in 707 patients comparing solifenacin and placebo, although their primary outcome measure was urgency rather than incontinence (12). Cure rates for urgency were 58% for solifenacin and 42% for placebo. Concerning an improvement in UUI, there have been no high-quality studies published since the AHRQ and Oregon systematic reviews (1,2), which already contained useful data on improvement in UI with solifenacin.

Trospium
Several authors (13-15) have done a secondary analysis of two previously published studies of trospium ER versus placebo (16,17). Cure rates for UUI were reported as 21% with trospium ER and 11% with placebo (14).

Evidence summary	**LE**
ER formulations of antimuscarinic agents are effective for improvement and cure of UUI.	1b
ER formulations of antimuscarinic agents result in higher rates of dry mouth compared to placebo.	1b
The clinical significance of prolonged QT for propiverine is uncertain.	3

4.1.2.3 References

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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. 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 (Table 4).

Table 4: Description of trials comparing antimuscarinic agents

Comparison of agents	No. of trials
Experimental IR agent vs. standard IR drug	11
Experimental ER agents vs. standard IR drug	19
Experimental ER agents vs. standard ER drug	12
Transcutaneous oxybutynin vs. standard IR oral drug	1
Transcutaneous oxybutynin vs. standard oral ER drug	1

In general, these studies have been designed for regulatory approval. They have a short treatment duration 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 the most recent systematic review (1) found that all the trials were of low or moderate quality.

Two, recent, high-quality systematic reviews from the USA included RCTs published up to the end of October 2008 (1,2). One review specifically addressed evidence of the comparative efficacy of antimuscarinic drugs (2). A European review included drugs not available in the USA and included literature published up to the end of August 2008 (3). Both reviews broadly agreed with two earlier reviews (4,5). Between December 2008 and July 2010 (the literature search cut-off date for the present review), two further relevant trials were published (6,9).

For cure of UI, there was weak evidence that oxybutynin ER was more effective than tolterodine ER (1,7). Three recent studies found some evidence that fesoterodine, 8 mg daily, was better than tolterodine ER, 4 mg daily, for cure of UI (6,8,9).

For improvement in UI, there was weak evidence that both oxybutynin ER and tolterodine ER were superior to tolterodine IR (2,3), and that oxybutynin ER was superior to tolterodine ER (3,7). The meta-analysis by Chapple et al. (4), which concluded that solifenacin was better than tolterodine IR for improving UI, has been challenged by more recent systematic reviews, which have concluded that there is no difference (1,2). Evidence from two trials where improvement in UI was the primary outcome suggests greater benefit is obtained with fesoterodine, 8 mg daily, compared with tolterodine ER, 4 mg daily (6,10). All other comparisons showed no difference in efficacy for improvement of UI.

There was no evidence that any one antimuscarinic agent improved QoL more than another agent (1).

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 (1,3). 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 (1,3). Overall, oxybutynin ER had 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 (1). Solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER (1). Fesoterodine, 8 mg daily, had a higher rate of dry mouth than tolterodine, 4 mg daily (6,10). 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 for the cure or improvement of UI. Recent trials with incontinence as the primary outcome suggest that fesoterodine, 8 mg daily, is superior to tolterodine ER, 4 mg daily, but meta-analysis is required to determine 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	**LE**
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
Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI.	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
A 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***

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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 four, recently published, high-quality reviews (1-4). Most of these studies were not funded by the pharmaceutical industry, whose main focus is on drug treatment rather than on conservative treatment.

The US Health Technology Appraisal 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 Health Technology Appraisal included a comparison between procedural and pharmaceutical treatments, including one RCT that showed a substantial benefit for sacral neuromodulation compared with medical therapy (5).

The most recently published systematic review in 2010 (3) found that medication was less effective than behavioural therapy in a comparative effectiveness trial (81% vs. 69% reduction in UI episodes). In addition, the use of antimuscarinic agents had side effects.

Two older RCTs (6,7), 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.

An important question addressed by multiple studies is how well the combination of antimuscarinic drugs and behavioural therapy compare to either treatment alone. This has been previously discussed in Section 3.3 Behavioural therapy/scheduled voiding. In summary, although medication may enhance the effect of behavioural therapy, there is no evidence that behavioural therapy enhances the effect of drugs.

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 long-term follow-up.

Evidence summary	**LE**
There is no consistent evidence to show superiority of drug therapy or behavioural therapy.	1b
Behavioural treatment results in increased patient satisfaction versus drug treatment alone.	1b

4.3.3 ***References***

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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 everyday clinical practice?

4.4.2 ***Evidence***

Twelve papers have been published on adherence/persistence to antimuscarinic medication in everyday clinical practice (1-12). Ten papers used established pharmaco-epidemiological parameters (1-7,9-11), including:

- 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 $\geq$ 0.8). This is the percentage of patients with MPR $\geq$ 0.8.

One study was in an open-label extension population (8). One study used only self-reports of patients and did not follow patients from the start of treatment (12). 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 (1-3,5,6).

Five articles reported 'median days to discontinuation' as between < 30 days and 50 days (2,3,5,6,10), with one study reporting 273 days in a military health system (which provides patients with free medication) (6).

Only one RCT (8) 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 (2,6,7,9). 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 (6).

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.

In addition, the source of data influenced the adherence figures.

Evidence summary	**LE**
More than half of patients will stop antimuscarinic agents within the first 3 months because of ineffectiveness, adverse events and cost.	2

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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 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). The Oregon systematic review of treatments for OAB reported specifically on outcomes in elderly patients (4).

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 (5,6). 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 (7), and in people with dementia with UUI (8). 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. There are also a number of studies that address the cardiovascular risk, which is mainly associated with antimuscarinic agents, in this age group. It should be noted that the definition of an elderly patient and the exclusion criteria vary from study to study.

Oxybutynin

There is substantial evidence that oxybutynin may cause or worsen cognitive dysfunction in adults (5,7,9).

A crossover RCT in elderly volunteers given oxybutynin IR reported increased cognitive dysfunction with oxybutynin, while a short-term RCT of oxybutynin ER in elderly women with cognitive dysfunction observed no increase in delirium (10).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 (11).

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 (12). 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.

Solifenacin
One pooled analysis from several RCTs (13) 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 (9).

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 (5). 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.

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 had no cognitive side effects (16,17). 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 (7).

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 good evidence that trospium does not impair cognitive function.

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 (18).

Evidence summary	**LE**
Oxybutynin IR may worsen cognitive function.	1b
Trospium chloride has not been reported to affect cognitive function.	1b
Solifenacin, tolterodine and darifenacin have not been shown to impair cognitive function in healthy volunteers.	3
Oxybutynin ER, 5 mg/day, does not cause delirium in the short term in cognitively impaired elderly women.	1b
Oxybutynin IR is less effective in people with impaired orientation, cerebral cortical underperfusion and reduced bladder sensation.	2
The effectiveness and risk of adverse events of solifenacin, tolterodine and darifenacin do not differ with patient age.	3
There is conflicting evidence about whether the efficacy of antimuscarinic drugs is different in elderly people compared to younger populations.	3

Recommendations for antimuscarinic drugs	GR
Offer IR or ER formulations of antimuscarinic drugs as initial drug therapy for adults with urgency urinary incontinence.	A
If IR formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.	A
Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.	B
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence (< 30 days).	A
When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of cognitive side effects, especially in those receiving cholinesterase inhibitors.	C
Avoid using oxybutynin IR in patients who are at risk of cognitive dysfunction.	A
Consider use of trospium chloride in patients known to have cognitive dysfunction.	B
Use solifenacin, tolterodine and darifenacin with caution in patients with cognitive dysfunction.	B
Do an objective assessment of mental function before treating patients whose cognitive function may be at risk.	C
Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction.	C

IR = Immediate release; ER = extended release.

4.5.3 ***Research priority***

As it is difficult to predict the longer-term benefit from the effect seen in short-term trials, it is recommended that cure of UUI should be a primary outcome measure in future research.

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4.6 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.

4.6.1 ***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 incontinence, or a greater improvement in QoL or a lesser likelihood of adverse effects, compared to any other intervention?

4.6.2 ***Evidence***

Duloxetine was evaluated as a treatment for female SUI or MUI in two systematic reviews (1,2) including 10 RCTs (3-12). The typical dose of duloxetine was 80 mg daily, with dose escalation up to 120 mg daily allowed in one study (4), 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 (6).

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 (3). An improvement in I-QoL was not found in the study using I-QoL as a primary endpoint (6). A further study compared duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo (13). 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 (14,15). 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 (16). Episodes of UUI were also significantly reduced by duloxetine.

One study (17) 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	**LE**
Duloxetine does not cure incontinence.	1b
Duloxetine, 80 mg daily, can modestly improve episodes of SUI and UUI in women and men.	1b
Duloxetine causes significant gastrointestinal and CNS side effects leading to a high rate of treatment discontinuation.	1b

Recommendations	**GR**
Duloxetine should not be offered to women or men who are seeking a cure for their incontinence.	A
Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms.	A
Duloxetine should be initiated using dose titration because of high adverse effect rates.	A

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4.7 Intravaginal oestrogen

Oestrogen treatment for UI can be given orally, vaginally or even intravesically. Oral 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.

*4.7.1 **Question***

In women with UI, does intravaginal oestrogen cure or improve UI compared to no treatment?

*4.7.2 **Evidence***

A recent Cochrane systematic review looked at the use of oestrogen therapy in post-menopausal women (1). The review identified 33 trials, with a total of 19,313 incontinent women, including 1,262 women who were 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 July 2010. Evidence from a large RCT showed that systemic oestrogen therapy leads to an increased incidence of UI in post-menopausal women, including both SUI and UUI (3).

Local oestrogen therapy can be given as conjugated equine, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. Besides improving vaginal atrophy (4), local oestrogen therapy reduces incontinence 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.

In conclusion, the evidence for the use of oestrogens in UI is consistent, but is only available in post-menopausal women. This means that any conclusions can only be applied to post-menopausal women with UI. Thus, post-menopausal women taking oral oestrogens should be advised that they have an increased risk for developing or worsening UI. Local oestrogens can be used to reduce incontinence, urgency and frequency in post-menopausal women.

Evidence summary	LE
Systemic oestrogen therapy can worsen existing UI and carries an increased risk of UI developing in post-menopausal women.	1a
Local oestrogen therapy in post-menopausal women can at least temporarily improve or cure UI.	1a
There is no evidence available on the neoadjuvant or adjuvant use of local oestrogens at the time of surgery for UI.	1a

Recommendations	GR
Women using systemic oestrogen should be counselled that they have an increased risk for developing urinary incontinence or worsening of their existing incontinence.	A
Offer post-menopausal women with urinary incontinence local oestrogen therapy, although the ideal duration of therapy and best delivery method are unknown.	A
Advise post-menopausal women who are taking oral oestrogens that they have an increased risk for developing urinary incontinence or worsening of their existing urinary incontinence.	A

*4.7.3 **References***

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4.8 Desmopressin

Desmopressin is a synthetic analogue of vasopressin (also known as antidiuretic hormone), which increases water re-absorbtion 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.

*4.8.1 **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?

*4.8.2 **Evidence***

4.8.2.1 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 176 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.

4.8.2.2 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	LE
The risk of UI is reduced within 4 hours of taking oral desmopressin, but not after 4 hours.	1b
Continuous use of desmopressin does not improve or cure UI.	1b
Regular use of desmopressin may lead to hyponatraemia.	3

Recommendations	GR
Offer desmopressin to patients requiring occasional short-term relief from urinary incontinence, inform them that this drug is not licensed for this indication.	B
Do not use desmopressin for long-term control of urinary incontinence.	A

*4.8.3 **References***

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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 incontinence 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. This applies mainly to post-prostatectomy incontinence in men without neurological disease affecting the lower urinary tract.
- Patients with refractory DO incontinence.

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 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 (6) 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 incontinence were 17% up to 5 years and 21% over 5 years. The re-operation rate for incontinence was 2%, but there was a higher rate of development of genitourinary prolapse than for other open operations.

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 (7). 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 incontinence 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 (5) 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-urethal sling.

Evidence summary	**LE**
Anterior colporrhaphy has lower rates of cure for UI especially in the longer term.	1a
Open colposuspension and autologous fascial sling are similarly effective for cure of SUI in women.	1b
Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of SUI and a similar risk of voiding difficulty or de-novo urgency.	1a
Laparoscopic colposuspension has a lower risk of other complications and shorter hospital stay than open colposuspension.	1a
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and post-operative UTI.	1b

5.1.1.3 References

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*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 purposes of this guideline, 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%) (7-15). 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 (5,12,13). 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) (3,4,14,16,17).

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 (18). 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

Thirty-four RCTs (5786 women) compared 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) (20-49). 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 (50). 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 (51). 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 (50).

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 pelvic organ prolapse, or a history of previous surgery for SUI.

The results of the EAU Panel meta-analysis were consistent with those of the Cochrane systematic review (52), except that in our meta-analysis the objective cure rates appeared slightly higher for retropubic (88%) compared to transobturator insertion (84%). The Panel finding is consistent with an additional systematic review and meta-analysis (53), 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 sling were similar to those calculated in the meta-analysis for the American Urological Association guidelines (54). In addition, our results and recommendations are consistent with those of the Society of Obstetricians and Gynaecologists of Canada (55) and those of the UK National Institute for Health and Clinical Excellence (66).

Evidence summary	**LE**
Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling gives equivalent patient-reported cure of SUI and superior clinician-reported cure of SUI at 12 months.	1a
Compared to colposuspension, the transobturator insertion of a mid-urethral synthetic sling gives equivalent patient-reported and clinician-reported cure of SUI at 12 months.	2
Insertion of a mid-urethral synthetic sling by the transobturator route gives equivalent patient-reported and clinician-reported cure rates at 12 months compared to retropubic insertion.	1a
The skin-to-vagina direction of retropubic insertion of mid-urethral sling is less effective than a vagina-to-skin direction.	1a
Mid-urethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.	1a
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.	1a
The transobturator route of insertion is associated with a higher risk of chronic perineal pain at 12 months than the retropubic route.	1a
The skin-to-vagina direction of both retropubic and transobturator insertion is associated with a higher risk of post-operative voiding dysfunction.	1b

5.1.2.3 References

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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.

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 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-urethal 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 TVT 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 mid-urethral sling to a Contasure® device found no difference in cure of UI or adverse events (9).

There are a number of case series with a minimum of 12 months' follow-up, including five series using the Miniarc device (10-15), two series using the TVTS device (11,16) and one series using the Minitape® device (17). 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 (17). One study reported a 24% rate of de-novo urgency but generally there were few reported adverse effects (11).

There are no RCTs relating to the Solyx® device. There is one retrospective review of 63 women with short-term follow-up (18), and one report of 12 months' follow-up of the Ophira® device 176 women (19). These studies did not report outcomes of interest for these Guidelines.

Evidence summary	LE
Single-incision mid-urethral slings are effective in curing SUI in women in the short term.	1b
Operation times for insertion of single-incision mid-urethral slings are shorter than for standard retropubic slings.	1b
Blood loss and immediate post-operative pain are lower for insertion of single-incision slings compared with standard mid-urethral slings.	1b
Single-incisions slings are less effective than other mid-urethral slings at medium-term follow-up*.	1b
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.	1b

**NB: Most evidence on single-incision slings comes from studies using the tension-free vaginal tape secure (TVTS) device.*

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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.

Saffyre®

Two cohort studies included a total of 208 patients with a minimum of 12 months follow-up (3,4). The reported cure rate was up to 92% with adverse effects of late vaginal erosion in 8% and dyspareunia in 11% (3).

Ajust®
A single cohort study reported an 80% success rate (patient's global impression of improvement) in 90 women after 12 months of follow-up.

Evidence summary	LE
Adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard mid-urethral slings.	4

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*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 is one Cochrane systematic review (1), 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 (2,3).

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 (4). 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 (4) 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 (5).

Autologous fat
One study found no difference in efficacy between autologous fat and saline injection (22% vs. 20% improvement at 3 months, respectively) (6). Due to a fatality from fat embolism, NICE 2006 (4) and the Cochrane Review (1) 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 (7). No significant difference in efficacy was found.

Carbon beads (Durasphere™)
Carbon beads have been compared to collagen in two RCTs (3,8). 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) (9).

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 (10).

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 (11).

Hydrogel cross-linked with polyacrilamide (BulkamidTM)
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 (12).

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 (13).

Stem cells
Early reports of dose-ranging studies (14) 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 (5,15).

Another trial found that a periurethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection (16). A recent small RCT found no difference in efficacy between a mid-urethral and bladder neck injection of collagen (2).

Evidence summary	**LE**
Periurethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.	2a
Repeat injections to achieve therapeutic effect are very common.	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.	2a
Adverse effect rates are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
Periurethral route of injection may be associated with a higher risk of urinary retention compared to transurethral route.	2 b

Recommendations for surgery for uncomplicated stress urinary incontinence in women	GR
Offer the mid-urethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.	A
Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if mid-urethral sling cannot be considered.	A
Warn women who are being offered a retropubic insertion synthetic sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.	A
Warn women who are being offered transobturator insertion of mid-urethral sling about the higher risk of pain and dyspareunia in the longer term.	A
Warn women undergoing autologous fascial 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.	A
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 cystocoele.	C
Women being offered a single-incision sling device for which an evidence base exists, should be warned that short-term efficacy is inferior to standard mid-urethral slings and that long-term efficacy remains uncertain.	C
Only offer single-incision sling devices, for which there is no level 1 evidence base, as part of a structured research programme.	A
Only offer adjustable mid-urethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.	C
Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.	A

5.1.5.3 References

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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 will be included in the next edition of these Guidelines in 2013.

*5.2.1 **Failed surgery***

The reported failure rates from any operation for SUI vary widely from 5-80%, depending on how failure was defined. Even using a very strict definition, this means that at least hundreds of the many thousands of women undergoing primary surgery for SUI will require further surgery for recurrent symptoms. A primary operation may fail from the start or may occur some years after the original procedure. There may be persistent or recurrent SUI, or the development of de-novo UUI or voiding difficulty. Expert opinion therefore considers careful urodynamic evaluation to be an essential part of the work-up of these patients.

However, the underlying reasons for failure are poorly understood. Consequently, which operation to offer women with failed previous surgery for UI is usually driven by individual clinician opinion about the mechanisms of failure, familiarity with certain procedures, and experience in personal series. Most surgeons believe the results of any operation will be inferior to the same operation used as a primary procedure and will warn their patients of this.

The Panel have 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 recurrent SUI following previous corrective surgery, what is the best surgical treatment?

5.2.1.2 Evidence

Most data on surgery for SUI are for primary surgery. When secondary procedures are included, it is unusual

for the outcomes to be separately reported. Even if they are, the numbers of patients are usually too small to allow meaningful comparisons.

The 4th International Consultation on Incontinence included a review of this topic up until 2008, and the subject has also been reviewed by Ashok and Wang (1). Cochrane reviews of individual operative techniques have not included a separate evaluation of outcomes in women undergoing second-line surgery. However, there is a current protocol advising on this issue (2). A further literature review up until October 2011 has been carried out since that time by the EAU Panel with the following findings.

Three RCTs were found. Two of the trials compared Burch colposuspension to a biological sling in recurrent SUI (3,4). There was no difference in efficacy between the procedures, but the complication rates were higher for slings. Another small RCT (abstract only) compared retropubic mid-urethral sling to laparoscopic colposuspension in women with recurrent SUI and reported similar short-term cure rates and adverse events (5).

Post-hoc analysis of high-quality RCTs comparing one surgical procedure to another reported higher failure rates for SUI and higher rates for adverse effects in women who had had previous surgery for SUI. There was no difference in these rates between the compared procedures (4,6-8). A history of prior surgery for UI was not an independent predictor of failure at 2 years in women undergoing open colposuspension or autologous fascial sling (4).

One large non-randomised cohort study suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for autologous sling (9).

Several cohort studies have reported outcomes for retropubic mid-urethral synthetic sling specifically for primary and secondary cases. There is conflicting evidence on the effectiveness of second-line retropubic sling insertion, with some series showing equivalent outcomes for primary and secondary cases (10-12) and other series showing inferior outcomes for secondary surgery (13,14). Other confounding variables make meaningful conclusions difficult. There appears to be no evidence supporting the concept that the original mid-urethral sling should be removed.

Many small case series report satisfactory outcomes for repeat procedures of many types, but this evidence is not suitable to generate guidance.

A systematic review of older trials of open surgery for SUI suggests that the longer-term outcomes of repeat open colposuspension may be worse than those seen with autologous fascial slings (15). Successful results have been reported from mid-urethral slings after various types of primary surgery, while good outcomes are reported for both repeat retropubic mid-urethral sling and for 'tightening' of existing mid-urethral slings, but data were limited to small case series only.

Finally, clinical guidelines have been developed by the Society of Obstetricians and Gynaecologists of Canada, based on a literature review and expert opinion. Unfortunately, the methodology and the rationale for grading decisions were not clear (16).

Evidence summary	**LE**
The risk of treatment failure from surgery for SUI is higher in women who have had prior surgery for incontinence or prolapse.	1b
Open colposuspension and autologous fascial sling appear to be as effective for first-time repeat surgery as for primary surgery.	1b
The mid-urethral sling is less effective as a second-line procedure than for primary surgery.	2

5.2.1.3 Research priority on failed SUI surgery

There is a need for well-structured research trials to compare surgical procedures in women who have had previous failed surgery for SUI.

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*5.2.2 **External compression devices***

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.

There are two intracorporeal external urethral compression devices available. They are the adjustable compression therapy (ACT) device and the artificial urinary sphincter (AUS). Using ultrasound 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 artificial sphincters over other anti-incontinence procedures is the perceived ability of women to be able to void normally. 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 (1).

Artificial urinary sphincter

The 2011 Cochrane review on AUS (2) 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 artificial sphincters in women (3).

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 (4-7). 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 (6). Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation (4).

Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions (8,9).

Adjustable compression device

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 (11-14). 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	**LE**
Implantation of an artificial sphincter may achieve continence in women with complicated SUI.	3
Implantation of the ACT device may improve complicated UI.	3
Failure and device explantation are common adverse effects of both the artificial sphincter and the adjustable compression device.	3
Explantation is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

Recommendations for surgery for complicated stress urinary incontinence in women	GR
The choice of surgery for recurrent stress urinary incontinence should be based on careful evaluation of the individual patient.	C
Women should be warned that the outcome of second-line surgical procedures is likely to be inferior to first-line treatment, both in terms of reduced benefit and increased risk of harm.	C
Offer implantation of AUS or ACT as an option for women with complicated stress urinary incontinence if they are available and appropriate monitoring of outcome is in place.	C
Warn women receiving AUS or ACT that there is a high risk of mechanical failure or a need for explantation.	C

AUS = Artificial Urinary Sphincter; ACT = Adjustable Compression Therapy.

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5.3 Men with SUI

*5.3.1 **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).

5.3.1.1 Question

In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

5.3.1.2 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 (4). 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**
There is no evidence that bulking agents cure post-prostatectomy incontinence.	2a
There is weak evidence that bulking agents can offer temporary improvement in QoL in men with post-prostatectomy incontinence.	3
There is no evidence that one bulking agent is superior to another.	3

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5.3.2 ***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®, 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 incontinence. However, the definitions of mild and moderate incontinence 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).

5.3.2.1 Question

In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

5.3.2.2 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 (6-14).

For the repositioning sling (AdVance), the benefit after a mean follow-up of 3 years has been published on 136 patients (15). Data were available on at least 614 patients with a mean follow-up of between 3 months and 3 years (2,12,15-21). 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 (13,21). Post-operative voiding dysfunction occurred in 5.7-1.3%, while erosions and chronic pain were uncommon (0-0.4%). The overall failure rate was about 20%.

For the compression sling (InVance), 5-year data were available on 27 patients, 3-year data were available on 45 patients, and 1-year data were available on an additional 177 patients (22,23-27) The cure rate for this device varied between 36% and 62.7%, with a mean of 51.8% (22,23,25,26). Radiotherapy was a negative prognostic factor. Infection occurred in 3.2-15%, while de-novo urgency was reported in 2.3-11.9% of patients. The overall failure rate was about 20%.

Evidence summary	**LE**
There is limited short-term evidence that fixed male slings cure post-prostatectomy incontinence in patients with mild-to-moderate incontinence.	3
Men with severe incontinence, previous radiotherapy or urethral stricture surgery have poor outcomes from fixed male slings.	3
There is no evidence that one type of male sling is better than another.	3

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*5.3.3 **Adjustable slings in males***

Adjustability in male sling surgery attempts to adjust the tension of the sling post-operatively. Two main systems are used in men:

- The Remeex® system consists of tension wires, which are adjusted using a type of screwdriver that temporarily comes out of the suprapubic wound. Once the ideal tension is achieved, it is easy to dislodge the screwdriver and close the wound. It is possible to repeat the procedure later during secondary surgery.
- The Argus® system consists of a silicone cushion, which is placed under the urethra and tensioned by two silicone arms, positioned either retropubically or in a transobturator fashion. Re-adjustment is usually carried out several months after the initial implant, by tightening or loosening the tensioning arms during a second surgical intervention.

5.3.3.1 Question

In men with post-prostatectomy incontinence or SUI, does insertion of an adjustable suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

5.3.3.2 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 (3-6), 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% (5,7,8). Infection of the device occurred in 5.4-8% (3,6,9). Erosions were reported in 5-10% (9,10). Urethral perforations occurred in 2.7-16% (3,4,6). Pain at the implant site was usually only temporary, but chronic pain has been reported (4,8,10,11). These complications resulted in explantation rates of 10-15% (5,8).

Evidence summary	LE
There is limited evidence that adjustable male slings are effective at curing SUI in men.	3
There is limited evidence that early explantation rates are high.	3
There is no evidence that adjustability of the male sling offers additional benefit over other types of sling.	3

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*5.3.4 **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.

5.3.4.1 Question

In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL, or cause adverse outcomes?

5.3.4.2 Evidence

Artificial urinary sphincter

Although the AUS is considered to be the standard treatment for men with SUI, the quantity and level of evidence is low. There are no well-designed prospective RCTs with most information gained from older case series (2). More recent case series confirm the previous data (3,5). A continence rate of about 80% can be expected, while this may be lower in men who have undergone pelvic radiotherapy (3).

Trigo Rocha et al. published a prospective cohort study on 40 patients with a mean follow-up of 53 months (6). 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 (7).

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 (8-10). The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking (11,12).

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 continence, while the availability of a 3.5-cm cuff may have eliminated the need for a dual cuff (13-15). Patients who experienced complete continence after AUS implantation had a higher erosion risk (16).

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 (17). 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) (18). 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% (3,19-23). 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 (24).

Evidence summary	**LE**
There is limited evidence that primary AUS implantation is effective for cure of SUI in men.	2b
Long-term failure rate for AUS is high although device replacement can be performed.	3
Previous pelvic radiotherapy does not appear to affect the outcome of AUS implantation.	3
Men who develop cognitive impairment or lose manual dexterity are likely to have difficulty operating an AUS.	3
Tandem-cuff placement is not superior to single-cuff placement.	3
The penoscrotal approach and perineal approach appear to give equivalent outcomes.	3
Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI.	3
The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.	3

Recommendations for surgery in men with stress urinary incontinence	GR
Only offer bulking agents to men with mild post-prostatectomy incontinence who desire temporary relief of UI symptoms.	C
Do not offer bulking agents to men with severe post-prostatectomy incontinence.	C
Offer fixed slings to men with mild-to-moderate post-prostatectomy incontinence.	B
Warn men that severe incontinence, prior pelvic radiotherapy or urethral stricture surgery, may worsen the outcome of fixed male sling surgery.	C
Offer AUS to men with persistent (more than 6 months) moderate-to-severe post-prostatectomy incontinence that has not responded to conservative management.	B
Warn about the long-term risk of failure and need for revision when counselling men for insertion of AUS.	C
Only offer the non-circumferential compression device (ProACT®) if arrangements for men with post-prostatectomy incontinence if arrangements for monitoring of outcome are in place.	C
Warn men considering a non-circumferential compression device (ProACT®) that there is a high risk of failure and subsequent explantation.	C
Do not offer non-circumferential compression device (ProACT®) to men who have had pelvic radiotherapy.	C

AUS = Artifical urinary sphincter.

5.3.4.3 References

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5.4 Surgical interventions for refractory DO

*5.4.1 **Intravesical injection of botulinum toxin A***

Botulinum toxin (BTX) A 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) and abobotulinumtoxina (Dysport in Europe) and that the doses are not interchangeable. 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). CIC in turn is associated with an increased risk of UTIs (1,2).

5.4.1.1 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?

5.4.1.2 Evidence

Two systematic reviews on the use of BTX have recently been published (1,2). The Cochrane analysis (1), which included patients with neurogenic or idiopathic DO, reported on RCTs comparing BTX with placebo. (It was not possible to draw conclusions about non-neurogenic incontinence from this review.) Reduction of incontinence episodes favoured BTX over placebo at both 4-6 weeks and 12 weeks. The mean difference in the reduction of incontinence episodes per day was -2.74 (95% CI: -4.47 to -1.01; p = 0.002). The rise in PVR favoured the placebo group, with a mean increase in PVR of 70.2 mL with the BTX. The question of the best injection technique remained largely unanswered. Studies were uniformly small with a maximum of 77 patients in any one study. Up to 66% of patients achieved complete continence, with an effect lasting between 3 and 12 months. The need for CIC was related to how aggressively patients are investigated for PVR. There was some evidence that lower doses produced fewer adverse events in terms of increased PVR and necessity for CIC. The UTI rates are consistently comparable to rates with cystoscopy alone but increase when CIC is required.

The systematic review by Mangera et al. (2) analysed the effect of BTX in adults with idiopathic DO in four RCTs (3-6). These studies (all using Onabotulinum toxin a) all demonstrated significant improvements in adults with idiopathic DO, at doses of 200 U in Brubaker et al. (4), 200/300 U in Flynn et al. (5) and 200 U in Sahai et al. (6). Dmochowski et al. compared a range of doses of BTX (3). These authors reported a change in incontinence episodes per day from baseline, but did not show the original baseline values, so that their results could not be included in the Mangera analysis. Additionally, an abstract from Tincello et al. (7) has recently reported results from the largest RCT of BTX to date. The study of 200 U Botox in 227 patients reported significant improvements in symptoms and QoL parameters versus placebo (7). The analysis of the efficacy data produced similar results to the Cochrane review.

The Cochrane and Mangera et al. reviews (1,2) also showed that the number of injection sites varied from 3 to 40, with 20 being most common, and the injection volume ranged between 3 and 30 mL, with 20 mL being the most common. The choice of injection site did not seem to impact on efficacy or adverse events. A range of 27-43% of patients had a PVR > 200 mL, while 13-44% suffered from UTI (1,2).

The Cochrane and Mangera et al. reviews accounted for all the major RCTs in BTX (1,2). However, cure-dry rates were not used as an outcome measure, and a separate meta-analysis using the original data (3,5-7) and data from a recent paper (8) was performed. Although the Dmochowski study (3) was not included in the analysis for the Mangera review, the EAU Panel have now obtained supplementary data from the authors, including dry rates at 6 and 12 weeks.

The meta-analysis (3,5-8) yielded the following results: the odds ratio (95% CI) of becoming dry with BTX versus placebo are 2.28 (0.95-5.49; p = 0.07) for 50 U, 4.39 (1.91-10.12; p = 0.0005) for 100 U, 4.96 (2.14-11.53; p = 0.0002) for 150 U, 4.34 (2.49-7.59, p < 0.00001) for 200 U and 7.05 (2.68-18.51, p < 0.0001) for 300 U. These results showed that 50 U had inferior efficacy to higher dosages. Although 300 U was the most efficacious dose, it is not a recommended dose because of the high rates of PVR necessitating CIC. A dose of 100-200 U seems to have comparable efficacy in the meta-analysis.

In the Dmochowski study, the cure-dry rate at 12 weeks was 37.0% and 50.9% for 100 U and 200U, respectively. Higher rates of PVR requiring CIC were found with higher doses showing a clear dose-response relationship (3).

Evidence summary	LE
A single treatment session of intravesical Onabotulinum toxin A (100-300 U) is more effective than placebo at curing and improving UUI for up to 12 months.	1a
There is no evidence that repeated injections of botulinum toxin A have reduced efficacy.	3
There is a high risk of increased PVR, which is dose dependent and may require intermittent self-catheterisation.	1b
There is a high risk of UTI in those who require intermittent self-catheterisation.	1b
There is no evidence that one technique of injecting botulinum toxin A is more efficacious than another.	1b

Recommendations	GR
Offer botulinum toxin A intravesical injections to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the possible need to self-catheterise and the associated risk of urinary tract infection; ensure that they are willing and able to do so.	A
Patients should also be warned of the licensing status of botulinum toxin A, and that the long-term effects remain unknown.	A

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5.4.1.4. Research priorities

More research is needed to investigate the optimum injection technique and regimen, as well as the long-term effects of intravesical injection of botulinum toxin.

5.4.2 ***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).

5.4.2.1 Question

In adults suffering from refractory UUI, what is the clinical effectiveness of sacral nerve neuromodulation compared to alternative treatments?

5.4.2.2 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) 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 incontinence, 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 outcome 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) experienced by 50-63% in those 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	**LE**
Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of UUI, but no sham controls have been used.	1b
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.	3
One-stage implantation results in more patients receiving the final implant than occurs with prior temporary test stimulation.	4

Recommendations	GR
If available, offer patients with urgency urinary incontinence that is refractory to conservative therapy, the opportunity to be treated by sacral nerve neuromodulation before bladder augmentation or urinary diversion is considered.	A

5.4.2.3 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 an accompanying health economic analysis is required.

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5.4.3 ***Cystoplasty/urinary diversion***

5.4.3.1 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).

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 (1-8), 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 (2). 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 (9). In addition, many patients may require self CIC to obtain adequate bladder emptying.

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Table 6: Complications of bladder augmentation

Short-term complications	**Affected patients (%)**
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4
Long-term complications	
Clean intermittent self-catheterisation	38
Urinary tract infection	70% asymptomatic; 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75

5.4.3.2 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 (10). An additional, non-randomised study (11), 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 (12) 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.

5.4.3.3 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 (13).

Evidence summary	**LE**
There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic DO.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short-term and long-term severe complications.	3
The need to perform clean intermittent self-catheterisation following augmentation cystoplasty is very common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty with urinary diversion.	3
There is no evidence on the long-term effectiveness of detrusor myectomy in adults with idiopathic DO.	3

Recommendations	GR
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.	C
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.	C
Do not offer detrusor myectomy as a treatment for urinary incontinence.	C
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of urinary incontinence and who will accept a stoma.	C
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.	C
Life-long follow-up is recommended for patients who have undergone augmentation cystoplasty or urinary diversion.	C

5.4.3.4 References

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APPENDIX A: MIXED URINARY INCONTINENCE

About one-third of women with UI have mixed 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 has been addressed by the 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 mange 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 that 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 the guideline.

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 (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 pelvic floor muscle training. 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 pelvic floor muscle training, with or without an instructive audiotape. It showed equal efficacy for different types of UI (6).

An RCT in 121 women with stress, urgency or mixed UI compared transvaginal electrical stimulation with sham stimulation and was found to be equally effective in urgency UI as in mixed UI (7).

A.3.2.1 Drugs

Duloxetine was found to have equal efficacy for Stress UI and Mixed UI 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 urgency UI symptoms, regardless of whether there was associated stress incontinence (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 (14). (This study included only a few patients with urodynamic detrusor overactivity.)

A.3.3 ***Large cohort studies, including a separate analysis of patients with MUI***

Following a RCT of pelvic floor muscle training, 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 detrusor overactivity, and found inferior outcomes in women with MUI (20).

However, in a study of the bulking agent, Bulkamid, 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 1,113 women treated with transvaginal obturator tape, Stress UI 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

Evidence summary	**LE**
Pelvic floor muscle training is less effective for mixed UI than for SUI alone.	2
Electrical stimulation is equally effective for mixed UI and SUI.	1b
Antimuscarinic drugs are equally effective in improving symptoms of urgency and urgency UI, in patients with mixed UI as in patients with urgency UI alone.	1a
Duloxetine is equally effective in improving SUI in patients with MUI as in patients with SUI alone.	1a
Women with mixed UI are less likely to be cured of their incontinence, by SUI surgery, than women with SUI alone.	1c
The response of pre-existing urgency symptoms to SUI surgery is unpredictable, and symptoms may improve or worsen.	3

A.5 Recommendations

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
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.	B
Offer antimuscarinic drugs to patients with urge-predominant mixed urinary incontinence.	A
Warn patients with mixed urinary incontinence that surgery is less likely to be successful than surgery in patients with stress urinary incontinence alone.	A

A.6 Research priority

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.

Researchers should be more precise about the definitions of MUI, when evaluating the effects of treatment in this group.

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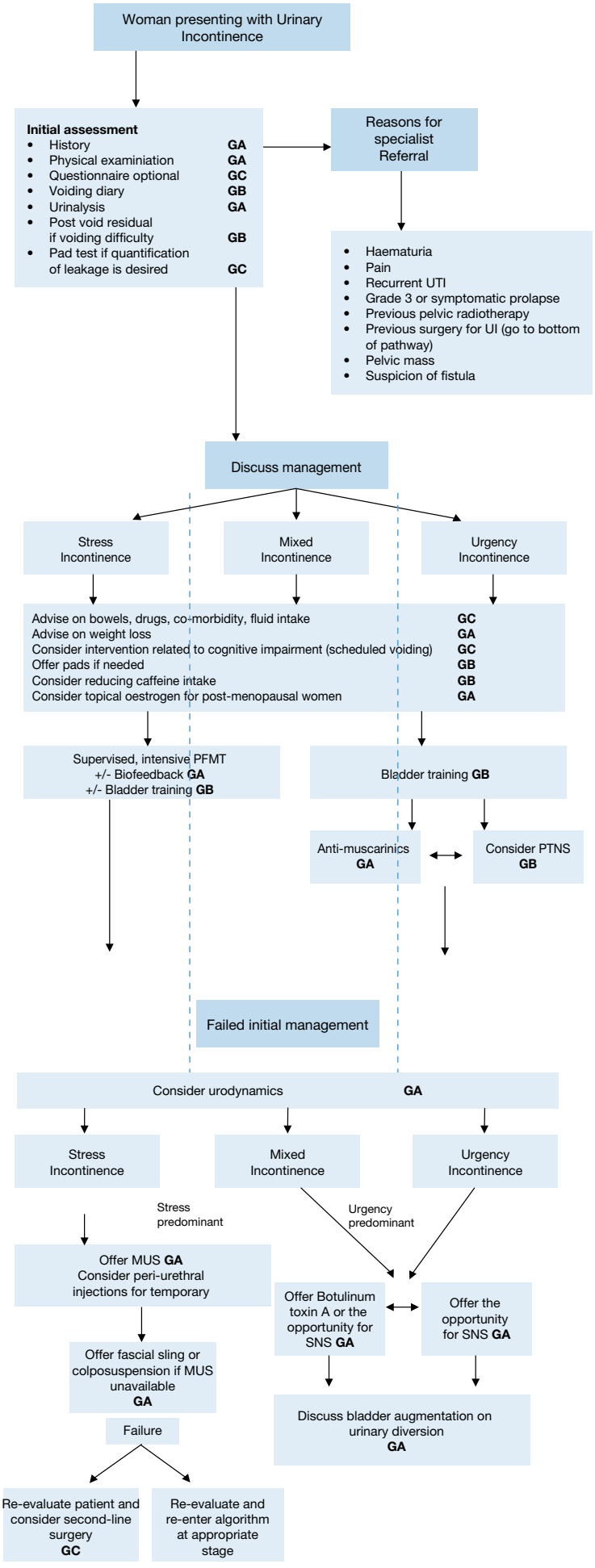
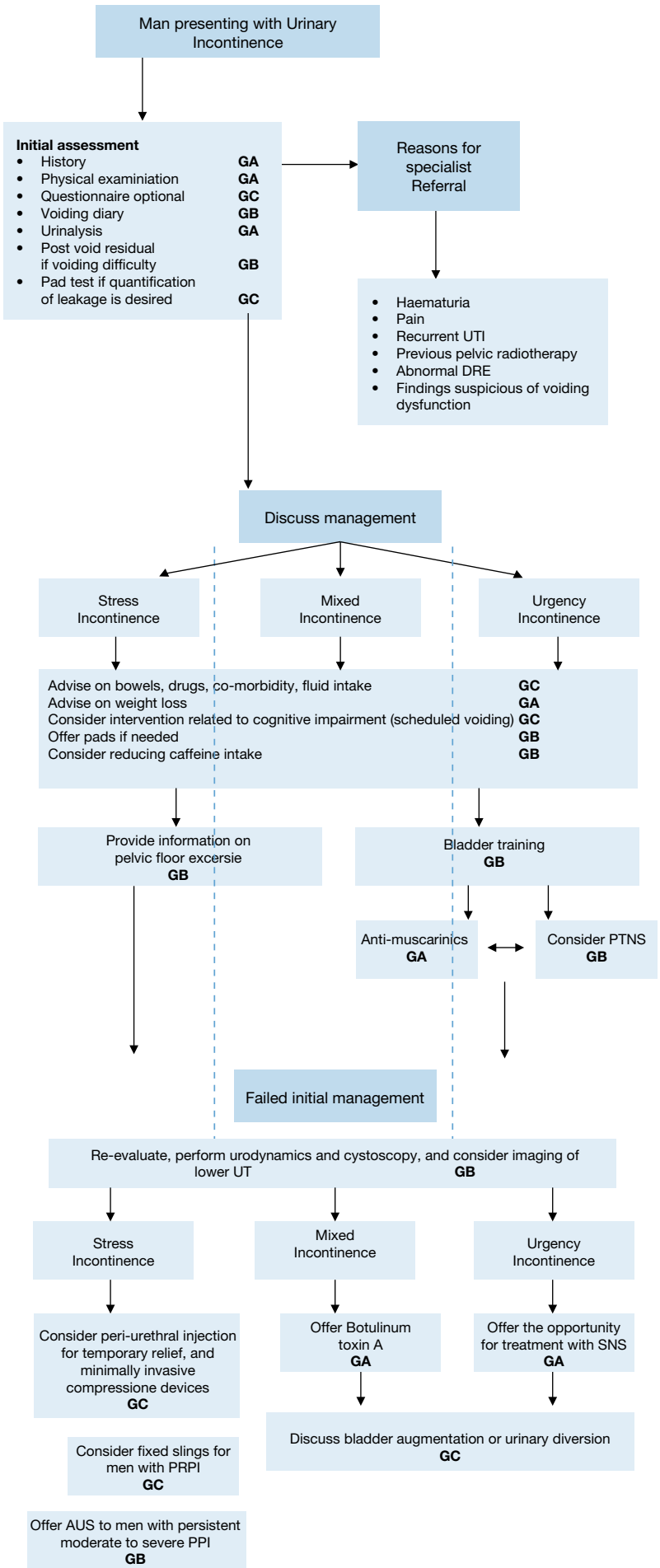

Woman presenting with Urinary Incontinence
Initial assessment
History GA
Physical examiniation GA
Questionnaire optional GC
Voiding diary GB
Urinalysis GA
Post void residual if voiding difficulty GB
Pad test if quantification of leakage is desired GC
Reasons for specialist Referral
Haematuria
Pain
Recurrent UTI
Grade 3 or symptomatic prolapse
Previous pelvic radiotherapy
Previous surgery for UI (go to bottom of pathway)
Pelvic mass
Suspicion of fistula
Discuss management
Stress Incontinence
Mixed Incontinence
Urgency Incontinence
Advise on bowels, drugs, co-morbidity, fluid intake GC
Advise on weight loss GA
Consider intervention related to cognitive impairment (scheduled voiding) GC
Offer pads if needed GB
Consider reducing caffeine intake GB
Consider topical oestrogen for post-menopausal women GA
Supervised, intensive PFMT +/- Biofeedback GA +/- Bladder training GB
Bladder training GB
Anti-muscarinics GA
Consider PTNS GB
Failed initial management
Consider urodynamics GA
Stress Incontinence
Mixed Incontinence
Urgency Incontinence
Stress predominant
Urgency predominant
Offer MUS GA Consider peri-urethral injections for temporary
Offer fascial sling or colposuspension if MUS unavailable GA
Failure
Re-evaluate patient and consider second-line surgery GC
Re-evaluate and re-enter algorithm at appropriate stage
Offer Botulinum toxin A or the opportunity for SNS GA
Offer the opportunity for SNS GA
Discuss bladder augmentation on urinary diversion GA


Man presenting with Urinary Incontinence
Initial assessment
History GA
Physical examiniation GA
Questionnaire optional GC
Voiding diary GB
Urinalysis GA
Post void residual if voiding difficulty GB
Pad test if quantification of leakage is desired GC
Reasons for specialist Referral
Haematuria
Pain
Recurrent UTI
Previous pelvic radiotherapy
Abnormal DRE
Findings suspicious of voiding dysfunction
Discuss management
Stress Incontinence
Mixed Incontinence
Urgency Incontinence
Advise on bowels, drugs, co-morbidity, fluid intake GC
Advise on weight loss GA
Consider intervention related to cognitive impairment (scheduled voiding) GC
Offer pads if needed GB
Consider reducing caffeine intake GB
Provide information on pelvic floor excersie GB
Bladder training GB
Anti-muscarinics GA
Consider PTNS GB
Failed initial management
Re-evaluate, perform urodynamics and cystoscopy, and consider imaging of lower UT GB
Stress Incontinence
Mixed Incontinence
Urgency Incontinence
Consider peri-urethral injection for temporary relief, and minimally invasive compressione devices GC
Offer Botulinum toxin A GA
Offer the opportunity for treatment with SNS GA
Consider fixed slings for men with PRPI GC
Discuss bladder augmentation or urinary diversion GC
Offer AUS to men with persistent moderate to severe PPI GB

6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

ACT	adjustable compression therapy (device)
AHRQ	Agency for Healthcare Research and Quality
AUS	artificial urinary sphincter
BT	bladder training
BTX	botulinum toxin
CIC	clean intermittent catheterisation
CNS	central nervous system
DO	detrusor overactivity
EAU	European Association of Urology
ER	extended release
FS2S	first stage of two-stage [implantation of sacral neuromodulator]
GR	grade of recommendation
HRQoL	health-related quality of life
ICI	International Consultation on Incontinence
I-QoL	Incontinence Quality of Life
IR	immediate release
LE	level of evidence
LUTS	lower urinary tract symptoms
MPR	medication possession rate [drug adherence]
MRI	magnetic resonance imaging
MUI	mixed urinary incontinence
NICE	National Institute for Health and Clinical Excellence (UK)
OAB	overactive bladder
PFMT	pelvic floor muscle training
PICO	Population, Intervention, Comparison, Outcome
PNE	percutaneous nerve evaluation
PROMS	patient-reported outcome measures
PTNS	posterior tibial nerve stimulation
PVR	post-voiding residual volume
Q_{max}	maximum urinary flow rate
QoL	quality of life
RCT	randomised controlled trial
RP	radical prostatectomy
SIGN	Scottish Intercollegiate Guideline Network
SUI	stress urinary incontinence
TDS	transdermal delivery system
TVTS	tension-free vaginal tape secure
UI	urinary incontinence
US	ultrasound
UTI	urinary tract infection
UUI	urgency urinary incontinence

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 kept on file in the European Association of Urology Central Office database. 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

Neurogenic Lower Urinary Tract Dysfunction

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European
Association
of Urology

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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)*

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

** 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 2: Grade of recommendation (GR)*

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

**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 adviced 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. Moreover, 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, 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 H_2O 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, as well those with SCI (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.

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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 (8-13). 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 was 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. Recent, 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 diagnosised 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 urethrovesical dysfunction in myelomeningocele 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 have been given 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 tramatic SCI with clinical concomitant brain injury has increased over the passed 50 years. These finding have consequences for the diagnosis and treatment of NLUTD (65).
In 25% of children with high anorecta malformationi, 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).
- Sarcoidosis: 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 erythematosus)***

Nervous system involvement occurs in about half of patients with systemic lupus erythematosus (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 transforaminal 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 has 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 to prevent it (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 guidelines will evolve as time goes by. The guidelines include definitions of important terms and procedures. 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

Acontractility, detrusor	*See below under voiding phase*
Acontractility, urethral sphincter	*See below under storage phase*
Autonomic dysreflexia	Increase of sympathetic reflex due to noxious stimuli with symptoms or signs of headache, hypertension, flushing face and perspiration
Capacity	*See below under storage phase*
Catheterisation, indwelling	Emptying of the bladder by a catheter that is introduced (semi-) permanently
Catheterisation, intermittent (IC)	Emptying of the bladder by a catheter that is removed after the procedure, mostly at regular intervals
• Aseptic IC	The catheters remain sterile, the genitals are disinfected, and disinfecting lubricant is used
• Clean IC	Disposable or cleansed re-usable catheters, genitals washed
• Sterile IC	Complete sterile setting, including sterile gloves, forceps, gown and mask
• Intermittent self-catheterisation (ISC)	IC performed by the patient
Compliance, detrusor	*See below under storage phase*
Condition	Evidence of relevant pathological processes

Diary, urinary	Record of times of micturitions and voided volumes, incontinence episodes, pad usage, and other relevant information
• 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*
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

Storage phase	
Maximum anaesthetic bladder capacity	Maximum bladder filling volume under deep general or spinal anaesthesia
Increased daytime frequency	Self-explanatory; the normal frequency can be estimated at about 8 times per day (124)
Nocturia	Waking at night one or more times to void
Urgency	The symptom of a sudden compelling desire to pass urine that is difficult to defer
Urinary incontinence	Any involuntary leakage of urine
• Stress urinary incontinence	On effort or exertion, or on sneezing or coughing
• Urge urinary incontinence	Accompanied by or immediately preceded by urgency
• Mixed urinary incontinence	Associated with urgency and also exertion, effort, sneezing, or coughing
• Continuous urinary incontinence	
Bladder sensation	

Normal	
• Symptom and history	Awareness of bladder filling and increasing sensation up to a strong desire to void
• 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	No sensation of bladder filling or desire to void
Non-specific	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 H_2O (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 ($\Delta pdet$):$C=\Delta V/\Delta pdet$ (mL/ cmH_2O)
• Low detrusor	compliance $C=\Delta V/\Delta pdet$ < 20 mL/cm H_2O (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	
Normal detrusor function	Voluntarily initiated detrusor contraction that causes complete bladder emptying within a normal time span
Detrusor underactivity	Contraction of reduced strength / duration
Acontractile detrusor	Absent contraction
Non-relaxing urethral sphincter	Self-explanatory
Detrusor sphincter dyssynergia (DSD)	Detrusor contraction concurrent with an involuntary contraction of the urethra and/or periurethral striated musculature
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***

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3. DIAGNOSIS

3.1 Introduction

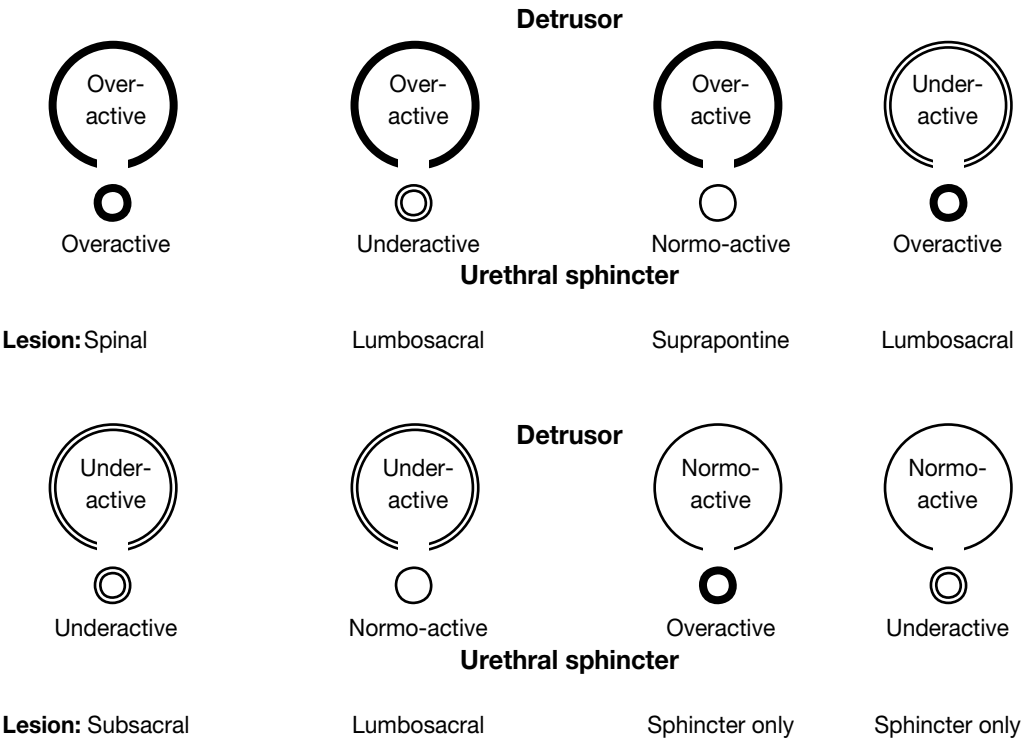
A thorough medical history and physical examination is mandatory, before any additional diagnostic investigations are planned. The clinical assessment of patients with NLUTD includes a detailed history, a

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. A simple classification focused on therapeutic consequences has been proposed 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*	
Past history	
	Childhood – adolescence – adult
	Hereditary or familial risk factors
	Menarche (age)*; may suggest metabolic disorder*
	Obstetric history
	History of diabetes; *in some cases correction will resolve the neurological problem*
	Diseases, *e.g. syphilis, Parkinsonism, multiple sclerosis, encephalitis*
	Accidents and operations, *especially those involving the spine and central nervous system*
Present history	
	Present medication
	Lifestyle (smoking, alcohol and drugs); *may influence bowel and urinary function*
	Quality of life
	Life expectancy
Specific urinary history	
	Onset urological history
	Relief after voiding; *to detect the extent of a neurological lesion in the absence of obstructive uropathy*
	Bladder sensation
	Initiation of micturition *(normal, precipitate, reflex, strain, Credé)*
	Interruption of micturition *(normal, paradoxical, passive)*
	Enuresis
	Mode and type of voiding (catheterisation)
	Urinary diary*; (semi)objective information about number of voids, day- and night-time voiding frequency, volumes voided, incontinence, urge episodes*
Bowel history	
	Frequency and faecal incontinence
	Desire to defecate
	Defecation pattern
	Rectal sensation
	Initiation of defecation *(digital rectal stimulation)*
Sexual history	
	Genital or sexual dysfunction symptoms
	Sensation in genital area
	Specific male: erection, (lack of) orgasm, ejaculation
	Specific female: dyspareunia, (lack of) orgasm
Neurological history	
	Acquired or congenital neurological condition
	Mental status and comprehension
	Neurological symptoms (somatic and sensory), with onset, evolution and any treatment
	Spasticity or autonomic dysreflexia (lesion above level Th 6) Mobility and hand function

** Extracted from Bors and Turner ([7] (LE: 4; GR: C) and Stöhrer, et al. [11] (LE: 4; GR: C).*

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. The 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 4). 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.

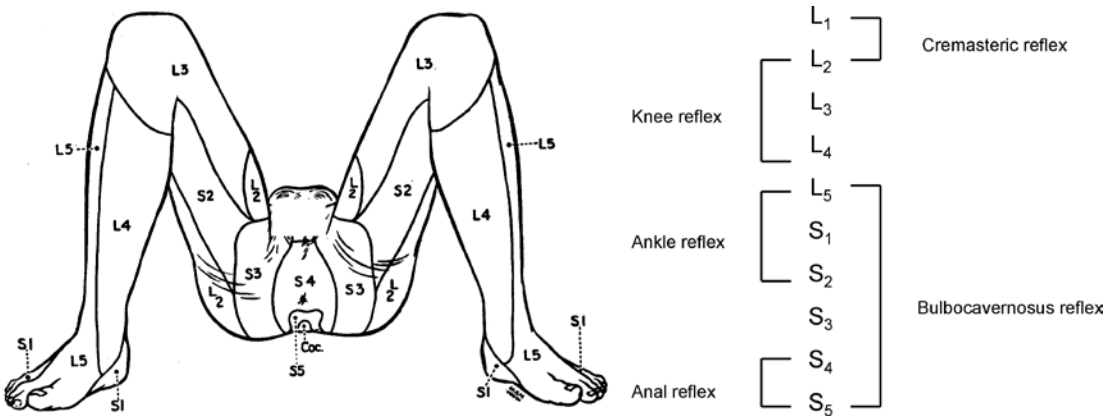


Figure 2: The neurological status of a patient with neurogenic lower urinary tract dysfunction (NLUTD) must be described as completely as possible: (a) dermatomes of spinal cord levels L2-S4; (b) urogenital and other reflexes in the lower spinal cord

Table 6: Neuro-urological items to be specified*

Sensations S2-S5 (both sides)	
	Presence (increased/normal/reduced/absent)
	Type (sharp/blunt)
	Afflicted segments
Reflexes (increased/normal/reduced/absent)	
	Bulbocavernous reflex
	Perianal reflex
	Knee and ankle reflexes
	Plantar responses (Babinski)
Anal sphincter tone	
	Presence (increased/normal/reduced/absent)
	Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
Prostate palpation	
Descensus (prolapse) of pelvic organs	

**From Stöhrer, et al. [11] (LE: 4; GR: C).*

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**

History taking	GR
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.	A
Special attention should be paid to the possible existence of alarm signs, such as pain, infection, haematuria, fever, etc, that warrant further specific diagnosis.	A
A specific history should be taken for each of the four mentioned	A
Physical examination	A
Individual patient handicaps should be acknowledged in planning further investigations.	A
The neurological status should be described as completely as possible. Sensations and reflexes in the urogenital area must all be tested.	A
The anal sphincter and pelvic floor functions must be tested extensively.	A
Urinalysis, blood chemistry, voiding diary, residual and free flowmetry, incontinence quantification and urinary tract imaging should be performed.	A

** 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 nonrelaxing 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 theurinary 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 (UMNL) and lower motor neuron lesion (LMNL) (33-38). Patients with UMNL 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 H_2O) 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*

Recommendations	GR
Urodynamic investigation is necessary to document the (dys-)function of the LUT.	A
The recording of a bladder diary is advisable.	B
Non-invasive testing is mandatory before invasive urodynamics is planned.	A
Video-urodynamics is the gold standard for invasive urodynamics in patients with NLUTD. If this is available, then a filling cystometry continuing into a pressure flow study should be performed.	A
A physiological filling rate and body-warm saline must be used.	A
Specific uro-neurophysiological tests are elective procedures.	C

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).

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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): Regretfully, 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 excitatoryand 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).

4.2.3.1.1 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.

4.2.3.1.1.1 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 (PDE5I)

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 antimuscarinicdrug 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

Conclusions	**LE**
Long-term efficacy and safety of antimuscarinic therapy for NDO is well documented.	1a
A combination of antimuscarinic agents is now used more frequently and is often considered to maximise outcomes for NDO.	1a
Alternative ways of administration of antimuscarinic agents, such as transdermally and intravescically, should now be considered.	2a
There is no drug with evidence of efficacy for underactive detrusor.	2a
Alpha-blockers have been partly successful in decreasing bladder outlet resistance and autonomic dysreflexia prophylaxis in spinal cord injury.	2a
There is a lack of prospective, randomised, controlled studies in the medical management of NLUTD.	

Recommendations on drug treatments	GR
Antimuscarinic therapy for NDO is effective and safe to use, including 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 intravescically, 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

*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***

Statements	LE
The first aim of any therapy is the protection of the upper urinary tract.	1
A condom catheter or pads may reduce urinary incontinence to a socially acceptable situation.	

Recommendations	GR
The mainstay of treatment for overactive detrusor is anticholinergic drug therapy.	A
Lower urinary tract rehabilitation may be effective in selected cases (patients that do not suffer from a complete spinal cord lesion).	
Any method of assisted bladder emptying should be used with the greatest caution.	A

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***

Recommendations	GR
Intermittent catheterisation is the standard treatment for patients who are unable to empty their bladder.	A
Patients should be well instructed in the technique and risks of IC.	
Aseptic IC is the method of choice.	B
The catheter size should be 12-14 Fr.	B
The frequency of IC is 4-6 times per day.	B
The bladder volume should remain below 400.	B
Indwelling transurethral and suprapubic catheterisation should be used only exceptionally, under close control, and the catheter should be changed frequently. Silicone catheters are preferred and should be changed every 2-4 weeks, while (coated) latex catheters need to be changed every 1-2 weeks.	A

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****

Recommendations	GR
Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity.	A
Sphincterotomy is the standard treatment for DSD.	A
Bladder neck incision is effective in a fibrotic bladder neck.	B

**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, cystolysis, 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 a urine collecting devic eis 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

Recommendations			**GR**
Detrusor	Overactive	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	B
		Sacral rhizotomy with SARS in complete lesions and sacral neuromodulation in incomplete lesions are effective treatments in selected patients	B
		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	B
	Underactive	SARS with rhizotomy and sacral neuromodulation are effective in selected patients	B
		Restoration of a functional bladder by covering with striated muscle is still experimental	
Urethra	Overactive (DSD)	refer to guidelines for minimal invasive treatment (see Section 4.3.6)	
	Underactive	The placement of a urethral sling is an established procedure	B
		The artificial urinary sphincter is very effective	B
		Transposition of the gracilis muscle is still experimental	

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5. URINARY TRACT INFECTION IN NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

5.1 Introduction

Complicated UTI is the name given to urinary tract infection (UTI) in neurogenic lower urinary tract dysfunction (NLUTD). 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

Recommendations	GR
Bacteriuria in patients with spinal cord injury (SCI) should not be treated, even in cases of intermittent catheterisation.	
As in the general population, the use of long term antibiotics in recurrent UTIs may cause bacterial resistance and caution is advised.	
Protection of the urinary tract is the main focus.	

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6. TREATMENT OF VESICO-URETERAL REFLUX

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.

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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 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

Recommendations	GR
Oral PDE5Is are the first-line treatment for erectile dysfunction in men with SCI.	A
Intracavernosal injections of vasoactive drugs (alone or in combination) are the second-line treatment when oral medications have failed.	A
Mechanical devices such as vacuum devices and rings may be effective but are not as popular.	C
Surgical prostheses should be reserved for selected patients who have not responded to conservative therapies.	B

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.

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8. QUALITY OF LIFE

8.1 Introduction

Quality of life (QoL) is a very important aspect of the global 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 HRQL 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

Conclusions	LE
One of the main aims of therapy is to improve qualify of life.	1
There is a lack of disease-specific outcome measures assessing HRQoL in patients with NLUTD.	

Recommendations	GR
Quality of life should be assessed when evaluating lower urinary tract symptoms in neurogenic patients and when treating neurogenic bowel dysfunction.	B
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.	B

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9. FOLLOW-UP

9.1 Introduction

NLUTD 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 specialistic 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.

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10. CONCLUSIONS

NLUTD is a multi-faceted pathology. It requires an extensive and specific diagnosis before we 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

CVA	cerebrovascular
DLPP	detrusor leak point pressure
DO	detrusor overactivity
DSD	detrusor sphincter dyssynergia
EMG	electromyography, electromyogram
FVC	frequency volume chart
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IC	intermittent catheterisation
ISC	intermittent self-catheterisation
ICS	international Continence Society
LPP	leak point pressure
LMNL	lower motor neuron lesion
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
MTC	micturition time chart
NDO	neurogenic detrusor overactivity
NLUTD	neurogenic lower urinary tract dysfunction
PNE	percutaneous nerve evaluation test
QoL	quality of life
SARS	sacral anterior root stimulation
SCI	spinal cord injury
SDAF	sacral deafferentation
SLE	systemic lupus erythematosus
UMNL	upper motor neuron lesion
UTI	urinary tract infection
VAS	visual analogue scale
VS	vibrostimulation

Conflict of interest

All members of the Neurogenic Lower Urinary Tract Dysfunction guidelines working group have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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 Urolithiasis

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European
Association
of Urology

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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 November 2010 to August 10th, 2011. 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.

For this limited update 124 unique records were identified of which 28 new references were selected for inclusion in this document. For a number of sections which included recommendations upgraded following panel consensus (High-risk stone formers and familiar risk [2.6], Patient evaluation [3.1.2] and Decompression of obstructed kidney [4.2.1]) additional verification searches were done to assess whether additional evidence has become available over the past year. These searches were not limited to level 1 data. Only in two instances could a higher level of evidence (not influencing the grade of recommendation) be found (3.2.2 Recommendations for repeat analysis of stone composition and 5.7.2.1 Indications for laparoscopic stone surgery). 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.

For the 2011 full text update, 4,013 papers were identified and 688 were included in the 2011 print, which also included key publications from other sources were proposed by panel members. Initial assessment and selection were based on citation and abstract only, and when in doubt, full-text papers were consulted. Meta-analysis of the stone-free rates for the section on ureteral calculi was updated. An overall scoping search was conducted to ensure that the individual searches met the minimum requirement of identification of all level 1 evidence. 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)*

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

** 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)*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without RCTs
C	Made despite the absence of directly applicable clinical studies of good quality

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

1.5 Publication history

The current guidelines present a limited update following a complete update of the 2011 print version. The first EAU Guidelines on Urolithiasis were published in 2000. Subsequent updates were in 2001 (partial), 2005 (comprehensive), 2008 (comprehensive), and 2009 and 2010 (limited). Several summaries have been published in scientific journals; the first in 2001 (5) and subsequently in 2007 (6,7).

A quick reference document presenting the main findings of the urolithiasis guidelines is also available with several scientific publications in the EAU journal European Urology and 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/.

This document was peer-reviewed prior to publication.

1.5.1 Summary of changes

New literature included

Section	Title
2.3	X-ray characteristics
2.6	Risk groups for stone formation (Table 6)
5.3.4	Factors affecting success of MET
5.5.3	Best clinical practice

5.6.1.5.4	Puncture
5.6.1.5.7	Management of complications following PNL (new Table 14)
5.6.2.2.1	Pre-operative work up and preparations
5.6.2.2.6	Stone extraction new data added
5.6.2.2.8	Stenting prior to, and after URS
5.7.2	Laparoscopic surgery
6.4	Selection of procedure for active removal of kidney stones

New literature resulting in a change of LE in the recommendation sections

3.1	Diagnostic imaging: Patient evaluation (3.1.2) for patients in whom treatment of renal stones is planned (NCCT recommended in favour of IVU)
3.2	Recommendations for repeat stone analysis in patients: (LE:2 - old listing LE:3)
5.7.2.1	Indications for laparoscopic stone surgery - recommendations (LE: 3 - old listing LE: 4)

New literature has been including in the following sections resulting in new recommendations or a change in ranking (GR)

5.7.2.1	Indications for laparoscopic stone surgery - New recommendation on large impact stones or when endoscopic lithotripsy or SWL have failed.
6.4.2	Selection of procedure for active removal of kidney stones.

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2. CLASSIFICATION OF STONES

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence.

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 radiography; KUB) (Table 3), which varies according to mineral composition. 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) (1,2).

Table 3: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dihydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-dihydroxyadenine
		'Drug-stones' (Section 11.11)

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*

Non-infection stones • Calcium oxalate • Calcium phosphate (including brushite and carbonate apatite) • Uric acid
Infection stones • Magnesium ammonium phosphate • Carbonate apatite • Ammonium urate
Genetic causes • Cystine • Xanthine • 2,8-dihydroxyadenine
Drug stones

*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, and that comprising the largest part is the most important. Table 5 lists the clinically most relevant substances and their mineral components.

Table 5: Stone composition

Chemical composition	Mineral
Calcium oxalate monohydrate	whewellite
Calcium oxalate dihydrate	wheddelite
Uric acid dihydrate	uricite
Ammonium urate	
Magnesium ammonium phosphate	struvite
Carbonate apatite (phosphate)	dahllite
Calcium hydrogenphosphate	brushite
Cystine	
Xanthine	
2,8-dihydroxyadenine	
'Drug stones'	

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 (3,4). 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) (5-7).

Table 6: High-risk stone formers (7-12)

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones (calcium hydrogen phosphate; $CaHPO_4 . 2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the solitary kidney itself does not particularly increase risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Nephrocalcinosis
Gastrointestinal diseases (i.e. jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion)
Sarcoidosis
Genetically determined stone formation
Cystinuria (type A, B, AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-dihydroxyadenine
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drugs associated with stone formation (Section 11.11)
Anatomical abnormalities associated with stone formation

Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele

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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 should be used as the primary diagnostic imaging tool although pain relief, or any other emergency measures should not be delayed by imaging assessments. It is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calices, pelvis, and pyelo-ureteric and vesicoureteric junctions, as well as upper urinary tract dilatation. For stones > 5 mm, ultrasound has a sensitivity of 96% and specificity of nearly 100% (1). For all stone locations, sensitivity and specificity of ultrasound reduces to 78% and 31%, respectively (1).

The sensitivity and specificity of KUB is 44-77% and 80-87%, respectively (2). KUB 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.

Recommendation	LE	GR
With fever or solitary kidney, and when diagnosis is doubtful, immediate imaging is indicated.	4	A*

**Upgraded following panel consensus.*

3.1.1 Evaluation of patients with acute flank pain

Non-contrast-enhanced computer tomography 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 with IVU, NCCT shows higher sensitivity and specificity for identifying urinary stones (Table 7) (4-8).

Table 7: Comparison of non-contrast-enhanced computer tomography (NCCT) and intravenous urography (IVU)

Reference	NCCT		IVU	
	Sensitivity	Specificity	Sensitivity	Specificity
Miller (5)	96%	100%	87%	94%
Niall (7)	100%	92%	64%	92%
Sourtzis (4)	100%	100%	66%	100%
Yilmaz (6)	94%	97%	52%	94%
Wang (8)	99%	100%	51%	100%

Recommendation	LE	GR
NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU (9,10).	1a	A

NCCT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones (11).

NCCT can determine stone density, inner structure of the stone and skin-to-stone distance; both of which affect extracorporeal shock wave lithotripsy (SWL) outcome (12-15). The advantage of non-contrast imaging must be balanced against loss of information about renal function and urinary collecting system anatomy, as well as higher radiation dose (Table 8).

Radiation risk can be reduced by low-dose CT (16). In patients with body mass index (BMI) < 30, low-dose CT was 86% sensitive for detecting ureteric stones < 3 mm and 100% sensitive for detecting calculi > 3 mm (17). A meta-analysis of prospective studies (18) showed that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (92.0-97.0).

Table 8: Radiation exposure of imaging modalities (19-22)

Method	Radiation exposure (mSv)
KUB	0.5-1
IVU	1.3-3.5
Regular-dose NCCT	4.5-5
Low-dose NCCT	0.97-1.9
Enhanced CT	25-35

Recommendation	LE	GR
In patients with BMI < 30, low-dose NCCT should be used.	1b	A

3.1.2 Evaluation of patients for whom further treatment of renal stones is planned

A contrast study is recommended if stone removal is planned and the renal collecting system anatomy is not known. 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.

Recommendation	LE	GR
A renal contrast study (enhanced CT or IVU) is indicated when planning treatment for renal stones.	3	A*

** Upgraded based on panel consensus.*

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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 analysis - emergency stone patient (1-4)

Urine	**GR**
Urinary sediment/dipstick test of spot urine sample • red cells • white cells • nitrite • approximate urine pH	A*
Urine culture or microscopy	A
Blood	

Serum blood sample • creatinine • uric acid • ionized calcium • sodium • potassium	A*
Blood cell count CRP	A*
If intervention is likely or planned: Coagulation test (PTT and INR)	A*

** Upgraded based on panel consensus.*
CPR = C-reactive protein; INR = international normalised ratio; PTT = partial thromboplastin time.

*3.2.1 **Basic analysis - non-emergency stone patients***

Biochemical work-up is similar for all stone patients. However, examination of sodium, potassium, CRP, blood coagulation time can be omitted for non-emergency cases.

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. 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).

The patient should be instructed to filter the 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 10: Accuracy of substance identification in stone analysis (5)

Accuracy of identification of substance (%)	Chemical analysis	Infrared spectroscopy	X-ray diffraction
Uric acid	81.0	97.6	97.9
Ammonium urate	83.1	95.0	96.0
Cystine	93.5	99.1	98.5
Xanthine	28.4	96.3	93.2
2,8-Dihydroxyadenine	6.0	80.0	69.6
Whewellite	85.6	97.8	98.7
Struvite	89.5	97.9	98.0
Brushite	69.6	97.4	100.0
Apatite	79.4	93.9	100.0
Calcite	66.0	98.5	98.2
Cholesterol	38.9	98.6	82.4
Silicium dioxide	21.6	95.6	98.1
Gypsum	38.6	96.0	77.1

Recommendations	LE	GR
Always perform stone analysis in first-time formers using a valid procedure (XRD or IRS).	2	A
Repeat stone analysis in patients: • presenting with reccurent stones despite drug therapy; • with early recurrence after complete stone clearance; • with late recurrence after a long stone-free period because stone composition may change (3).	2	B

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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 with NSAIDs, and carry a greater likelihood of further analgesia being needed (7,8) (see Section 4.1.3). If an opioid is used, it is recommended that it is not pethidine.

Recommendations	GR
In acute stone episodes, pain relief should be initiated immediately.	A
Whenever possible, an NSAID should be the first drug of choice.	A

4.1.2 ***Prevention of recurrent renal colic***

Most ureteral stones pass spontaneously (Section 5.1.1), and facilitation of passage 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). Although diclofenac can affect renal function in patients with already reduced function, it has no effect in patients with normal kidney function (LE: 1b) (11).

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 (10).

Daily α-blockers reduce recurrent colic (LE: 1a) (Section 5.3) (12,13).

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***

	LE	GR	Refs.
First choice: start with an NSAID, e.g. diclofenac*, indomethacin or ibuprofen.	1b	A	1-4
Second choice: hydromorphine, pentazocine and tramadol.	4	C	
*Recommended to counteract recurrent pain after ureteral colic.	1b	A	7

**Affects glomerular filtration rate (GFR) in patients with reduced but not normal renal function (LE: 2a) (14).*

Although NSAIDs constitute the first choice for medical management of acute renal colic pain, spasmolytics may be given when parenteral administration of a non-narcotic agent is mandatory (third-line treatment) (15,16).

4.1.4 ***References***

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4.2 Management of sepsis in obstructed kidney

Obstructed, infected kidney is a urological emergency. Urgent decompression is necessary to prevent further complications in infected hydronephrosis secondary to a stone-induced, either 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 under general anaesthesia;
- percutaneous placement of a nephrostomy catheter.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting as primary treatment of infected hydronephrosis. There is no good-quality evidence to suggest that ureteric stenting under general anaesthesia has more complications than percutaneous nephrostomy. However, the latter has the advantage of avoiding general anaesthesia and instrumentation in the urinary tract (1,4-6).

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).

A “stent first where possible” approach may reduce the requirement for out-of-hours nephrostomy placement in patients with infected hydronephrosis, although it does not eliminate the demand for nephrostomy (1-8).

Definitive treatment of the stone should be delayed until the infection is cleared following a complete course of antimicrobial therapy (9).

Exceptionally, emergency nephrectomy may become necessary for severe sepsis and/or abscess formation.

Statement	LE
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendation	LE	GR
For sepsis with obstructing stones, the collecting system should be urgently decompressed, using percutaneous drainage or ureteral stenting. Definitive treatment of the stone should be delayed until sepsis is resolved.	1b	A

*4.2.2 **Further measures***

Following urgent decompression of the obstructed and infected system, urine samples should be sent for culture-antibiogram sensitivity testing, and antibiotics should be initiated immediately thereafter. The regimen should be revisited in the light of the culture-antibiogram test. Intensive care might become necessary.

Recommendations	GR
Collect urine for antibiogram test following decompression.	A*
Start antibiotics immediately thereafter (+ intensive care if necessary).	
Revisit antibiotic treatment regimen following antibiogram findings.	

** Upgraded based on panel consensus.*

*4.2.3 **References***

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5. STONE RELIEF

When deciding between active stone removal and conservative treatment with medical expulsive therapy (MET), it is important to consider all the circumstances of a patient that may affect treatment decisions.

5.1 Observation of ureteral stones

5.1.1 Stone-passage rates

There are only limited data about spontaneous stone passage according to size (1,2). A meta-analysis of 328 patients harbouring ureteral stones < 10 mm investigated the likelihood of ureteral stone passage (Table 11) (1). 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 11: Likelihood of ureteral stone passage of ureteral stones (1)

Stone size	passage	CI
< 5 mm (n = 224)	68%	(95% CI 46-85%)
> 5 mm (n = 104)	47%	(95% CI 36-58%)
< 2 mm	31 days	
2-4 mm	40 days	
> 4-6 mm	39 days	

95% of stones up to 4 mm pass within 40 days (2).

Recommendations	LE	GR
In patients with newly diagnosed ureteral stones < 10 mm, and if active removal is not indicated (Chapter 6), observation with periodic evaluation is optional initial treatment.	1a	A
Such patients may be offered appropriate medical therapy to facilitate stone passage during observation.*		

**see also Section 5.3, Medical expusive 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	LE
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.	4

Recommendations	GR
Kidney stones should be treated in case of growth, formation of de novo obstruction, associated infection, and acute or chronic pain.	A
Comorbidity and patient preference need to be taken into consideration when making treatment decisions.	C
If kidney stones are not treated, periodic evaluation is needed.	A

** 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 (3,4).

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 less episodes of colic than those not receiving such therapy (3,5).

Statement	LE
There is growing evidence that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain (3-15).	1a

*5.3.1 **Choice of medical agent***

5.3.1.1 Alpha-blockers

Tamsulosin is one of the most commonly used alpha-blockers (3,5,16-19). However, one small study has suggested that tamsulosin, terazosin and doxazosin are equally effective, indicating a possible class effect (20). This is also indicated by several trials demonstrating increased stone expulsion using doxazosin (4,20,21) terazosin (20,22) alfuzosin (23-26) and naftopidil (27,28).

Statement	LE
Several trials have demonstrated increased stone expulsion using tamsulosin, doxazosin, terazosin, alfuzosin and naftopidil.	1b

5.3.1.2 Calcium-channel blockers

With regard to the class effect of calcium-channel blockers, only nifedipine has been investigated (LE = 1a) (3,8-10, 29,30).

5.3.1.2.1 Tamsulosin versus nifedipine

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 (10,29,30).

5.3.1.3 Corticosteroids

Based on studies with a limited number of patients (31,32: LE 1b), no recommendation for the use of corticosteroids in combination with alpha-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 alpha-blockers as an accelerating adjunct (3,20,31,32).	1b

Recommendations for MET	LE	GR
For MET, alpha-blockers or nifedipine are recommended.		A
Patients should be counselled about the attendant risks of MET, including associated drug side effects, and should be informed that it is administered as 'off-label' use.†		A*
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.		A
Patients should be followed once between 1 and 14 days to monitor stone position and to assess for hydronephrosis.	4	A*

† It is not known if tamsulosin harms the human foetus or if it is found in breast milk.
** Upgraded based on panel consensus.*

*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 (4,33-36) (LE: 1b). However, MET does reduce the need for analgesics (3,5) (LE: 1a).

5.3.2.2 Stone location

The vast majority of trials have investigated distal ureteral stones (3). 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 (37) (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 stone-free rates and reduce analgesic requirements (6,11,38-46) (LE: 1a).

5.3.2.4 Medical expulsive therapy after ureteroscopy

MET following holmium:YAG laser lithotripsy increases stone-free rates and reduces colic episodes (47) (LE: 1b).

5.3.2.5 Medical expulsive therapy and ureteral stents (section 5.6.2.2.8)

5.3.2.6 Duration of medical expulsive therapy treatment

Most studies have included a duration of 1 month or 30 days. No data is currently available to support other time-intervals.

*5.3.3 **Medical expulsive therapy in the paediatric population***

A recent study has investigated the expulsion rate and time to expulsion of ureteral stones ≤ 10 mm in children aged 2-14 years receiving doxazosin or ibuprofen, but failed to demonstrate the effectiveness of doxazosin (48) (LE: 2a).

Statements	**LE**
MET has an expulsive effect also on proximal ureteral stones.	1b
After SWL for ureteral or renal stones, MET seems to expedite and increase stone-free rates, reducing additional analgesic requirements.	1a
MET in children cannot be recommended due to the limited data in this specific population.	4

*5.3.4 **References***

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5.4 Chemolytic dissolution 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), URS or open surgery to support elimination of small residual fragments. However, because its use as first-line therapy may take weeks to be effective, it is mainly used as an adjunct to endourological therapy.

Combined treatment with SWL and chemolysis is a minimal invasive option for patients with partial or complete infection staghorn stones who are not suitable 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***

Recommendations	GR
In percutaneous chemolysis, at least two nephrostomy catheters should be used to allow irrigation of the renal collecting system, while preventing chemolytic fluid draining into the bladder and reducing the risk of increased intrarenal pressure*.	A
Pressure- and flow-controlled systems should be used if available.	

** Alternatively, one nephrostomy catheter with a JJ stent and bladder catheter can serve as a through-flow system preventing high pressure.*

Table 12: Methods of percutaneous irrigation chemolysis

Stone composition	Refs.	Irrigation solution	Comments
Struvite Carbon apatite	1-6	10% hemiacidrin, pH 3.5-4 Suby's G	Combination with SWL for staghorn stones
			Risk of cardiac arrest due to hypermagnesaemia
Brushite	7	Hemiacidrin Suby's G	Can be considered for residual fragments
Cystine	8-13	Trihydroxymethyl aminomethane (THAM; 0.3 or 0.6 mol/L), pH 8.5-9.0 N-acetylcysteine (200 mg/L)	Takes significantly longer time than for uric acid stones
			Used for elimination of residual fragments
Uric acid	10,14-18	THAM (0.3 or 0.6 mol/L), pH 8.5-9.0	Oral chemolysis is the preferred option

*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 (14,16,18,19).

When chemolitholysis is planned, the pH should be adjusted to 7.0-7.2. Addition of allopurinol may support chemolysis and prevention of recurrent stones. No formal recommendation on allopurinol use can be given.

In case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated (6).

Recommendations	GR
The dosage of alkalising medication must be modified by the patient according to urine pH, which is a direct consequence of alkalising medication.	A
Dipstick monitoring of urine pH by the patient is required at regular intervals during the day. Morning urine must be included.	A
The physician should clearly inform the patient of the significance of compliance.	A

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5.5 Extracorporeal shock wave lilthotripsy (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 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 urinary tract infections (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 stone-free rate (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 correct stent position, the stent must be removed and replaced by a new JJ stent or a percutaneous nephrostomy tube, even when ultrasound does not reveal any dilatation.

5.5.2.2 Stenting in ureteral stones

The 2007 AUA/EAU Guideline on the management of ureteral calculi states 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).

Recommendation	LE	GR
Routine stenting is not recommended as part of SWL treatment of ureteral stones.	1b	A

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 stone-free rate (12-16). Tissue damage increases with shock wave frequency (17,18).

Statement	LE	GR
The optimal shock wave frequency is 1.0-1.5 Hz (16).	1a	A

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 (19), which prevents renal injury (20). Animal studies (21) and a prospective randomised study (22) have shown better stone-free rate (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 (23).

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).

Statement	LE
Clinical experience has shown that repeat sessions are feasible (within 1 day for ureteral stones).	4

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. Only a 2% defect in the gel layer covering the cushion reduces stone fragmentation by 20-40% (24). Ultrasonography gel is probably the optimum agent available for use as a lithotripsy coupling agent (25). To reduce air pockets, ultrasonography gel should be applied to the water cushion straight from the container, rather than by hand (26).

Recommendation	LE	GR
Ensure correct use of the coupling gel because this is crucial for effective shock wave transportation (24).	2a	B

5.5.3.5 Procedural control

Results of treatment are operator dependent, and better results are obtained by urologists who treat larger numbers of patients. During the procedure, careful imaging control of localisation contributes to outcome quality (27).

Recommendation	LE	GR
Maintain careful fluoroscopic and/or ultrasonographic monitoring during the procedure.	4	A*

** 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 (28-30).

Recommendation	LE	GR
Use proper analgesia because it improves treatment results by limiting induced movements and excessive respiratory excursions.	4	C

5.5.3.7 Antibiotic prophylaxis

No standard 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, infectious stones) (31,32).

Recommendation	LE	GR
In case of infected stones or bacteriuria, antibiotics should be given prior to SWL.	4	C

5.5.3.8 Medical expulsive therapy after extracorporal shock wave lithotripsy

MET after SWL for ureteral or renal stones can expedite expulsion and increase stone-free rates, as well as reduce additional analgesic requirements (33-43) (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 (44,45) (Table 13).

Table 13: SWL-related complications (1,4,44-46)

Complications			%	Refs.
Related to stone fragments		Steinstrasse	4-7	47-49
		Regrowth of residual fragments	21-59	50
		Renal colic	2-4	46
Infectious		Bacteriuria in non-infection stones	7.7-23	50,51
		Sepsis	1-2.7	50,51
Tissue effect	Renal	Haematoma, symptomatic	< 1	1,52
		Haematoma, asymptomatic	4 - 19	1,52
	Cardiovascular	Dysrhythmia	11-59	50,53
		Morbid cardiac events	Case reports	50,53
	Gastrointestinal	Bowel perforation	Case reports	54-56
		Liver, spleen haematoma	Case reports	56-58

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached (9,59-61).

*5.5.5 **References***

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5.6 Endourology techniques

*5.6.1 **Percutaneous nephrolithotomy (PNL)***

Since Goodwin et al. first punctured the kidney in 1955 and Harris et al. used a bronchoscope for nephroscopy in 1975, rapid technological advances have revolutionised endourological procedures. Currently, percutaneous nephrolithothomy (PNL) is a minimally invasive surgical procedure for removal of kidney stones (1,2). Rigid and flexible nephroscopes of different sizes have been developed.

5.6.1.1 Rigid nephroscopes

Rigid nephroscopes are available in diameters up to 28 Ch [Charrière (French) gauge], allowing maximal working and irrigation channels. Thinner nephroscopes are available for Mini-PNL (also known as Mini-perc), which uses nephroscopes of diameter 11-18 Ch. The term Mini-PNL (Mini-perc), although not precisely defined, indicates the use of smaller diameter nephroscopes compared with standard PNL. The smaller diameter results in smaller working channels.

Mini-PNL is associated with less morbidity than standard PNL. However, the benefit of using a smaller-calibre nephroscope to preserve renal parenchyma has not been confirmed (3-5). The use of Mini-PNL in adult patients is controversial, but Mini-PNL is the standard procedure for percutaneous stone removal in children (3,4) (Section 9.2.3).

5.6.1.2 Flexible nephroscopes

In complex cases, such as multiple or staghorn stones, or difficult anatomy, such as horseshoe kidneys, the use of rigid nephroscopes may require multiple access procedures. However, the use of flexible nephroscopes, or combination of retrograde flexible ureteroscopy with standard nephroscopy, reduces the need for multiple-access procedures. New 'chip-on-the-tip' endoscopes are equipped with a camera on the tip of the instrument and a light-emitting diode to improve visibility and handling. Complete stone clearance is viewed endoscopically and by X-ray.

5.6.1.3 Intracorporeal lithotripsy

Intracorporeal lithotripsy can be performed in several different ways (devices are discussed in Section 5.6.2.2.7). During PNL procedures, ultrasonic or pneumatic lithotripters are most commonly used. Electrohydraulic intracorporeal lithotripsy is effective even for hard kidney stones; however, due to potential damage to surrounding tissue, it should only be used in carefully selected cases, such as hard cystine stones.

With the increase in the use of flexible nephroscopes, the holmium:yttrium-aluminium-garnet (Ho:YAG) laser is becoming more important in ureteroscopy and PNL. It can be used for lithotripsy in parts of the calyceal system that are only accessible with flexible nephroscopes. Where flexible devices are used for PNL, the Ho:YAG laser has become the preferred intracorporeal lithotripter (5).

Recommendations	**GR**
Ultrasonic, ballistic and Ho:YAG devices are recommended for intracorporeal lithotripsy using rigid nephroscopes.	A*
When using flexible instruments, the Ho:YAG laser is currently the most effective device.	

** Upgraded based on panel consensus.*

5.6.1.4 Extraction tools

Stones or stone fragments are extracted from the kidney through the access sheath of the nephroscope using forceps or baskets, washing out with irrigation fluid, or using a suction device. New baskets made of nitinol (nickel-titanium alloy) provide additional advantages compared with steel wire baskets. Tipless versions of nitinol baskets are also available for use in calices.

5.6.1.5 Best clinical practice

5.6.1.5.1 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 (6).

Other important contraindications include:

- untreated UTI;
- atypical bowel interposition;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (see Section 8.2).

5.6.1.5.2 Preoperative imaging

Preprocedural evaluations are summarised in Chapter 3. In particular for PNL, ultrasonography 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, lung) (7,8).

Recommendation	GR
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.*

5.6.1.5.3 Positioning of the patient

Traditionally, the patient is positioned prone for PNL. Supine position is also possible, with or without flank upholstering. Both positions are equally safe. The advantages of the supine position for PNL are (9,10):

- shorter operating time;
- possibility of simultaneous retrograde transurethral manipulation;
- more convenient position for the operator;
- easier anaesthesia.

Although the supine position confers some advantages (9,10), it depends on appropriate equipment being available to position the patient correctly, e.g. X-ray devices and operating table. The supine position can limit the manoeuvrability of instruments (11).

5.6.1.5.4 Puncture

After the insetion of a ureteric catheter, balloon or otherwise, the appropriate calyx is punctured, using fluoroscopy or ultrasonography guidance. Ultrasonography guidance is associated with decreased radiation hazards (12).

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. The colon is not reliably detectable with ultrasound, so preprocedural imaging is recommended. In particular, preoperative CT provides further information (13,14). However, ultrasound-guided puncture will allow identification of the tissue between the skin and kidney and lower the incidence of bowel injury (15).

5.6.1.5.5 Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a ureteral balloon dilatator. Use of balloon dilatation can reduce blood transfusion rates (16). One-stage dilatation has been shown to be safe and effective, even in patients with a history of open surgery on the same kidney (17,18).

5.6.1.5.6 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.

Ureteral stenting at the end of the procedure is common procedure using antegrade placement of a JJ stent. They are usually placed using the antegrade approach at the end of the procedure. The most important criteria for ureteral stenting are residual stone fragments, inadequate transureteral drainage, or alterations to the pyeloureteral junction. An external ureteral catheter can be used instead of a JJ stent (19).

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 (20-24).

Recommendation	LE	GR
In uncomplicated cases, tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and without ureteral stent) PNL procedures provide a safe alternative.	1b	A

5.6.1.5.7 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 14). See also the EAU Guidelines on Reporting and Grading of Complications after Surgical Procedures (26).

Table 14: Complications following PNL

Complications	Transfusion	Embolisation	Urinoma	Fever	Sepsis	Thoracic complication	Organ injury	Death	LE
(Range)	(0-20%)	(0-1.5%)	(0-1%)	(0-32.1%)	(0.3-1.1%)	(0-11.6%)	(0-1.7%)	(0-0.3%)	1a
N = 11,929	7%	0,4%	0,2%	10,8%	0,5%	1,5%	0,4%		

Urinary leakage and stone clearance can be viewed endoscopically and by X-ray. 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 (27,28). 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 (29-31).

Bleeding after PNL may be due to intraparenchymal haemorrhage or acquired intrarenal aneurysm. With the former, brief clamping of the nephrostomy may stem bleeding. The latter may be marked by intense bleeding, and it can be treated by super-selective embolic occlusion of the artery supplying the aneurysm (32).

5.6.1.6 References

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5.6.2 ***Ureterorenoscopy (URS) (including retrograde access to renal collecting system)***

During the past 20 years, ureterorenoscopy (URS) has dramatically changed the management of ureteral calculi. Major technical improvements include endoscope miniaturization, enhanced optical quality and tools, and introduction of disposables. URS has had a great impact on active stone removal and is performed increasingly worldwide.

5.6.2.1 Instruments

5.6.2.1.1 Rigid scopes

Semi-rigid ureteroscopy for urinary stone removal became a standard procedure in the 1990s. Today, small endoscopes with tip diameters < 8 Ch are mainly used. In Europe, rigid URS is used for proximal and distal ureteral calculi, but an increasing number of urologists prefer flexible endoscopes for proximal calculi. However, rigid URS is safe even for proximal ureteral calculi (1-11).

5.6.2.1.2 Flexible endoscopes

Technological advances have been responsible for the evolution of flexible URS (12), especially for improved deflection mechanisms, which have reached almost 300° in the latest generation, facilitating intrarenal manoeuvrability (13,14). The latest endoscopes have also made it possible to visualise the lower pole in almost all kidneys. Although a secondary active deflection mechanism has been introduced, it has not yet demonstrated its superiority over conventional flexible URS (15,16).

The durability of the latest generation of flexible scopes has been improved by stiffer shaft construction (17,18).

As with rigid scopes, the tip diameters of flexible scopes usually do not exceed 8.7 Ch.

5.6.2.1.3 Digital scopes
The miniaturisation of flexible scopes has significantly improved their effectiveness (19-21), but it has also reduced the number of fibreoptics, and therefore, the optical quality and durability.

Digital URS eliminates the need for fragile low-resolution fibreoptics. The tips of digital ureteroscopes contain digital camera chips (complementary metal-oxide semiconductors or charge-coupled devices), which produce superior image resolution. The tips also have light-emitting-diode-driven light carriers, which provide a substitute for an external light source (22).

Initial experience with digital scopes has demonstrated marked improvement in image quality, with efficacy comparable to that achieved with analogue URS (23,24). To prevent damage to the camera chip, ballistic lithotripsy can no longer be used.

5.6.2.2 Best clinical practice in ureterorenoscopy (URS)
5.6.2.2.1 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/anticoagulation (anti-platelet drugs) should be discontinued if possible, however URS can be performed in patients with bleeding disorders,with a moderate increase in complications (25,26);
- imaging.

Recommendation	LE	GR
Short-term antibiotic prophylaxis should be administered (27).	4	A*

** Upgraded based on panel consensus.*

5.6.2.2.2 Contraindications
Apart from general problems, e.g. with general anaesthesia or untreated urinary infections, URS can be performed in all patients without any specific contraindications. Specific problems such as ureteral strictures may prevent successful retrograde stone management.

5.6.2.2.3 Access to the upper urinary tract
Most interventions are performed under general anaesthesia, although local anaesthesia or spinal anaesthesia are possible. Instrument miniaturisation means that intravenous sedation can be used to achieve the same outcome (28,29).

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 flexible URS.

Antegrade URS is an option for large, impacted proximal ureteral calculi (5,30) (see Section 6.5.3).

5.6.2.2.4 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.

Recommendation	GR
Placement of a safety wire is recommended.	A*

** Upgraded based on panel consensus.*

5.6.2.2.5 Ureteral access sheaths
Hydrophilic-coated ureteral access sheaths, which are available in different calibres (usual inner diameter of 9 or 12/13 Ch), 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, decrease intrarenal pressure and potentially reduce operating time (19,33-36).

Ureteral access sheaths allow continuous outflow of irrigation fluid, which improves visual quality and maintains a low-pressure system (36,37).

Ureteral access sheaths are widely accepted and used regularly, despite ongoing debate about potential hazards, including increased ureteral stricture, which has not yet been demonstrated (33).

5.6.2.2.6 Stone extraction
The aim of endourological intervention is complete stone removal (especially in ureteric stones). “Smash and go” strategies might have a higher risk of stone regrowth and postoperative complications (38).

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 (nickel-titanium alloy) can be used for flexible URS (39-42).

Recommendations	LE	GR
Stone extraction using a basket without endoscopic visualisation of the stone (blind basketing) should not be performed.	4 3	A* B
Nitinol baskets preserve the tip deflection of flexible ureterorenoscopes, and the tipless design reduces the risk of mucosal injury.		
Nitinol baskets are most suitable for use in flexible URS.		

** 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 (*see* Section 6.4.2) (43).

5.6.2.2.7 Intracorporeal lithotripsy
Intracorporeal lithotripsy is usually necessary before stone extraction.

5.6.2.2.7.1 Electrohydraulic systems
Flexible electrohydraulic lithotripsy probes are available for semi-rigid and flexible ureterorenoscopes. If lasers are unavailable, electrohydraulic lithotripsy can disintegrate all types of stones (even cystine or hard stones, such as calcium oxalate monohydrate), even though there is an increased risk of surrounding tissue damage (44-46).

5.6.2.2.7.2 Pneumatic systems
Pneumatic or ballistic lithotripters are often used with 2.4 Ch probes for safe rigid URS and can achieve > 90% disintegration (47-49). Proximal stone migration is a common occurrence (50,51), but can be avoided by using a basket or special tools (6,52-56).

5.6.2.2.7.3 Ultrasound
Ultrasound can be used alone or in combination with pneumatic lithotripsy. However, ultrasound can only be used in larger but not in flexible endoscopes (57,58).

5.6.2.2.7.4 Laser systems

The most efficient laser system for treatment of all types of stones in all locations is the Ho:YAG system (59-70) (LE: 3), which is the gold standard for rigid and flexible URS (65). Compared with the Nd-YAG laser, its rapid absorption in water (3 mm) and minimal tissue penetration (0.4 mm) reduces thermal damage and improves safety (69). Contact with the surface of the stone is required. Other laser systems are being evaluated, but have yet to prove superior in efficacy or safety.

Recommendation	LE	GR
Ho:YAG laser lithotripsy is the preferred method for (flexible) URS.	3	B

5.6.2.2.8 Stenting before and after URS

Routine stenting is no longer necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the stone-free rate, and reduces complications (71-73).

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 no longer necessary (71,74-85). Ureteric stenting can be associated with lower urinary tract symptoms and pain reducing quality of life (86).

Stents should be inserted in patients who are at increased risk of complications (e.g. residual fragments, bleeding, perforation, urinary tract infections 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 (71,74). Patients should be followed up with a plain abdominal film (kidney-ureter-bladder), CT or ultrasound.

Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability (87-90). A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin (91).

Recommendation	LE	GR
Stenting is optional after uncomplicated URS.	1a	A

5.6.2.2.9 Complications

The overall complication rate after URS is 9-25% (1,9,33,35,66,92) (Table 15). 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 15: Complications of URS*

	Rate (%)
Intraoperative complications	3.6
Mucosal injury	1.5
Ureteral perforation	1.7
Significant bleeding	0.1
Ureteral avulsion	0.1
Early complications	6.0
Fever or urosepsis	1.1
Persistent haematuria	2.0
Renal colic	2.2
Late complications	0.2
Ureteral stricture	0.1
Persistent vesicoureteral reflux	0.1

**From Geavlete, et al. (9).*

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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 1.0-5.4% of cases only (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 16).

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 and less-invasive therapy, in terms of stone-free rates, 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 16: Indications for open surgery

Complex stone burden
Treatment failure of SWL and/or PNL, or failed ureteroscopic procedure
Intrarenal anatomical abnormalities: infundibular stenosis, stone in the calyceal diverticulum (particularly in an anterior calyx), obstruction of the ureteropelvic junction, stricture if endourologic procedures have failed or are not promising
Morbid obesity
Skeletal deformity, contractures and fixed deformities of hips and legs
Comorbidity
Concomitant open surgery
Non-functioning lower pole (partial nephrectomy), non-functioning kidney (nephrectomy)
Patient choice following failed minimally invasive procedures; the patient may prefer a single procedure and avoid the risk of needing more than one PNL procedure
Stone in an ectopic kidney where percutaneous access and SWL may be difficult or impossible
For the paediatric population, the same considerations apply as for adults

*5.7.2 **Laparoscopic surgery***

Laparoscopic urological surgery is increasingly replacing open surgery as a result of accumulated surgical experience. Laparoscopy is associated with lower postoperative morbidity, shorter hospital stay and time to convalescence, and better cosmetic results with comparably good functional results (17-24).

Laparoscopic surgery is now 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.
Surgical pyelolithotomy is rarely indicated (see Table 16) and feasible laparoscopically, e.g. stone removal from an anterior caliceal diverticulum (34).

Laparoscopic ureterolithotomy is relatively easy, with stone-free rates up to 100% provided expertise is available (25-28). It can replace open surgery in most situations (15,16). Retroperitoneal and transperitoneal laparoscopic access to all portions of the ureter have been reported (28-33,35) 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 (25-28) (Table 17).

5.7.2.1 Indications for laparoscopic stone surgery (Table 17)

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 stones • Multiple ureteral stones • In cases of concurrent conditions requiring surgery • When other non-invasive or low-invasive procedures have failed • If indicated, for upper ureteral calculi, laparoscopic urolithomy has the highest stone free rate compared to URS and SWL (LE: 1a)

Recommendations	**LE**	**GR**
Laparoscopic or open surgical stone removal may be considered in rare cases where SWL, URS, and percutaneous URS fail or are unlikely to be successful.	3	C
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.	3	C
For ureterolithotomy, laparoscopy is recommended for large impact stones or when endoscopic lithotripsy or SWL have failed.	2	B

Skolarikos, et al. have tried to identify the level of evidence and grade of recommendation, according to the evidence-based medicine criteria, in studies supporting laparoscopic stone extraction. The highest level of evidence (2a) was found for laparoscopic ureterolithotomy.

5.7.3 ***References***

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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 Indication for active removal of ureteral stones (1,2)

- Stones with low likelihood of spontaneous passage;
- persistent pain despite adequate pain medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, single kidney).

6.2 Indication for active removal of kidney stones (2)

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g., pain, 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, travelling);
- > 2-3 years stone persistence.

The suspected stone composition might influence the choice of treatment.

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, timing and type of intervention.

Statement	LE
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 (1-3).	3

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% (4). In a recent retrospective study, 77% of asymptomatic patients with renal stones experienced disease progression, with 26% requiring surgical intervention (5).

In a retrospective study, Hubner and Porpaczy have reported that infection developed in 68% of patients with asymptomatic caliceal stones, and 45% had increased stone size after 7.4 years follow-up. They have suggested that 83% of caliceal calculi require intervention within the first 5 years of diagnosis (6). Inci et al. have investigated lower pole caliceal stones, and observed that no patient required intervention during 24 months follow-up. In addition, an increase in stone size without any need for intervention was observed in eight of 27 renal units (29.6%). When the follow-up period was increased to 52.3 months, nine (33.3%) patients had increased stone size, but only three (11%) required intervention (7).

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 stone-free rate, symptoms, requirement for additional treatment, quality of life, renal function, or hospital admission (10). Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection or stone growth conflicting data have been reported (4,6,11).

Statement	LE
SWL has been increasingly used for treatment of caliceal stones to reduce the risk of complications and the need for invasive procedures.	4

Excellent stone-free rates 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).

Recommendations	GR
For asymptomatic caliceal stones in general, active surveillance with annual follow-up of symptoms and stone status [KUB, ultrasonography (US), NCCT] is an option for 2-3 years, whereas intervention should be considered after this period provided patients are adequately informed.	C
Observation might be associated with a greater risk of necessitating more invasive procedures.	

6.2.2 ***References***

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6.3 General recommendations and precautions for stone removal

*6.3.1 **Infections***

Urinary 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.

Recommendation	GR
Urine culture or urinary microscopy is mandatory before any treatment is planned.	A*

**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;
- 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. The problem of coagulation disorder is less pronounced in URS than in SWL and PNL.

Recommendations	LE	GR
Anticoagulation therapy including salicylates should be stopped before stone removal, in particular if SWL is planned.	3	B
If intervention for stone removal is essential and salicylate therapy should not be interrupted, retrograde URS is the preferred treatment of choice.		

*6.3.3 **Obesity***

Obesity can cause a higher risk due to anaesthesiological measurements, and a lower success rate after SWL and PNL (see Section 5.5).

Statement	LE
In case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

6.3.4 *Hard stones*

Stones composed of brushite or calcium oxalate monohydrate are particularly hard. Percutaneous removal of these stones might be appropriate, particularly if they are large. Chemolytic treatment of brushite stone fragments is possible. Cystine stones respond well or poorly to SWL (10). PNL or retrograde intrarenal surgery (RIRS) are alternatives for removal of large SWL-resistant stones.

Recommendation	LE	GR
Consider the stone composition before deciding on the method of removal (former stone analysis of the patient, HU in unenhanced CT). Stones with medium density > 1,000 HU on NCCT are less likely to be disintegrated by SWL.	2a	B

6.3.5 *Radiolucent stones*

Uric acid concrements can be localised using US or intravenous or retrograde administration of contrast medium. Stones composed of uric acid, but not sodium or ammonium urate, can be dissolved by oral chemolysis. Differentiation is done by urinary pH measurement (see Section 5.4.2). Postoperative monitoring of radiolucent stones during chemolysis or after SWL is the domain of ultrasound, however repeat NCCT might be necessary.

Recommendation	GR
Careful monitoring of radiolucent stones during/after therapy is imperative.	A*

** 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 (13-15), 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 (16). Symptoms include flank pain, fever, nausea and vomiting, bladder irritation, or it may asymptomatic. A major problem of steinstrasse is ureter obstruction, which can be silent in 23% of cases (14) and lead to kidney failure (17). Anuria occurs in 5% of cases of steinstrasse in treatment of solitary kidneys (14).

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).

Statement	LE
Medical expulsion therapy increases stone expulsion rate of steinstrasse (16).	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). There is an 80% chance of clearance of the steinstrasse (13).

Ureteroscopy is equally effective as SWL for treatment of steinstrasse (13,20,21). Placement of a percutaneous nephrostomy tube is indicated for symptomatic ureteric obstruction with/without UTI, and it is effective in 83% of cases (13).

Table 18: Treatment of steinstrasse

Asymptomatic	LE		Symptomatic		LE		Symptomatic + fever	LE
1. MET	1b		1. URS		3		1. PCN	1a
2. SWL	3		1. PCN		3		2. Stent	
3. URS	3		1. SWL		3			
			2. Stent		3			

Numbers 1,2, and 3 indicate first, second and third choice.

Recommendations	LE	GR
PCN is indicated for steinstrasse associated with UTI/fever.	4	C
SWL is indicated for steinstrasse when large stone fragments are present.	4	C
Ureteroscopy is indicated for symptomatic steinstrasse and treatment failure.	4	C

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6.4 Selection of procedure for active removal of kidney stones

*6.4.1 **Stones in renal pelvis or upper/middle calices***

SWL, PNL or flexible URS are available treatment modalities for renal calculi. Although PNL efficacy is hardly affected by stone size, the stone-free rates (SFRs) after SWL or URS are inversely proportional to stone size (1-4). SWL 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 by PNL primarily, because SWL often requires multiple treatments, and has the risk of ureteral obstruction (colic, steinstrasse) with the need for adjunctive procedures (Figure 1) (6). Flexible URS cannot be recommended as first-line treatment, especially for stones > 15 mm, for which SFR is decreasing, and staged procedures have become necessary (7,8).

*6.4.2 **Stones in the lower renal pole***

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intrarenal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-85%. The preferential use of endoscopic procedures is under discussion (1-6).

The following can impair successful stone treatment by SWL:

- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 19) (7-13).

Further anatomical parameters cannot yet be established. The value of supportive measures such as inversion, vibration or hydration remains under discussion (7,8).

Table 19: Unfavourable factors for SWL success (9-15)

Factors that make SWL less likely
Shockwave-resistant stones (calcium oxalate monohydrate, brushite, cystine)
Steep infundibular-pelvic angle
Long lower pole calyx (> 10 mm)
Narrow infundibulum (< 5 mm)

SWL for the lower pole is often disappointing, therefore, endourological procedures (PNL, flexible URS) are recommended for stones > 15 mm. If there are negative predictors for SWL, PNL and flexible URS might be a reasonable alternative even for smaller calculi.

Flexible URS seems to have comparable efficacy to SWL (5,6). Recent clinical experience with last-generation ureterorenoscopes suggests an advantage of URS over SWL, by paying the price of greater invasiveness (16,17). Depending on operator skills, stones up to 3 cm can be treated efficiently by flexible URS (16,18-20). However, staged procedures are frequently required.

Recommendations	GR
SWL remains the method of first choice for stones < 2 cm within the renal pelvis and upper or middle calices. Larger stones should be treated by PNL.	B*
Flexible URS cannot be recommended as first-line treatment, especially for stones > 1.5 cm in renal pelvis and upper or middle calices, for which SFR after flexible URS is decreasing, and staged procedures become necessary.	B*
For the lower pole, PNL or flexible URS are recommended even for stones > 1.5 cm because the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	B*

Figure 1: Treatment algorithm for renal calculi within the renal pelvis or upper and middle calices

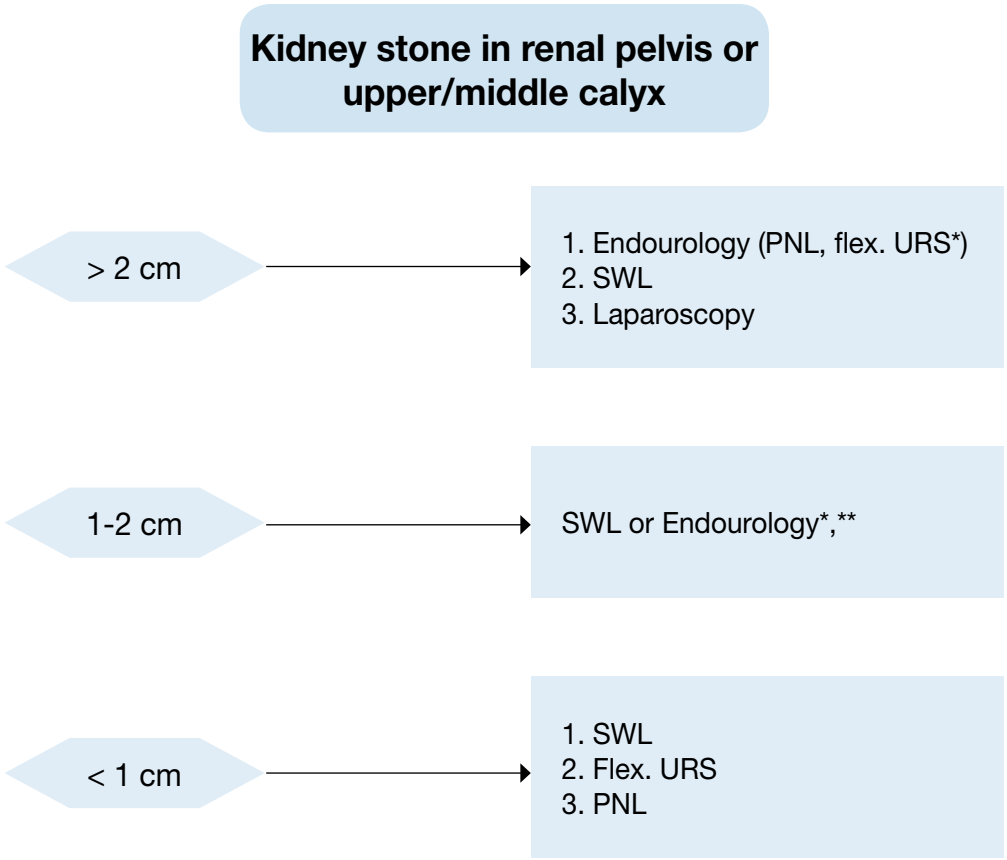
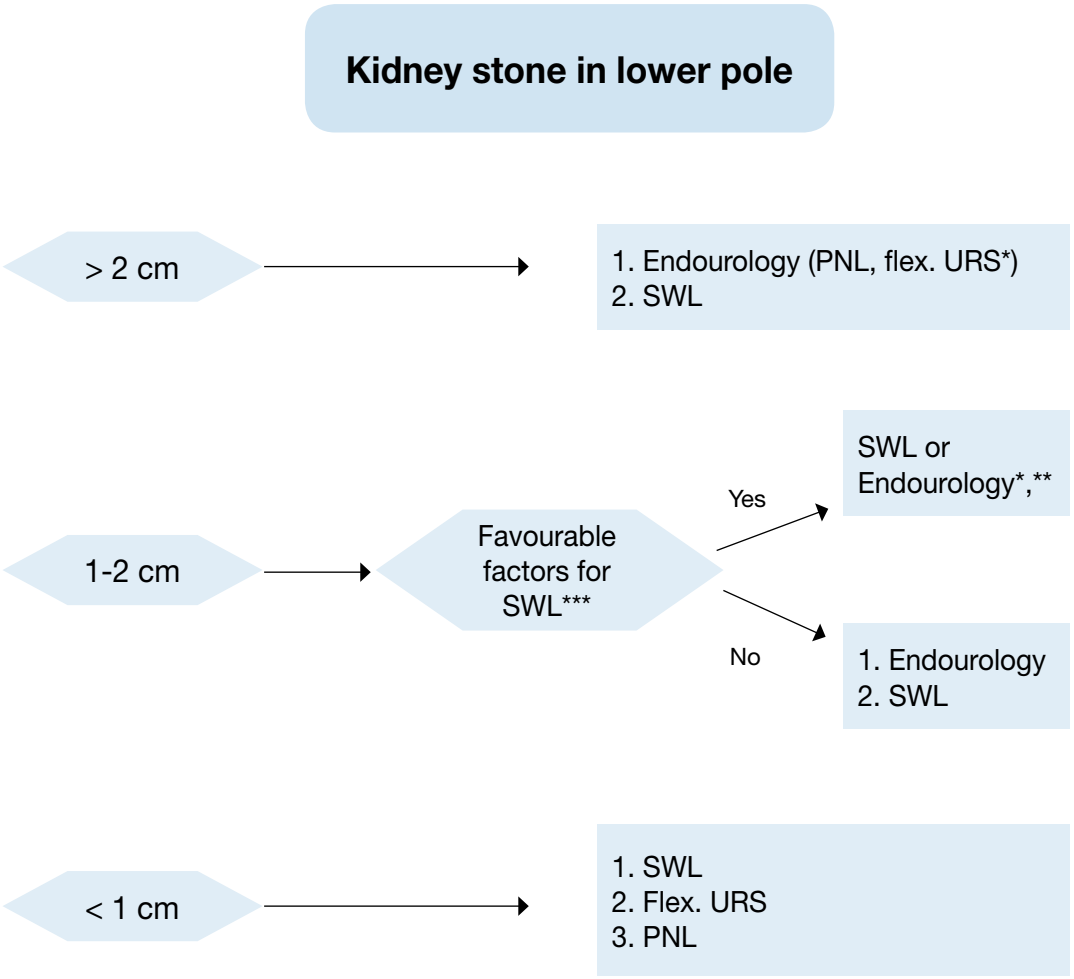


Figure 2: Treatment algorithm for renal calculi in the inferior calyx



*Flexible URS is used less as first-line therapy for renal stones > 1.5 cm, although some expert centers have reported such for renal stones > 1.5 cm.
The high number of staged procedures of URS underline the superiority of PNL. A combined approach (PNL+flexible URS) might be an option in specialised centres.
** The ranking of the recommendations reflects a panel majority vote.
*** see Table 19 on page 55.

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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 number was used. If not, and the study reported the SFR after the first procedure, then that number 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. 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 20 shows the results of a meta-analysis of SFRs. The results are presented as medians of the posterior distribution (best central estimate) with 95% Bayesian Credible Intervals (CIs). This represents an update of the EAU/AUA collaborative guidelines project (1). Outcomes show no significant changes.

Table 20: SFRs after primary treatment with SWL and URS in the overall population (1-5)

	SWL		URS	
	Number of patients	**SFR/95% CI**	**Number of patients**	**SFR/95% CI**
Distal ureter	7217	74% (73-75)	10372	93% (93-94)
< 10 mm	1684	86% (80-91)	2013	97% (96-98)
> 10 mm	966	74% (57-87)	668	93% (91-95)
Mid ureter	1697	73% (71-75)	1140	87% (85-89)
< 10 mm	44	84% (65-95)	116	93% (88-98)
> 10 mm	15	76% (36-97)	110	79% (71-87)
Proximal ureter	6682	82% (81-83)	2448	82% (81-84)
< 10 mm	967	89% (87-91)	318	84% (80-88)
> 10 mm	481	70% (66-74)	338	81% (77-85)

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 receiving 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 statistically flexible and rigid URS for proximal ureteral stones, favourable SFRs have been reported using flexible URS (87%) compared with rigid or semi-rigid URS (77%) (1). SFRs probably continue to improve as the distribution and technical improvement of flexible URS continue.

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, 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). With SFRs of 85-100%, its superiority to standard techniques has been evaluated (7,10-13). The complication rate is low, acceptable, and not different from 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).

Recommendations	GR
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 (13-15).	A
A patient must be informed about the existing active treatment modalities, including the relative benefits and risks associated with each modality.	A

Table 21: Recommended treatment options (if indicated for active stone removal) (GR A*)

	First choice	Second choice
Proximal ureter < 10 mm	SWL	URS
Proximal ureter > 10 mm	URS (retrograde or antegrade) or SWL	
Distal ureter < 10 mm	URS or SWL	
Distal ureter > 10 mm	URS	SWL

**Upgraded following panel consensus.*

Recommendation	GR
Treatment choices should be based on stone size and location and available equipment for stone removal.	A

6.5.4 Other methods for ureteral stone removal

Few studies have reported laparoscopic stone removal (see Section 5.7.2), and open surgery (see 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

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7. RESIDUAL STONES

7.1 Clinical evidence

Residual fragments are commonly seen after SWL and sometimes after intracorporeal lithotripsy, and mostly in the lower calix.

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 (1-5).

Recommendations	LE	GR
Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones (3-5).	1b	A
Patients with residual fragments or stones should be followed up regularly to monitor disease course.	4	C

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 (6). For all stone compositions, 21-59% of patients with residual stones require treatment within 5 years. Fragments > 5 mm are more likely than smaller ones to require intervention (2,3,5,7).

Table 22: Recommendations for the treatment of residual fragments

Residual fragments, stones (largest diameter)	Symptomatic residuals	Asymptomatic residuals	LE	GR
< 4-5 mm	Stone removal	Reasonable follow-up (dependent on risk factors)	4	C
> 6-7 mm	Stone removal			

7.2 Therapy

To avoid residual fragments or facilitate further clearance, medical and physical adjunctive therapy can be suggested:

Recommendations	LE	GR
After SWL and URS, MET is recommended using an alpha-blocker to improve fragment clearance and reduce probability of residual stones (Chapter 7).	1a	A
For well-disintegrated stone material in the lower calix, inversion therapy during high diuresis and mechanical percussion facilitate clearance (8).	1a	B

The indication 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 (9).

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 (10-13).

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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 options

Diagnostic options are limited in pregnant women due to the possible teratogenic, carcinogenic, and mutagenic risk of foetal radiation exposure. The risk depends crucially on gestational age and amount of radiation delivered. Clinicians must consider carefully the risk-benefit ratio of an examination that involves radiation during the first trimester (1,2,5,6).

Currently, when evaluating pregnant patients suspected of renal colic, US (using change in resistive index and transvaginal ultrasound when necessary) has become the primary radiological diagnostic tool, with a limited excretory urogram only necessary in complicated cases. NCCT results in an even higher dose of radiation exposure. However, US is limited by poor sound transmission through gas and bone and its operator-dependent nature. Similarly, it can be difficult to differentiate physiological dilation of pregnancy from ureteral obstruction, and US is therefore of limited value in acute obstruction (7,8).

Transvaginal/endoluminal US might be important for evaluation of possible stones at the vesicoureteral junction. An endoluminal ultrasound probe can help to elucidate the level of obstruction and facilitate subsequent endoscopic ureteral stent placement.

Among other modalities, magnetic resonance urography (MRU) can be used to evaluate the urinary tract, thus avoiding ionising radiation and iodinated contrast medium, which is important in pregnancy. Magnetic resonance imaging can define the level of obstruction, and stones can be seen as a filling defect. However, these findings are non-specific. There is little experience with using this imaging modality during pregnancy (9-11).

Statements	LE	GR
US is the method of choice for practical and safe evaluation of pregnant women.	1a	A
In symptomatic patients with suspicion of ureteral stones during pregnancy, limited IVU, MRU, or isotope renography is a possible diagnostic method.		

8.2 Management

Management of pregnant urolithiasis patients poses significant multiple challenges to the patient, obstetrician and urologist, but many symptomatic stones (70-80%) pass spontaneously. Conservative management with analgesia can result in spontaneous passage.

If spontaneous passage does not occur, or if complications develop (e.g. induction of premature labour),

placement of an internal stent or percutaneous nephrostomy tube, or ureteroscopy is an alternative treatment (12-19). However, the temporising therapies (e.g. ureteral stenting or percutaneous nephrostomy) are often associated with poor tolerance, and they require multiple exchanges of stents or nephrostomy tubes during pregnancy, due to the potential for rapid encrustation of these devices (20-23).

Improvements in diagnostic technology, as well as experience in endoscopic instrumentation have made the endoscopic approach feasible and safe for diagnosis and treatment of ureteral stones. Nevertheless, one cannot overemphasise the necessity for care during URS, which should be performed only in centres with sufficient experience (20,22-24). When intracorporeal lithotripsy is necessary during URS in pregnant patients, the holmium laser has the advantage of minimal tissue penetration, thereby theoretically limiting risk of foetal injury.

Although percutaneous stone removal in the early stages of pregnancy has been reported in a few studies (21), SWL is still experimental, and pregnancy remains an absolute contraindication.

Recommendation	GR
Following correct diagnosis, 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).	A

Statements	LE
If intervention becomes necessary, placement of a internal stent, percutaneous nephrostomy, or ureteroscopy are options.	3
Regular follow-up until final stone removal is necessary due to higher encrustation tendency of stents during pregnancy.	

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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 Far East); elsewhere, the rates are similar to those observed in developed countries (4-11).

9.1 Investigations

Paediatric patients with urinary stones have a high risk of recurrence, therefore, standard diagnostic procedures for high-risk patients apply (see Chapters 2.6 and 11).

Statement	LE
In paediatric patients, the most common non-metabolic disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, or other voiding difficulties (11,12).	4

Recommendation	GR
In all paediatric patients, complete metabolic stone evaluation based on stone analysis (if available) is necessary.	A

*9.1.1 **Imaging***

When selecting diagnostic procedures to identify urolithiasis in paediatric patients, it should be remembered that these patients might be uncooperative, require anaesthesia, or are sensitive to ionising radiation (13).

9.1.1.1 Ultrasound

Ultrasound is the most popular and practical imaging technique (13). In paediatrics, its advantages are absence of irradiation and no need for anaesthesia. US can be used to obtain information about the presence, size and location of a stone, and the grade of dilatation and obstruction of the urinary collecting system. It also indicates signs of abnormalities that facilitate stone formation.

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. Ultrasound is part of the metaphylactic work-up in these cases.

Statement	LE
Ultrasound evaluation is the first choice for imaging in children and should include the kidney, filled bladder, and adjoining portions of the ureter (14,20).	2a

9.1.1.2 Plain films (KUB)

KUB can help to identify stones and their radio-opacity, and facilitate follow-up.

9.1.1.3 Intravenous urography (IVU)

IVU 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).

9.1.1.4 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. like 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).

9.1.1.5 Magnetic resonance urography (MRU)

MRU 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).

9.1.1.6 Nuclear imaging

^{99m}Tc-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 or DPTA) 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).

9.2 Stone removal

Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL, and all stones should be evaluated for further metaphylactic measures (26). For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. To eliminate radiation exposure, US can be used for localisation during SWL or endourological procedures. Anticipation of the expected stone composition helps with selection of the appropriate procedure for removal (cystine stones are more resistant to SWL).

Statement	LE
Spontaneous passage of a stone is more likely in children than adults (6,11,12).	4

*9.2.1 **Medical expulsive therapy (MET) in children***

MET in children has already been discussed in Section 5.3.2.6. Although the use of nifedipine or α-blockers is very common in adults, there are insufficient data to demonstrate their safety and efficacy in children (27).

*9.2.2 **Extracorporeal shock wave lithotripsy***

Despite increasing application of PNL, and development of smaller-diameter flexible ureteroscopes and ancillary instruments, SWL is still the least-invasive procedure for stone management in children (28-36).

Stone free rates 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 has 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).

Compared to adults, children pass stone fragments easily, and stenting is rarely needed. If the stone burden requires a ureteral stent, alternative procedures should be considered. Although internal stents are seldom needed following SWL of upper tract stones, ureteral pre-stenting decreases the SFR after initial treatment (28,30-32).

Statements	LE
In children, the indications for SWL are similar to those in adults, however they pass fragments more easily.	3
Children with renal stones of a diameter up to 20 mm (~300 mm^2) are ideal for SWL.	1b

*9.2.3 **Endourological procedures***

Improvement in intracorporeal lithotripsy devices and development of smaller instruments facilitate PNL and URS in children.

9.2.3.1 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 ultrasound 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).

Statement	LE
For paediatric patients, the indications for PNL are similar to those in adults.	1a

Recommendation	GR
In children, PNL is recommended for treatment of renal pelvic or caliceal stones with a diameter > 20 mm (~300 mm^2).	A

9.2.3.2 Ureteroscopy

While 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. The success rate of SWL decreases for stones in the more distal parts of the ureter. Overall SFRs after SWL range from 75 to 100% (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 in middle and larger distal ureteric stones in children (48-50).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective. As a result of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases (53,54) (see Section 5.6.2.2.7).

Statements	LE	GR
For intracorporeal lithotripsy, the same devices as in adults can be used (Ho:Yag laser, pneumatic and ultrasound lithotriptors).	3	C

Finally, 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).

9.2.4 ***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).

9.3 Special considerations on recurrence prevention

It should be kept in mind that, in addition to stone removal procedures, treatment of paediatric urolithiasis requires a thorough metabolic and environmental evaluation on an individual basis. In case of obstructive pathologies along with the established metabolic abnormalities treatment should not be delayed. Children are in the high-risk group for stone recurrence (see Chapter 11).

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10. STONES IN URINARY DIVERSION AND OTHER VOIDING PROBLEMS

10.1 Management of stones in patients with urinary diversion

*10.1.1 **Aetiology and preventive measures***

Patients with urinary diversion are at risk for stone formation in the renal collecting system, ureters, and conduit or continent reservoir (1-3). Metabolic factors such as hypercalciuria and hypocitraturia, infection with urease-producing organisms, foreign bodies, mucus secretion, and urinary stasis could be involved in stone formation in these cases (4).

These patients are also at high risk for stone recurrence, which warrants close follow-up for effective prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and regular irrigation of continent reservoirs (5). One study showed that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at 5 years (6).

*10.1.2 **Management***

Although patients with smaller upper-tract stones can be treated effectively with SWL (7,8) other well-established endourological techniques might be necessary to achieve stone-free status.

Some patients with small- or large-bowel conduits can be treated with URS under fluoroscopic guidance. Although identification of the targeted ureteral orifice is difficult, it can be localised by flexible cystoscopy and/or administration of intravenous indigo carmine. and a hydrophilic guidewire can be placed followed by regular flexible ureteroscopy. Stone removal and fragmentation are then undertaken using standard techniques. This approach might be difficult or impossible in individuals with long, tortuous conduits; percutaneous placement of an antegrade guidewire may facilitate stone removal procedures.

PNL is the preferred treatment alternative for removal of large renal stones in patients with urinary diversion, as well as ureteral stones that cannot be accessed via a retrograde approach or are not amenable to SWL (9).

Stones can form in the conduits after urinary diversion procedures, which is typically associated with a foreign body. A trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy. However, for calculi in continent urinary diversion, although a trans-stomal approach might be successful in some patients, there is a risk of disturbing the continence mechanism. A success rate of 89% has been reported for trans-stomal management of patients with stones in Kock reservoirs with afferent nipples (10). Patients with relatively larger stones are the best candidates for percutaneous removal. 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 (11), and if present, an open surgical approach should be considered. In patients with no overlying viscera, ultrasound- or CT-guided access is recommended to facilitate safe placement of a sheath into the reservoir followed by standard PNL. Jarrett and colleagues have described an approach in which a 12-mm laparoscopic trocar is placed in the continent reservoir, through which a specimen retrieval bag is inserted (12). Trans-stomal flexible endoscopy facilitates manipulation of the stones into the entrapment bag. The stones are then fragmented in the bag using a rigid nephroscope and standard intracorporeal lithotripsy. This technique allows total stone removal without dispersal of fragments in a capacious reservoir. At the end of the procedure, a large-calibre catheter is placed in the reservoir through the trocar or sheath, and left in place for at least 2-3

weeks to allow tract maturation.

10.1.3 References

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10.2 Management of stones in patients with neurogenic bladder

*10.2.1 **Aetiology and clinical presentation***

Patients with neurogenic bladder can develop urinary calculi because of additional risk factors such as urinary stasis and infection. Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction can facilitate the introduction of foreign bodies and infection. 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 (1,2). Rare cases have been reported of vaginal calculi secondary to urinary stasis (3) or vesicovaginal fistulae (4). Bacteriuria, pelvicalicectasis, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect are risk factors for renal stone formation in patients with neurogenic bladder (5).

Kondo has found that bladder lithiasis is 10 times more prevalent in patients with myelomeningocele (MMC) treated with enterocystoplasy (2). The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols (6). Diagnosis is more difficult because of the absence of clinical expression and difficult visualisation by imaging. As a result of their sensory impairment and vesicourethral dysfunction, these patients generally do not report troublesome symptoms until their calculi become large (7). Difficulty in self-catheterisation should lead to suspicion of possible bladder calculi.

10.2.2 ***Management***

Management of calculi in patients with neurogenic bladder is similar to that described above (see Section 10.1). Regardless of the treatment used, latex allergy is common in patients with MMC and appropriate measures need to be taken (8). 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 and the necessary venous access. These deformities can even prevent general anaesthesia (9), which makes early diagnosis of lithiasis essential.

Statements	LE
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3
Careful patient follow-up, utilisation of the appropriate stone-removal approach, and implementation of effective preventive strategies are the cornerstones of successful management.	3

10.2.3 ***References***

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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, therefore, any impairment causing urinary stasis requires immediate intervention. Although immunosuppression renders these patients more vulnerable to infection, they also have conditions that predispose them to urolithiasis, for example, hyperfiltration, excessively alkaline urine, renal tubular acidosis, recurrent UTIs, and increased serum calcium caused by persistent tertiary hyperparathyroidism (1). Stones in kidney allografts have a incidence of 0.2-1.7% (2-4). Unexplained fever, graft rejection, or unexplained failure to thrive requires US or NCCT to rule out calculi (5).

10.3.2 ***Management***

Treatment of renal calculi in the transplant patient is difficult, however, management principles are similar to those applied in other single renal units (6-9).

Conservative treatment under close surveillance is only possible for small asymptomatic stones. Although SWL for small calyceal stones is appealing because of minimal complications, localisation can be difficult and SFRs are poor (10,11). However, for large or ureteral stones, percutaneous and antegrade endoscopic techniques are more favourable, but concerns exist about potential injury to adjacent organs (12-14).

The introduction of small flexible ureteroscopes and holmium laser has made ureteroscopy another treatment option for transplant calculi. Retrograde access to transplanted kidneys is difficult owing to the anterior location of the ureteral anastamosis and ureteral tortuosity (15-17).

Recommendations	GR
All contemporary endoscopic treatment modalities, including SWL, (flexible) ureteroscopy and percutaneous nephrolithotomy are management options in patients with transplanted kidneys.	B
Metabolic evaluation should be completed after stone removal.	A*

**Upgraded following panel consensus.*

10.3.3 ***References***

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10.4 Special problems in stone removal

Table 23: Special problems in stone removal

Caliceal diverticulum stones	•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
Horseshoe kidneys	• Can be treated in line with the options described above (6) • Passage of fragments after SWL might be poor
Stones in pelvic kidneys	• SWL, RIRS or laparoscopic surgery • For obese patients, the options are SWL, PNL, RIRS or open surgery
Stones formed in a continent reservoir	• See 10.1 • Each stone problem must be considered and treated individually
Patients with obstruction of the ureteropelvic junction	• When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy (15-35) 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 pelvi-ureteral incision (7-10)

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11. METABOLIC EVALUATION AND RECURRENCE PREVENTION

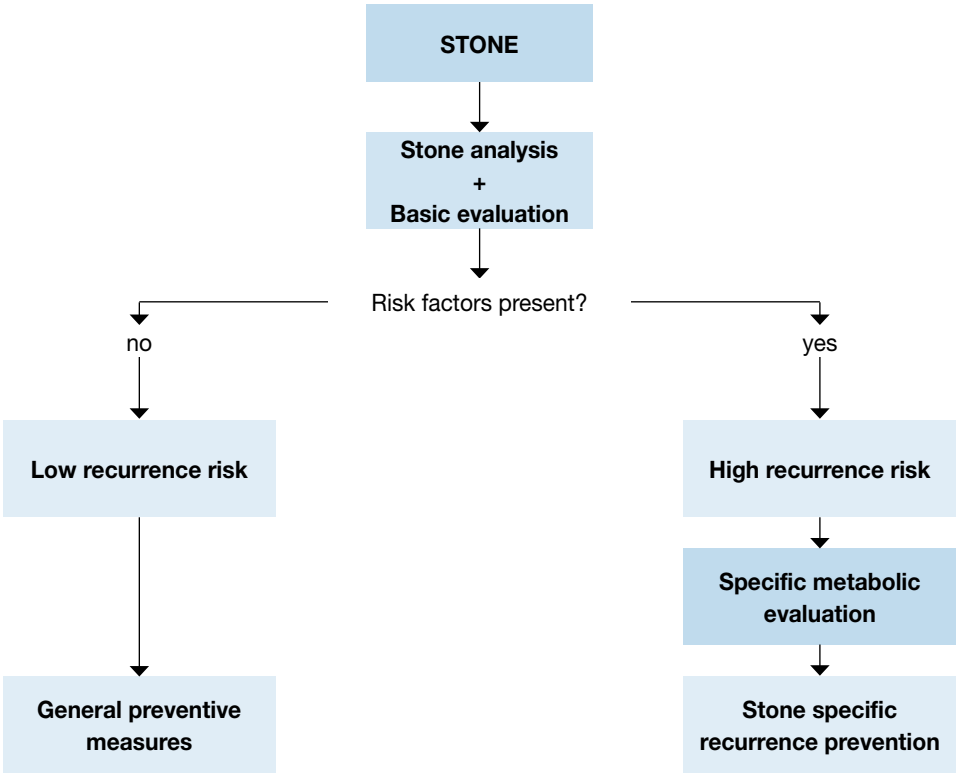
11.1 General metabolic considerations for patient work-up

*11.1.1 **Evaluation of patient risk***

After stone passage, every patient should be assigned to a low- or high-risk group of stone formers (Figure 3). For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (*see* Section 3.2).

Figure 3: Assignment of patients to low- or high-risk groups of stone formers



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 (4). Preanalytical errors can be minimised by carrying out urinalysis immediately after collection. Urine pH should be assessed during collection of freshly voided urine four times daily (5).

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. Alkalinisation 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, e.g. in younger children (7,8). Spot urine studies normally link the excretion rates to creatinine (8,9). Spot urine studies 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 be stone free. A minimum of 20 days is recommended between stone expulsion or removal and 24-h urine collection (4).

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 24-26 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 24: Normal laboratory values for blood parameters in adults

Blood parameter	Reference range	
Creatinine	20-100 µmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 µmol/L	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO_2	80-90 mmHg
	pCO_2	35-45 mmHg
	HCO_3	22-26 mmol/L
	BE	± 2

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:

- AP_{CaOx} index (10,11);
- EQUIL (12-14);
- Bonn Risk Index (15-17).

Another approach to risk assessment is the Joint Expert Speciation System (JESS), which is based on an extensive database of physiochemical constants and is most like the EQUIL (18).

However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing and the benefit remains controversial.

Table 25: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 Constantly > 7.0 Constantly ≤ 5.8
Specific weight	> 1010
Creatinine	7-13 mmol/day females 13-18 mmol/day males
Calcium	> 5.0 mmol/day ≥ 8.0 mmol/day
Oxalate	> 0.5 mmol/day 0.45-0.85 mmol/day ≥ 1.0 mmol/day
Uric acid	> 4.0 mmol/day
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 26: Reference urinary values in paediatric patients (19)

Soluble:creatinine ratio (spot urine samples)

Calcium:creatinine ratio			Citrate:creatinine ratio			Cystine:creatinine ratio			Oxalate:creatinine ratio			Urate:creatinine ratio		
	mol/mol	g/g		mol/mol	g/g		mmol/mol	mg/g		mmol/mol	mg/g		mol/mol	g/g
< 12 mos	< 2.2	< 0.8	0-5 y	> 0.12-0.25	> 0.2-0.42	< 1 month	< 85	< 180	0-6 mos	< 325-360	< 260-88	< 12 mos	< 1.5	< 2.2
1-3 y	< 1.5	< 0.53							7-24 mos	< 132-174	< 110-39	1-3 y	< 1.3	< 1.9
3-5 y	< 1.1	< 0.4				1-6 mos	< 53	< 112	2-5 y	< 98-101	< 80-81	3-5 y	< 1.0	< 1.5
5-7 y	< 0.8	< 0.3	> 5 y	> 0.08-0.15	> 0.14-0.25				5-14 y	< 70-82	< 60-65	5-10 y	< 0.6	< 0.9
> 7 y	< 0.6	< 0.21				> 6 mos	< 18	< 38	> 14 y	< 40	< 32	> 10 y	< 0.4	< 0.6

Urinary excretion of soluble excretion in 24-hour urine samples

Calcium excretion		Citrate excretion		Cystine excretion		Oxalate excretion		Urate excretion	
All age groups	< 0.1 mmol/kg/24 h < 4 mg/kg/24 h	All age groups	Boys > 1.9 mmol/1.73 m²/24 h > 365 mg/1.73 m²/24 h Girls > 1.6 mmol/1.73 m²/24 h > 310 mg/1.73 m²/24 h	< 10 y	< 55 µmol/1.73 m²/24 h < 13 mg/1.73 m²/24 h	All age groups	< 0.5 mmol/1.73 m²/24 h < 45 mg /1.73 m²/24 h	< 1 year	< 70 µmol/kg/24 h < 1.3 mg/kg/24 h
				> 10 y	< 200 µmol/1.73 m²/24 h < 48 mg/1.73 m²/24 h			1-5 y	< 65 µmol/kg/24 h < 1.1 mg/kg/24 h
								> 5 y	< 55 µmol/kg/24 h < 0.9 mg/kg/24 h

11.1.6 ***References***

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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/m^2 (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.*

*** Exception: Patients with absorptive hypercalciuria, calcium excretion ≥ 8 mmol/day.*

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).

Recommendation	LE	GR
The aim should be to obtain a 24-h urine volume ≥ 2 L.	1b	A

11.2.2 ***Diet***

A common sense approach to diet should be taken, i.e. 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 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 (8-11). However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein should not be taken in excess (12-14) 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 (15). The minimum daily requirement for calcium is 800 mg and the general recommendation is 1000 mg/day (16). Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate (14,17-19).

Sodium: the daily sodium 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 (13,14). A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women (15,20). 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 stones (21-24) and uric acid stones (16). Intake should not exceed 500 mg/day.

11.2.3 ***Lifestyle***

Lifestyle factors may influence the risk of stone formation, e.g. overweight and obesity (25-27). Another risk factor is arterial hypertension (28,29).

11.2.4 ***References***

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11.3 Stone-specific metabolic work-up and pharmacological recurrence prevention

11.3.1 ***Introduction***

Pharmacological treatment is necessary in patients at high risk for recurrent stone formation, which is normally used with general preventive measures. 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. The following descriptions highlight the most important characteristics of commonly used medication.

11.3.1.1 Thiazides and thiazide-like agents

Hydrochlorothiazide, bendroflumethiazide, trichlorothiazide and the non-thiazide indapamide have been used for recurrence prevention in patients with calcium stones. Thiazide treatment aims to reduce excretion

of calcium in hypercalciuria, but calcium reduction is also found in patients with normocalciuria (1,2). The hypocalciuric action of thiazides is thought to be mediated by increased reabsorption of calcium in the proximal and distal nephron (3).

Good evidence from RCTs has proven that thiazides are effective in preventing calcium stone recurrence (Table 28) (4).

Table 28: RCTs of thiazides for the prevention of recurrent stone formation (LE: 1b)

Author	Treatment	Selection	Duration of Study (yrs)	No. pts.	Stones/ pt/yr	Remission rate (%)	p-value
Borghi, et al. (5)	Indapamide No tx	Hypercalciuria	3	19 21	0.06 0.28	84.2 57.1	< 0.05
Brocks, et al. (6)	BFMZ Placebo	Non-selective	4	33 29	0.09 0.11	84.8 82.8	NS
Ettinger, et al. (7)	Chlorthalidone Placebo	Non-selective	4	23 31	0.05 0.22	87.0 54.8	< 0.05
Mortensen, et al. (8)	BFMZ Placebo	Non-selective	2	12 10	- -	100.0 60.0	< 0.1
Laerum and Larsen (9)	HCTZ Placebo	Non-selective	3	23 25	0.07 0.18	78.3 52.0	< 0.05
Ohkawa, et al. (10)	Triclorme-thiazide No Tx	Hypercalciuria	2	82 93	0.13 0.31	86.5 55.9	< 0.05
Robertson, et al. (11)	BFMZ No Tx	Non-selective	3	13 9	0.22 0.58	- -	"sig"
Scholz, et al. (12)	HCTZ Placebo	Non-selective	1	25 26	0.20 0.20	76.0 76.9	NS
Wilson, et al. (13)	HCTZ No Rx	Non-selective	3	23 21	0.15 0.31	- -	< 0.05

BFMZ = bendroflumethiazide; HCTZ = hydrochlorothiazide; Tx = treatment.

However, thiazide treatment has side effects. The unmasking of normocalcaemic hyperparathyroidism, development of diabetes and gout, as well as erectile dysfunction, contribute to limited tolerance and a high drop-out rate, resulting in 50-70% overall compliance.

The use of thiazide induces potassium loss. This can be compensated for by giving potassium citrate (3.5-7.0 mmol twice daily), which is preferable to KCl because it results in better potassium substitution (14).

11.3.1.2 Alkaline citrate

Commonly used alkalinising agents are: sodium potassium citrate, potassium citrate, sodium citrate, potassium magnesium citrate, potassium bicarbonate and sodium bicarbonate. Tubular cell alkalinisation is responsible for increased levels of urinary citrate, although only a small fraction of the administered citrate is directly excreted. Alkaline citrates are used for:

- correction of hypocitraturia;
- urine alkalinisation;
- inhibition of growth and aggregation of calcium oxalate;
- inhibition of agglomeration of calcium phosphate (15).

There is evidence from RCTs that alkaline citrates are effective in preventing calcium stone recurrence (4) (Table 29).

Table 29: RCTs evaluating alkali citrate therapy in preventing stone recurrence (LE: 1b)

Author	Treatment	Selection	Duration of Study (yrs)	N	Stones/ pt/yr	Remission (%)	p-value
Barcelo, et al. (16)	K-cit	Hypocitraturia	3	18	0.01	73.23	< 0.05
	Placebo			20	1.1	20	
Hofbauer, et al. (17)	Na-K-cit	Non-selective	3	16	0.9	31.3	NS
	No Rx			22	0.7	27.3	
Ettinger, et al. (18)	K-Mag-C	Non-selective	3	16	-	87.1	rr=0.06
	Placebo			25	-	36.4	

Potassium citrate (16,19), sodium citrate and potassium magnesium citrate (4) significantly reduce recurrence rate. A favourable effect has been reported with potassium magnesium citrate (18), but not sodium potassium citrate. Although potassium magnesium citrate appears to prevent stone recurrence, it is not yet generally available. Further studies are necessary to show whether it is superior to potassium citrate.

Alkaline citrate has a high occurrence of side effects, therefore, overall compliance rates do not exceed ~50%.

11.3.1.3 Magnesium
Magnesium oxide, magnesium hydroxide, potassium magnesium citrate and magnesium aspartate increase urinary magnesium excretion. Biochemically increased urinary magnesium levels reduce the ion-activity product of calcium oxalate and inhibit growth of calcium phosphate crystals. Magnesium is important for the transformation between various calcium phosphate crystal phases. A high urinary concentration of magnesium is thought to decrease the risk of brushite formation.

There is still not enough evidence to recommend magnesium as monotherapy in calcium stone prevention. In two RCTs, magnesium hydroxide was compared with placebo (7) and magnesium oxide with untreated controls (13). Neither showed a significant effect on stone formation, despite follow-up of 4 and 3 years, respectively. The previously reported positive effects of magnesium (20,21) have not been confirmed by recent studies (22).

11.3.1.4 Calcium supplements
See Section 11.2.2.

11.3.1.5 Allopurinol
Allopurinol is an inhibitor of xanthine oxidase. It has been used to prevent recurrence of calcium oxalate stones ever since a relationship was found between hyperuricosuria and calcium oxalate stone formation (23).

Although allopurinol tolerance is normally good, there are severe side effects with high doses.
The potential benefits of allopurinol on calcium oxalate stone formation are:

- reduced salting-out effect;
- decreased risk of uric acid or urate crystals as promoters of calcium oxalate precipitation;
- complex formation between colloidal urate and macromolecular inhibitors;
- reduced excretion of oxalate.

In a placebo-controlled, randomised study of hyperuricosuric calcium-oxalate stone formers, 75% of those treated with allopurinol were free of recurrent stone formation compared with 45% in the placebo group (significant difference) (24). The effectiveness of allopurinol (300 mg/day) has been tested in RCTs in calcium oxalate stone formers (13,24,25). Only one trial demonstrated a significant benefit of allopurinol in preventing stone recurrence (25). However, this trial solely enrolled patients with hyperuricosuria, while the other three enrolled patients regardless of metabolic background.

11.3.1.6 Pyridoxine
Theoretically, pyridoxine (vitamin B6) might favourably influence endogenous production of oxalate, probably due to increased transamination of glyoxylate resulting from action of the coenzyme pyridoxal phosphate.

Due to the rarity (and severity) of primary hyperoxaluria, there are no randomised studies on pyridoxine efficacy. However, it has been confirmed that a few patients with type 1 hyperoxaluria respond favourably to large doses of pyridoxine (26-28).

Due to the lack of other effective treatments, it is worth trying pyridoxine, with the aim of reducing oxalate excretion in patients with primary hyperoxaluria type I.

There are no controlled studies to support the use of pyridoxine in patients with idiopathic calcium oxalate stones.

11.3.1.7 L-Methionine

Acidification of urine can be achieved with 600-1500 mg/day L-methionine. Methionine acidifies urine pH by donating protons. Stable acidification is difficult to achieve. Long-term acidification in children is not justified (4).

11.3.1.8 Tiopronin-α-mercaptopropionylglycine

Tiopronin - which has a thiol-containing biomolecule - is able to form drug-cysteine complexes by splitting the disulphide binding of cystine. Consequently, cystine saturation of urine decreases, while solubility increases significantly (29-31). Although no RCTs have been reported, tiopronin lowers cystine stone formation, when rates before and after treatment are compared (32-35). Due to the significant level of side effects, tiopronin (and other cysteine-binding drugs) should be reserved for patients who are unable to control stone formation with high fluid intake, dietary modification and urine alkalinisation. The side effects appear to be dose related, including: nausea, rash, fatigue, fever, and proteinuria.

11.3.2 ***Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition***

Urinary risk factor	**Suggested treatment**	**LE**	**GR**
Hypercalciuria	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Hypocitraturia	Potassium citrate	1b	A
Enteric hyperoxaluria	Potassium citrate Calcium supplement Oxalate absorption	3-4 2 3	C B B
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A
Distal renal tubular acidosis	Potassium citrate	2b	B
Primary hyperoxaluria	Pyridoxine	3	B
No abnormality identified	High fluid intake	2b	B

11.3.3 ***References***

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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, ionized calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) in case of increased calcium levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, and magnesium.

11.4.2 ***Interpretation of results and aetiology***

- 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 UTI has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (see Section 11.6.4).
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m^2/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.

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, while hyperuricosuric stone formers benefit from daily dietary reduction of purine. Table 30 summarises pharmacological treatment of calcium oxalate stones.

Table 30: Pharmacological treatment of calcium oxalate stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion 5-8 mmol/day	Alkaline citrate, 9-12 g/day, **OR** Sodium bicarbonate, 1.5 g 3 times daily
	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, 25 mg/day initially, up to 50 mg/day
hypocitraturia	Citrate excretion < 2.5 mmol/day	Alkaline citrate, 9-12 g/day
Hyperoxaluria (enteric)	Oxalate excretion > 0.5 mmol/day	Calcium, ≥ 500 mg/day with meals **NB: BE AWARE OF EXCESS CALCIUM EXCRETION** Magnesium, 200-400 mg/day **NB: NO MAGNESIUM THERAPY IN PATIENTS WITH RENAL INSUFFICIENCY**
Hyperuricosuria	Uric acid excretion > 4.0 mmol/day	Alkaline citrate, 9-12 g/day **OR** Sodium bicarbonate, 1.5 g, 3 times daily **PLUS** Allopurinol,100 mg/day
	Hyperuricosuria and hyperuricemia > 380 µmol	Alkaline citrate, 9-12 g/day **PLUS** Allopurionol, 100-300 mg/day, depending on kidney function
Hypomagnesiuria	Magnesium excretion < 3.0 mmol/day	Magnesium, 200-400 mg/day **NB: NO MAGNESIUM THERAPY IN CASE OF RENAL INSUFFICIENCY**

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 **Specific treatment***

General preventive measures are recommended for fluid intake and diet.

*11.5.3 **Pharmacological therapy (Table 31)***

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 thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be helpful. For

infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

Table 31: Pharmacological treatment of calcium phosphate stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, initially 25 mg/day, increasing up to 50 mg/day
Inadequate urine pH	pH constantly > 6.2	L-Methionine, 200-500 mg 3 times daily, with the aim of reducing urine pH to 5.8-6.2
Urinary tract infection	Eradication of urea-splitting bacteria	Antibiotics

11.6 Disorders and diseases related to calcium stones

11.6.1 ***Hyperparathyroidism (1-6)***

The clinical appearance of HPT typically comprises bone loss, gastric ulcers and urolithiasis. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcaemia and hypercalciuria. If HPT is suspected, neck exploration should be performed to confirm the diagnosis (7). Primary HPT can only be cured by surgery.

11.6.2 ***Primary hyperoxaluria (PH) (8-14)***

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/m^2 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).

11.6.3 ***Enteric hyperoxaluria (15-20)***

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, jejunoileal bypass for treatment of obesity, 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.

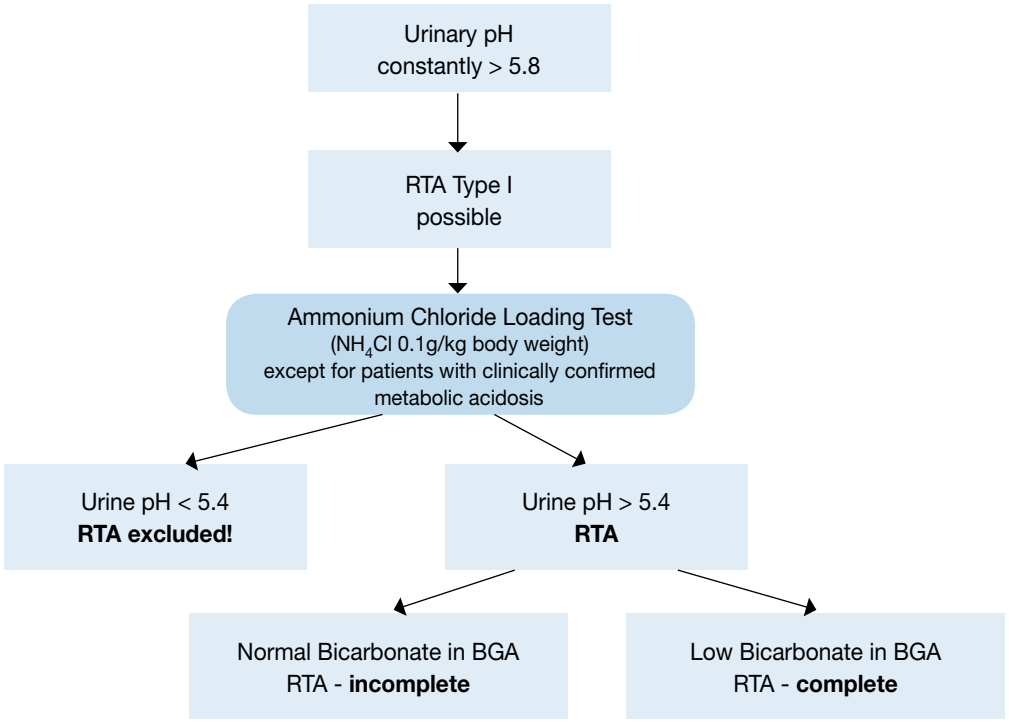
Specific preventive measures are:

- 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 (22).

11.6.4 ***Renal tubular acidosis (RTA) (24,25)***

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 4 outlines the diagnosis of RTA.

Figure 4: Diagnosis of renal tubular acidosis (RTA)



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 32). 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) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Table 32: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	**Rationale for pharmacological therapy**	**Medication**
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults, 25 mg/day initially, up to 50 mg/day - in children, 0.5-1 mg/kg/day
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day **OR** Sodium bicarbonate, 1.5 g 3 times daily

11.6.5 ***Nephrocalcinosis (26,27)***

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 and Bartter's syndrome. 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.

11.6.5.1 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 a day), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

11.6.6 ***References***

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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). Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs, gout or catabolism (2). Ammonium urate crystals are associated with UTI, malabsorption and malnutrition.

11.7.1 ***Diagnosis***

Blood analysis requires measurement of creatinine and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level.

Interpretation of results

Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 6) 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. Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration, and in the presence of cations.

11.7.2 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction of their daily diet. Table 33 describes pharmacological treatment.

Table 33: Pharmacological treatment of uric acid and ammonium urate stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Inadequate urine pH	Urine pH constantly ≤ 6.0; 'acidic arrest' in **uric acid stones**	Alkaline citrate, 9-12 g/day **OR** Sodium bicarbonate, 1.5 g 3 times daily **NB: DOSE DEPENDS ON TARGETED URINE PH** Prevention: targeted urine pH **6.2-6.8** Chemolitholysis: targeted urine pH **7.0-7.2**
	Urine pH constantly > 6.5 in **ammonium urate stones**	Adequate antibiotics in case of urinary tract infection with urea-degrading bacteria L-Methionine, 200-500 mg 3 times daily; targeted urine pH **5.8-6.2**
Hyperuricosuria	Uric acid excretion > 4.0 mmol/day	Allopurinol, 100 mg/day
	Hyperuricosuria and hyperuricemia > 380 µmol	Allopurinol, 100-300 mg/day, depending on kidney function

11.7.3 ***References***

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11.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence.

11.8.1 ***Diagnosis***

Blood analysis requires measurement of creatinine, and urinalysis requires urine pH profile and urine culture.

Interpretation

- Infection stones contain struvite and/or carbonate apatite and/or ammonium urate.
- Urine culture typically provides evidence for urease-producing bacteria (Table 34).

Table 34: Most important species of urease-producing bacteria

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: About 0-5% of strains of *Escherichia coli*, *Entercoccus* and *Pseudomonas aeruginosa* may produce urease.

11.8.2 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal (1), short- or long-term antibiotic treatment (2), urinary acidification using methionine (3) or ammonium chloride (4), and urease inhibition (5,6). For severe infections, acetohydroxamic acid (Lithostat) may be an option.

Recommendations for therapeutic measures	**Refs.**	**LE**	**GR**
Surgical removal of the stone material as completely as possible	1		
Short-term antibiotic course	2	3	B
Long-term antibiotic course	2	3	B
Urinary acidification: ammonium chloride, 1 g x 2-3 daily	4	3	B
Urinary acidification: methionine, 200-500 mg, 1-3 times daily	3	3	B
Urease inhibition	5,6	1b	A

11.8.3 ***References***

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11.9 Cystine stones

All cystine stone formers are deemed at high risk of stone 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 crystallizes spontaneously within the physiological range of urine pH.
- 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.
- Reductive therapy targets disulphide bond splitting in cystine; it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only HPLC-based analysis differentiates between the different complexes formed by therapy.

11.9.2 ***Specific treatment***

General preventative measures for fluid intake and diet are recommended. Although theoretically a diet low in methionine may reduce urinary excretion of cystine, patients are unlikely to comply sufficiently with such a diet. However, 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 (1).

A high diuresis is of fundamental importance, aiming for 24-h urine volume of ≥ 3 L (2,3). A considerable fluid intake evenly distributed during 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 above 7.5 to improve cystine solubility (Table 35) and to ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children.

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cystine

Tiopronin: Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, e.g. 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 troublesome disease.

Ascorbic acid is used when cystine excretion is < 3.0 mmol/day. However, it has limited reductive power and is estimated to lower urinary cystine levels by ~20% (4). The effectiveness and use of ascorbic acid as a standard therapeutic regimen are controversial (5).

Results for the angiotensin-converting enzyme inhibitor, captopril, are controversial (6-10). Captopril remains a second-line option, for use when tiopronin is not feasible or unsuccessful.

Table 35: Pharmacological treatment of cystine stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Cystinuria	Cystine excretion > 3.0-3.5 mmol/day	Tiopronin, 250 mg/day initially, up to a maximum dose of 2 g/day **NB: TACHYPHYLAXIS IS POSSIBLE**
Inadequate urine pH	Improvement of cystine solubility. Urine pH optimum 7.5-8.5	*Alkaline Citrate* dose according to urine pH alternative *Sodium Bicarbonate* dose according to urine pH

Recommendations for the treatment of cystine stones

Therapeutic measures	Refs.	LE	GR
Urine dilution High fluid intake recommended so that 24-h urine volume exceeds 3 L. Intake should be ≥ 150 mL/h.	1-3,5	3	B
Alkalinisation For cystine excretion < 3 mmol/day: potassium citrate 3-10 mmol 2 or 3 times daily, to achieve pH > 7.5.	1-3,5	3	B
Complex formation with cystine For patients with cystine excretion > 3 mmol/day, or when other measures are insufficient: tiopronin, 250-2000 mg/day; captopril, 75-150 mg remains a second-line option in case tiopronin is unfeasible or unsuccessful.	1-10	3	B

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11.10 2,8-dihydroyadenine 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 causeshigh urinary excretion of poorly soluble 2,8-dihydroxyadenine. High-dose allopurinol is an option, but should only be tried 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 < 1.01. A purine-reduced diet decreases risk of spontaneous crystallisation in urine.

11.11 Drug stones (2)

Drug stones are induced by pharmacological treatment (3,4) (Table 36). Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 36: Compounds that cause drug stones

Active compounds crystallizing in urine
• Allopurinol/oxypurinol
• Amoxicillin/ampicillin
• Ceftriaxone
• Ciprofloxacin
• Ephedrine
• Indinavir
• Magnesium trisilicate
• Sulfonamide
• Triamterene
Substances impairing urine composition
• Acetazolamide
• Allopurinol
• Aluminium magnesium hydroxide
• Ascorbic acid
• Calcium
• Furosemide
• Laxatives
• Methoxyflurane
• Vitamin D

11.12 Unknown stone composition (5)

An accurate medical history is the first step towards identifying risk factors (Table 37).

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 > 6 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, as crystals of 2,8-dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease.

Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow.

However, if any expulsed stone material is available, it should be analysed by diagnostic confirmation or correction.

Table 37: Investigating patients with stones of unknown composition

Investigation	Rationale for investigation
Medical history	Stone history (former stone events, family history) Dietary habits Medication chart
Diagnostic imaging	Ultrasound in case of a suspected stone Unenhanced helical-CT (Determination of Hounsfield units provides information about the possible stone composition)
Blood analysis	Creatinine Calcium (ionised calcium or total calcium + albumin) Uric acid
Urinalysis	Urine pH profile (measurement after each voiding, minimum 4 times daily) Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight Urine culture Microscopy of urinary sediment (morning urine)

11.13 References

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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 pertaacetic acid (radiotracer)
EAU	European Association of Urology
SWL	(extracorporeal) shock wave lithotripsy
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 acidosis
SFR	stone free rate
SIGN	Scottish Intercollegiate Guidelines Network
THAM	tris-hydroxymethyl-aminomethane
UPJ	ureteropelvic junction
URS	ureterorenoscopy
US	ultrasonography
UTI	urinary tract infection
XRD	X-ray diffraction

Conflict of interest

All members of the Urolithiasis Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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 Paediatric Urology

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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*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports

4	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: Grade of recommendation*

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

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

1.4 Publication history

The Paediatric Urology Guidelines were first published in 2001 with subsequent partial updates achieved in 2005, 2006, 2008, 2009, 2010, 2011, and this 2012 publication includes a considerable number of updated chapters and sections detailed below.

This 2012 guidelines publication underwent a blinded peer-review process before publication.

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/).

1.4.1 Summary of updated and new information

Amended: new literature included and the text has been revised for:
Chapter 6 - Hypospadias
Chapter 12 - Monosymptomatic enuresis. A new algorithm has been included and the text was revisited.
Chapter 13 - sections

- Botulinum toxin injections
- Follow-up of neurogenic bladder patients

Chapter 15 - Vesicoureteric reflux. The literature has been updated and the text has been revised.
Section 16.5.3 - Ureterorenoscopy. A small section has been added with new literature.
Chapter 17 - Obstructive pathology of renal duplication: ureterocele and ectopic ureter. This section has been completely revised and a new algorithm included.

New topics included in this 2012 print
Urinary tract infections in children (Chapter 10)
Post-operative fluid management in children (Chapter 20)
Post-operative pain management in children (Chapter 21)

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

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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). The 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. 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 (3-6) (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. 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 (7,8). Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason (9-12) (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 (13-16) (LE: 1; GR: A). This

treatment has no side effects and the mean bloodspot cortisol levels are not significantly different from an untreated group of patients (17) (LE: 1). Agglutination of the foreskin does not respond to steroid treatment (14) (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 (18) (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.

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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 males (1). The most useful classification of cryptorchidism is into palpable and non-palpable testes, as clinical management is decided by the location and existence of the testis.

- Retractile testes require only observation as 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

A 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 an examination of the child in both a supine and crossed-leg position. The examiner should inhibit the cremasteric reflex with his 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) will retract it again into the groin (4).

A unilateral, non-palpable testis and an enlarged contralateral testis may 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 region 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) (LE: 1b; GR: A). Before carrying out laparoscopic assessment, an examination under general anaesthesia is recommended because some, originally nonpalpable, testes become palpable under anaesthetic conditions.

3.3 Treatment

If a testis has not descended by the age of 1 year, there is no benefit in waiting for a spontaneous descent. To prevent histological deterioration, treatment should be carried out and finished before 12-18 months of age (6-9).

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). Hormonal therapy for testicular descent has lower success rates, the higher the undescended testis is located. A total dose of 6000 to 9000 units of hCG is given in four doses over a period of 2 to 3 weeks depending on weight and age, along with GnRH, given for 4 weeks as a nasal spray in a dose of 1.2 mg/day, divided into three doses per day.

Medical treatment may be beneficial before surgical orchidolysis and orchidopexy (dosage as described earlier) or afterwards (low intermittent dosages) (12), in terms of increasing the fertility index, which is a predictor for fertility in later life (12). However, long-term follow-up data are awaited. But there is data reporting that hCDG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells (13).

3.3.2 ***Surgery***

Palpable testis: surgery for the 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, e.g. 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 either 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.

Non-palpable testis: inguinal surgical exploration with possible laparoscopy should be attempted. 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 orchidolysis and orchiopexy can be performed via laparoscopic access (15). Before starting diagnostic laparoscopy, examine the child under general anaesthesia since a previously non-palpable testes might now be palpable under anaesthesia.

An intra-abdominal testis in a 10-year-old boy or older, with a normal contralateral testis, should be removed. In bilateral intra-abdominal testes, or in a boy 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 either 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 a one-stage procedure varies between 50% and 60%, with success rates rising up to 90% in a two-stage procedure (17). Microvascular autotransplantation can also be performed with a 90% testicular survival rate. However, the procedure requires very skilful and experienced surgical techniques (18).

3.4 Prognosis

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as boys with bilateral descended testes. Boys with bilateral undescended testes have a lower fertility and paternity rate.

Boys with an undescended testis have a 20-fold higher risk of developing testicular malignancy, a risk uninfluenced by any kind of treatment. Screening both during and after puberty is therefore recommended for these boys. Recently, a Swedish study, with a cohort of almost 17,000 men who were treated surgically for undescended testis and followed for a total of almost 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 orchiopexy 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 of age or older 5.40 (19). A systematic review and meta-analysis of the literature by an American group has also concluded that prepubertal orchiopexy 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 crytorchidism

Due to the lack of spontaneous testicular descent after the age of 1 year, and because of the potential loss of testicular quality, it is recommended that surgical orchidolysis and orchidopexy should be performed at the latest by 12-18 months of age.

To date, it seems that pre- or post-operative hormonal treatment may have a beneficial effect on fertility later in life.

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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 obliteration of processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults (3). If complete obliteration of 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; physical investigation and transillumination of the scrotum make the diagnosis in the majority of cases (5). 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: 4; GR: C). Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology (6). The question of contralateral disease should be addressed by both history and examination at the time of initial consultation (5). 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. 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 (1,5,6) (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 of chemical peritonitis in communicating processus vaginalis peritonei (5,6) (LE: 4; GR: C). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

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5. ACUTE SCROTUM IN CHILDREN

5.1 Background

Acute scrotum is a paediatric urology emergency case, most commonly caused by torsion of the testis, torsion of the appendix testis and 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 (Henoch-Schönlein purpura) (7-19).

Torsion of the testis occurs most often in the neonatal period and around puberty, while torsion of the appendix testes occurs over a wider age range. Acute epididymitis affects two age groups: below the age of 1 year and between 12 and 15 years (5,20,21). Acute epididymitis was found most often (37-64.6%) in boys with acute scrotum (1-4). One study predicted the incidence of epididymitis as about 1.2 per 1,000 male children per year (22).

5.2 Diagnosis

Patients usually present with scrotal pain. The duration of symptoms is shorter in testicular torsion (69% present within 12 hours) 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 the diagnosis. Patients with acute epididymitis experience a tender epididymitis, while 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 was more frequent in testicular torsion than in patients with epididymitis (20). Looking for the absence of the cremasteric reflex is a simple method with a sensitivity of 100% and specificity of 66% for the presence of 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% 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 an acute scrotum, with a sensitivity of 63.6-100% and a specificity of 97-100%, and a positive predictive value of 100% and negative predictive value 97.5% (26-31) (LE: 3; GR: C). 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% patients had normal or increased testicular vascularisation (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 a 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 emergent 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 the detorsion and degree of twisting of the cord (44). Severe testicular atrophy occurred after torsion for as little as 4 hours when the turn was more than 360°. In cases of incomplete torsion (180° to 360°), with symptom duration up to 12 hours, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion of more than 360° and symptom duration of more than 24 hours (45).

Early surgical intervention with detorsion (mean torsion time < 13 hours) was found to preserve fertility (46). Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of the onset of symptoms.

In those patients with testicular torsion of more than 24 hours, semi-elective exploration is necessary (44,45) (LE: 3; GR: C). 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 hours).

A recent study in humans found that sperm quality was preserved in both orchiectomy and orchiopexy groups in comparison to control normal men, although orchiectomy resulted in better sperm morphology (47).

During exploration, fixation of the contralateral testis is also performed. Recurrence after orchiopexy is rare (4.5%) and may occur several years after operation. There is no common recommendation about the preferred type of fixation and suture material; however, many urologists currently use a Dartos pouch orchiopexy (48).

External cooling before exploration and several medical treatments seem effective in reducing ischaemia-reperfusion injury and preserving the viability of the torsed testis 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 hours) with detorsion was found to preserve fertility, but a prolonged torsion period (mean torsion time of 70 hours) followed by orchiectomy jeopardises fertility (46).

One study identified antisperm antibodies in the semen of patients with testicular torsion and correlated antibody levels with infertility, while other studies 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 antisperm 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 in patients 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 to the torsed testicle (44).

*5.4.5 **Nitric oxide***

A study in rats found that spermatic cord torsion did not lead to impairment in nitric oxide-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%, with bilateral perinatal torsion comprises 11-21% of all perinatal torsions (55). Most cases are extravaginal torsion in contrast to the usual intravaginal torsion, which occurs during puberty.

Intrauterine torsion may present as:

- patients with a testicular nubbin;
- patients with a small and hard testis;
- patients with a normal-sized and hard testis;
- patients with an acute scrotum.

Torsion occurring in the postnatal period within the first month of life presents with signs of an acute scrotum. The clinical signs correlate well with surgical and histological findings and thus define the need and the urgency to explore the history (56). Doppler ultrasound can be an additional diagnosis tool. The sensitivity for diagnosis of torsion of the testis is high, though 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 References

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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 are 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): There is a 7% familial recurrence risk for hypospadias (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; GR: B).

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, require a complete genetic and endocrine work-up immediately after birth to exclude intersexuality, especially congenital adrenal hyperplasia.

Urine trickling and ballooning of the urethra requires 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 future patient's 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; GR: C) (Figure 1).

The use of magnifying spectacles and special fine synthetic absorbable suture materials (6/0-7/0) is 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 has been recommended to postpone the surgery 3 months after completion of hormonal therapy (9) (LE: 2b; GR: B).

*6.3.1 **Age at surgery***

The age at surgery for primary hypospadias repair is usually 6-18 [24] months (3) (LE: 4; GR: C). However, earlier repair between 4 and 6 months of age has been reported recently (10) (LE: 3; GR; B).

*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% (11). The urethral

plate has well vascularised 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; GR: B).

6.3.3 ***Preservation of the well-vascularised urethral plate***

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become the mainstay of hypospadias repair (14). Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection (11,13,15) (LE: 2b; GR: B).

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 (though the complication rate is higher) (16-21).

The onlay technique is preferred in proximal hypospadias and in cases of 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; GR: B).

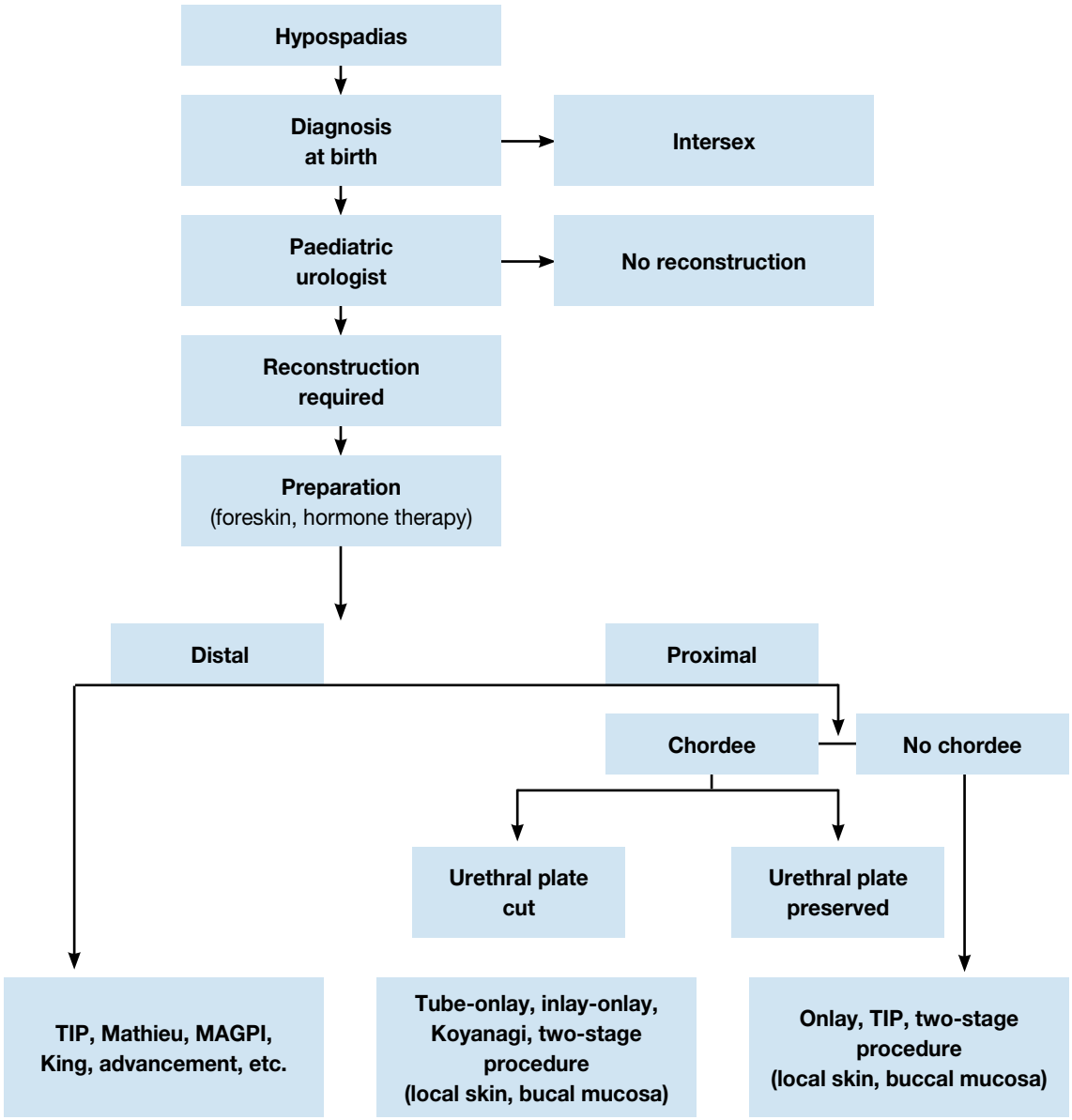
If the continuity of the urethral plate cannot be preserved, a modification of the tubularised flap, such as a tube-onlay or an inlay-onlay flap, is used to prevent urethral stricture (23,24) (LE: 3; GR: C). In this situation, as well as in severe scrotal or penoscrotal hypospadias, the Koyanagi technique or two-stage procedure may be an option (25-27).

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 (28-30) (LE: 3; GR; C). The use of inlay skin grafts may allow an increased number of single-stage repairs to be performed (31).

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



TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and granulaplasty.

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 use of a preputial dartos flap reduces the fistula rate (17, 21) (LE: 2; GR: B).

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. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures (LE: 4; GR: C) (32). Postoperative prophylaxis is associated with a lower complication rate (LE: 1b; GR: A) (33).

A large variety of duration of stenting and dressing is described. No recommendation can be given due to the low level of evidence.

6.3.7 Outcome

Long-term follow-up, into adolescence, is necessary to detect urethral strictures, voiding dysfunction and recurrent penile curvature.

The complication rate of TIP and onlay repairs is similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty (11).

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. Spontaneous improvement has been described (34,35) (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 (36,37) (LE: 2a-2b). The later corrective surgery is completed, the more likely the patients may become insecure with regard to gender-role behaviour. (38-39) (LE: 2b).

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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).

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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 15-20% 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 (1,2).

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 have reported controversial results (3,4).

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents (LE: 2) (5,6). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels (LE: 2) (7).

In about 20% of adolescents with varicocele, fertility problems will arise (8). The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy (3,9) (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) (10). 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 (11). 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 compared to the other testis is considered to be hypoplastic (1) (LE: 4).

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, as histopathological testicular changes have been found in these patients (9,12).

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 (13-16).

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 (13-15,17). The recurrence rate is usually less than 10%. Angiographic occlusion is based on retrograde or antegrade sclerotisation of the internal spermatic veins (18,19).

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 (LE: 2; GR: A) (7,13,16,17,20). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs.

Angiographic occlusion of the internal spermatic veins also meets these requirements. However, although this method is less invasive, it appears to have a higher failure rate (1,19) (LE: 2; GR: B).

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 (1,21):

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- varicocele associated with a supranormal response to LHRH stimulation test;
- symptomatic varicocele.

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; GR: C).

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9. MICROPENIS

9.1 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:

- Hypogonadotropic hypogonadism (due to an inadequate secretion of GnRH)
- Hypergonadotropic hypogonadism (due to failure of the testes to produce testosterone).

9.2 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).

9.3 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).

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10. URINARY TRACT INFECTIONS IN CHILDREN

10.1 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 bacteremia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteremia in around 12% (8), however, it is less frequent in community-acquired than in nosocomial UTI (8,9).

10.2 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.

*10.2.1 **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.

10.2.2 ***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.

10.2.3 ***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.

10.2.4 ***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.

10.2.5 ***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.

10.3 Diagnosis

10.3.1 ***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.

10.3.2 ***Clinical signs and symptoms***

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability 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.

10.3.3 ***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.

10.4 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).

10.4.1 ***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.

*10.4.2 **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 3: Sensitivity and specificity of component of urinalysis, alone and in combination (22)*

Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy, WBCs	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (16-99)	83 (11-100)
Leucocyte esterase test, nitrite test or microscopy positive	99.8 (99-100)	70 (60-92)

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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.

(3) 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).

*10.4.3 **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 > 10^5 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 İnfection 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])

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	≥ 1,000-50,000 cfu/mL	≥ 10^4 cfu/mL with symptoms ≥ 10^5 cfu/mL without symptoms

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.

10.5 Therapy

10.5.1 ***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 hyperkalemia 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).

10.5.2 ***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).

*10.5.3 **Antimicrobial agents***

Table 5: Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children*

Chemotherapeutics	Daily dosage	Application	Comments
Parenteral cephalosporins			
Group 3a, e.g. cefotaxime	100-200 mg/kg *(Adolesc.: 3-6 g)*	i.v. in 2-3 D	
Group 3b, e.g. ceftazidime	100-150 mg/kg *(Adolesc.: 2-6 g)*	i.v. in 2-3 D	
Ceftriaxone	75 mg/kg,	i.v. in 1 D	
Oral cephalosporins			
Group 3, e.g. ceftibuten	9 mg/kg *(Adolesc.: 0,4 g)*	p.o. in 1-2 D p.o. in 1-2 D	
Group 3, e.g. cefixime	8-12 mg/kg *(Adolesc.: 0,4 g)*	p.o. in 1-2 D	
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kg *(Adolesc.: 0,4 g)*	p.o. in 2D	
Group 2, e.g. cefuroximaxetil	20-30 mg/kg (Adolesc.: 0,5-1 g)	p.o. in 3 D	
Group 1, e.g. cefaclor	50 -100 mg/kg *(Adolesc.: 1,5-4 g)*	p.o. in 2-3 D	
Trimethoprim or Trimethoprim/sulfamethoxazole	5-6 mg/kg 5-6 mg/kg (TMP-Anteil) *(Adolesc.: 320 mg)*	p.o. in 2 D p.o. in 2 D	
Ampicillin	100-200 mg/kgKG *(Adolesc.: 3-6 g)*	i.v. in 3 D i.v. in 3-4 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Amoxicillin	50-100 mg/kg *(Adolesc.: 1,5-6 g)*	p.o. in 2-3 D[1] p.o. in 2-3 D	
Amoxicillin/clavulanic acid (parenteral) Amoxicillin/clavulanic acid (oral)	60-100 mg/kg *(Adolesc.: 3,6-6,6 g)* 45-60 mg/kg (Amoxicillin-fraction) *(Adolesc.: 1500 + 375 mg)*	i.v. in 3 D i.v. in 3 D p.o. in 3 D p.o.in 3 D	
Piperacillin	300 mg/kg	i.v. in 3-4 D	
Tobramycin	5 mg/kg *(Adolesc.: 3-5 mg/kg, max. 0,4 g)*	i.v. in 1 D	Drug monitoring
Gentamicin	5 mg/kg *(Adolesc.: 3-5 mg/kg, max. 0,4g)*	i.v. in 1 D	
Ciprofloxacin	Children and adolesc. (1-17 years of age): 20-30 mg/kg (max. D: 400 mg) (parenterally) Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	i.v. in 3 D p.o. in 2 D	Approved in most European countries as second- or third line medication for complicated UTIs, „reserve-antibiotic“ !
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*

Diagnosis	Proposal	Application	Duration of therapy	LE
Pyelonephritis during the first 0-6 months of life	Ceftazidime + Ampicillin[1] or Aminoglycoside + Ampicillin[1]	3-7 days parenterally, for at least 2 days after defervescence, then oral therapy[2] In newborns: parenteral therapy for 7-14 days, then oral therapy[2]	10 (-14) days Newborns 14-21 days	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3[2]	Orally (initially parenterally, if necessary)	(7-)10 days	1
Complicated pyelonephritis/ urosepsis (all ages)	Ceftazidime + Ampicillin[1] or Aminoglycoside + Ampicillin[1]	7 days parenterally, then oral therapy[2]	10-14 days	4

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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)*

Chemotherapeutics	Daily dosage	Application
Oral cephalosporins		
Group 1, e.g. cefaclor	50 (-100) mg/kgbw	p.o. in 2-3 D
Group 1, e.g. cefalexin	50 mg/kgbw	p.o. in 3-4 D
Group 2, e.g. cefuroximaxetil	20-30 mg/kgbw	p.o. in 2 D
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kgbw	p.o. in 2 D
Group 3, e.g. ceftibuten	9 mg/kgbw	p.o. in 1 D
Trimethoprim	5-6 mg/kgbw	p.o. in 2 D
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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*10.5.4 **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*

Substance**	Prophylactic dosage (mg/kgbw/d)	Limitations in young infants
Trimethoprim	1	until 6 weeks of age
Nitrofurantoin	1	Until 3 months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns
Ceftibuten	2	***
Cefuroximaxetil	5	***

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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.*

10.6 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 congenitaluropathy 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.

10.7 Imaging

*10.7.1 **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.

*10.7.2 **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).

*10.7.3 **Voiding cystourethrography***

VCUG 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).

10.8 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.

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11. DAYTIME LOWER URINARY TRACT CONDITIONS

11.1 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.

11.2 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.

*11.2.1 **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** (formerly known as 'lazy bladder'). Some children habitually postpone micturition leading to **voiding postponement**.

*11.2.2 **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.

11.3 Diagnosis

A non-invasive screening, consisting of history-taking, clinical examination, uroflow, ultrasound and voiding diary, is essential to reach a diagnosis.

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 (9,10).

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, syringocoeles, 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.

11.4 Treatment

Treatment of voiding dysfunction consists of lower urinary tract rehabilitation, mostly referred to as urotherapy. Urotherapy means non-surgical, non-pharmacological, treatment of LUT function. It is a very broad therapy field, incorporating many treatments used by urotherapists and other healthcare professionals (11). Urotherapy can be divided into standard therapy and specific interventions.

11.4.1 ***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.

11.4.2 ***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, there have been no randomised controlled treatment trials (RCTs), so that the level of evidence is low (11-15).

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 (16), while another RCT on propiverine showed both safety and efficacy (17) (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 (18). Botulinum toxin injection seems promising, but can only be used off-label (19).

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12. MONOSYMPTOMATIC ENURESIS

12.1 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.

12.2 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).

12.3 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).

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 insispidis diabetis.

12.4 Treatment

Before using alarm treatment or medication, simple therapeutic interventions should be considered.

*12.4.1 **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.

*12.4.2 **Alarm treatment***

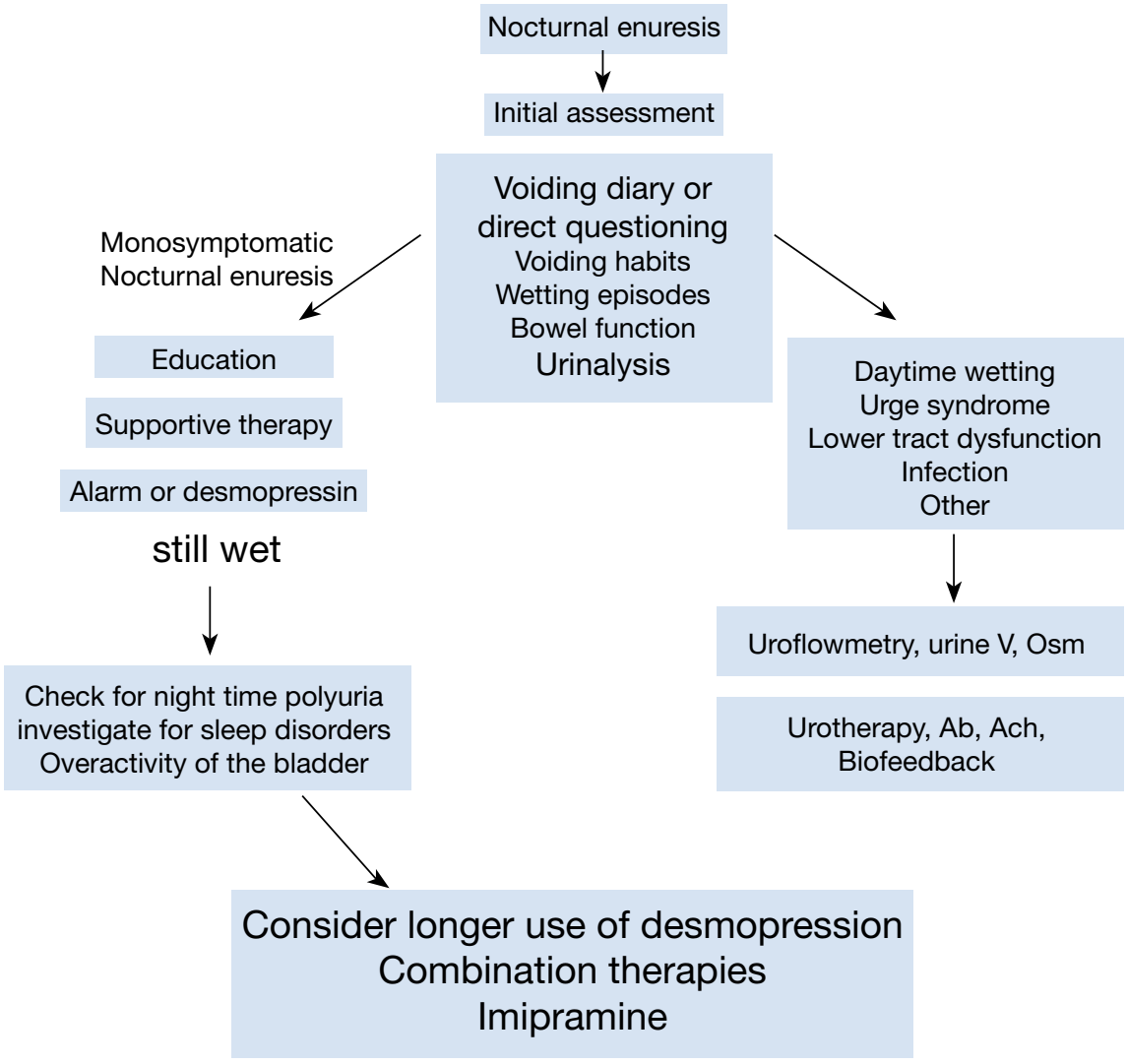
Alarm treatment is the best form for arousal disorder (LE: 1; GR: A). Initial success rates of 80% are realistic,

with low relapse rates, especially when night-time diuresis is not too high and bladder capacity is not too low (5).

12.4.3 ***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 mono-symptomatic.
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



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13. MANAGEMENT OF NEUROGENIC BLADDER IN CHILDREN

13.1 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 urodynamic 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.

13.2 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.

13.3 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.

13.4 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.

13.4.1 ***Method of urodynamic study***

There is very little comparative data evaluating the complexity and invasiveness of urodynamic testing for neurogenic bladders in children.

13.4.2 ***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).

13.4.3 ***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 neurogenic 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).

13.5 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.

13.5.1 ***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).

13.5.2 ***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).

13.5.3 ***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).

13.5.3.1 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 cmH_2O and bladder compliance was increased to at least 20 cmH_2O/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 300 U/kg. 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).

13.5.4 ***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).

13.5.5 ***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).

13.5.6 ***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.

13.5.7 ***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).

13.5.8 ***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 continence. 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.

13.5.9 ***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.

13.5.10 ***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).

13.5.11 ***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 (f.i: 10 years), an annual diagnostic work-up including cystoscopy should be considered.

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14. DILATATION OF THE UPPER URINARY TRACT (URETEROPELVIC JUNCTION AND URETEROVESICAL JUNCTION OBSTRUCTION)

14.1 Background

Dilatation of the upper urinary tract still presents a significant clinical challenge in determining which patient may gain benefit by therapy.

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 ranked as second in the differential diagnosis of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side (2).

Much more difficult is the definition of obstruction. Creating a divide between ‘obstructed’ and ‘nonobstructed’ urinary tracts, as if entities could be as clearly differentiated as ‘black’ and ‘white’, is impossible.

Currently, the most popular definition is that obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration (3).

14.2 Diagnosis

Due to the widespread use of ultrasonography during pregnancy, antenatal hydronephrosis is being detected with increasing frequency (4). The challenge in the management of dilated upper urinary tracts is to decide which child can be observed, which one should be managed medically, and which one requires surgical intervention. There is no single definitive test able to distinguish obstructive from non-obstructive cases (Figure 3).

14.2.1 ***Antenatal ultrasound***

Usually between the 16th and 18th week 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 the laterality, severity of dilatation, and echogenicity of the kidneys, hydronephrosis or hydro-ureteronephrosis, bladder volume and bladder emptying, sex of the child, and amniotic fluid volume, respectively (5).

14.2.2 ***Postnatal ultrasound***

Since transitory neonatal dehydration lasts about 48 hours, imaging should be performed after this period of postnatal oliguria. In severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended (6). During ultrasound examination, the anteroposterior diameter of the renal

pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine are assessed.

*14.2.3 **Voiding cystourethrogram (VCUG)***

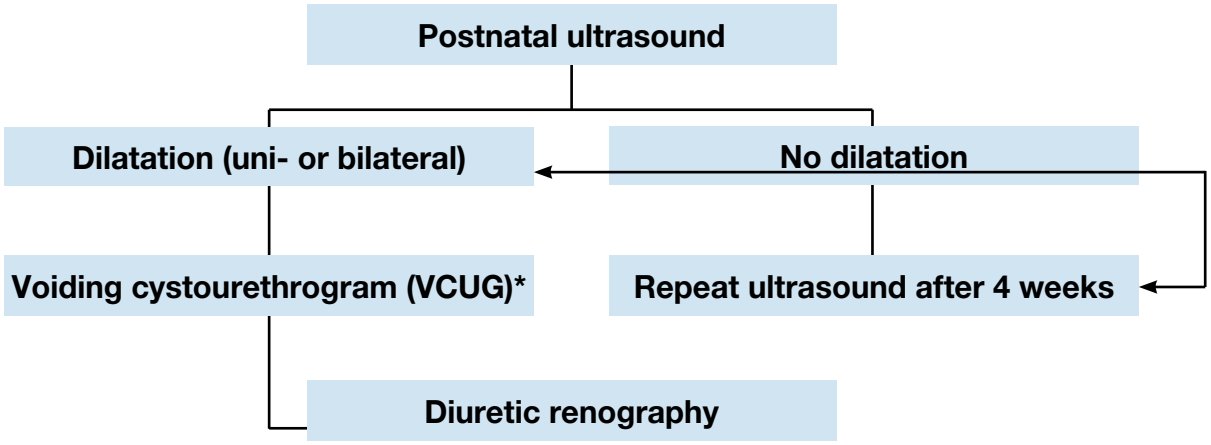
In newborns with identified upper urinary tract dilatation, the presence of primary or important associated factors that must be detected include vesicoureteral reflux in up to 25% of affected children (15), urethral valves, ureteroceles, diverticula and neurogenic bladder. Conventional VCUG is the method of choice for primary diagnostic procedures (7).

*14.2.4 **Diuretic renography***

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of urine transport problems. ^{99}mTc-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 (8).

Oral fluid intake is encouraged prior to examination. Fifteen minutes before injection of the radionuclide, it is mandatory to give normal saline intravenous infusion at a rate of 15 ml/kg over 30 minutes and then at a maintenance rate of 4 ml/kg/hour throughout the whole time of the investigation (9). 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



** A diagnostic work-up including VCUG has to be discussed with the parents since a possibly detected reflux might have absolutely no clinical impact. On the other hand, a reflux rate of up to 25% in cases of prenatally detected and postnatally confirmed hydronephrosis is reported in the literature (15) and might therefore have some forensic impact as well.*

14.3 Treatment

*14.3.1 **Prenatal management***

Counselling the parents is one of the most important aspects of care. The prognosis for an hydronephrotic kidney, even if severely affected, is hopeful. An hydronephrotic kidney may still be capable of providing meaningful renal function, whereas a severely hypoplastic and dysplastic kidney has a hopeless outlook. It is important to explain to the parents the timing and accuracy of establishing the definitive diagnosis for their child. In some cases, there is an obvious indication of severity, including massive bilateral dilatation, bilateral evidence of hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres (10).

*14.3.2 **Ureteropelvic junction obstruction***

It is most important to make the decision on the basis of serial investigations, applying the same technique and 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 standardised open technique of Hynes and Anderson (11). Recently, increasingly more data have become available supporting the use of a laparoscopic or retroperitoneoscopic approach to achieve a dismembered pyeloplasty.

In addition, laparoscopic suturing has been improved by the use of robotics (16). However, these methods lack very long-term data and will require time to be fully proven. In asymptomatic cases, conservative follow-up can be the treatment of choice.

Indications for surgical intervention are an impaired split renal function (< 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.

14.4 Megaureter

Concerning the treatment options of secondary megaureters (*see Chapter 15, Vesicoureteric reflux in children*). 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 prevention of urinary tract infections, although there are no prospective randomised trials to evaluate this regimen (12).

With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent UTI, deterioration of split renal function and significant obstruction (13).

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. There are several tailoring techniques, e.g. ureteral imbrication or excisional tapering (14).

14.5 Conclusion

With the use of routine perinatal sonography, hydronephrosis caused by UPJ or UVJ obstruction is now increasingly recognised. Meticulous and repeat postnatal evaluation is mandatory to try to identify any obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are fairly standardised and have a good clinical outcome.

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15. VESICOURETERIC REFLUX IN CHILDREN

15.1 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.

15.2 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).

15.3 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), voiding cystourethrography (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)

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

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 LUTSs, 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.

*15.3.1 **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).

*15.3.2 **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.

Recommendations for paediatric screening for VUR
The parents of children with VUR should be informed that siblings and offspring have a high prevalence of VUR.
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.
In older children who are toilet-trained, there is no added value in screening for VUR.

*15.3.3 **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).

*15.3.4 **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 video-urodynamic 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.

15.4 Treatment

There are two main treatment approaches: conservative (non-surgical) and surgical.

*15.4.1 **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).

15.4.1.1 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.

15.4.1.2 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/LUTSs, 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.

15.4.2 ***Surgical treatment***

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation.

15.4.2.1 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.

15.4.2.2 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 suprahiatal reimplantation (Politano-Leadbetter technique) and infrahiatal 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.

15.4.2.3 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, laparascopic 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).

15.5 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

Risk Groups	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months

Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT, infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed.		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

PNH = prenatal diagnosed hydronephrosis.

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16. URINARY STONE DISEASE

16.1 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 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. In the UK and other European countries, 75% of calculi in children are composed of organic matrix and struvite, with many coinciding with Proteus infection and urinary tract anomalies (2).

16.2 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.

When supersaturated in urine calcium, oxalate, uric acid and cystine molecules may cause stone formation. A decreased concentration of crystallisation inhibitors (citrate, magnesium, pyrophosphate, macromolecules and glycosaminoglycans) may sometimes be the sole factor playing a role in the formation of urinary stones. Urinary pH changes also affect stone formation.

An impaired flow of urine due to abnormal morphology may facilitate stasis and increase the concentration of stone-forming substances.

16.2.1 ***Calcium stones***

Calcium stones are usually made from calcium oxalate or calcium phosphate. Either supersaturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors like citrate (hypocitraturia) play a major role in calcium oxalate stone formation.

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 (3).

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, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) (4).

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 (3,4). 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 (3-6).

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 (6).

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 (7).

A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake is contributing to a 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 (2,8) (LE: 3; GR: C). Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies (2,9) (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 (2,10), 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 (2,10) (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 (11,12).

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 emphasize 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 (12) (LE: 3; GR: B).

16.2.2 ***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 (2).

The formation of uric acid stones is dependent, mainly 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 (2).

16.2.3 ***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 α-mercaptopropionil glycine or D-penicillamine 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 (13) (LE: 4; GR: C).

16.2.4 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 alkalinising 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.

16.3 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 (14,15).

16.4 Diagnosis

16.4.1 ***Imaging***

Generally, ultrasonography should be used as a first study. Renal ultrasonography is very effective for identifying stones in the kidney. Many radiolucent 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 (16-18) (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.

16.4.2 ***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 (1,19,20).

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.

16.5 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 (19,21,22).

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.

16.5.1 ***Extracorporeal shock wave lithotripsy (SWL)***

Many reports confirm that shock wave lithotripsy (SWL) can be performed in children with no suspicion of long-term morbidity of the kidney (23-28).

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 (21,29,30). Concerns about anaesthesia do not seem to be a problem any more 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 (31) (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 (21,29,30,32-36).

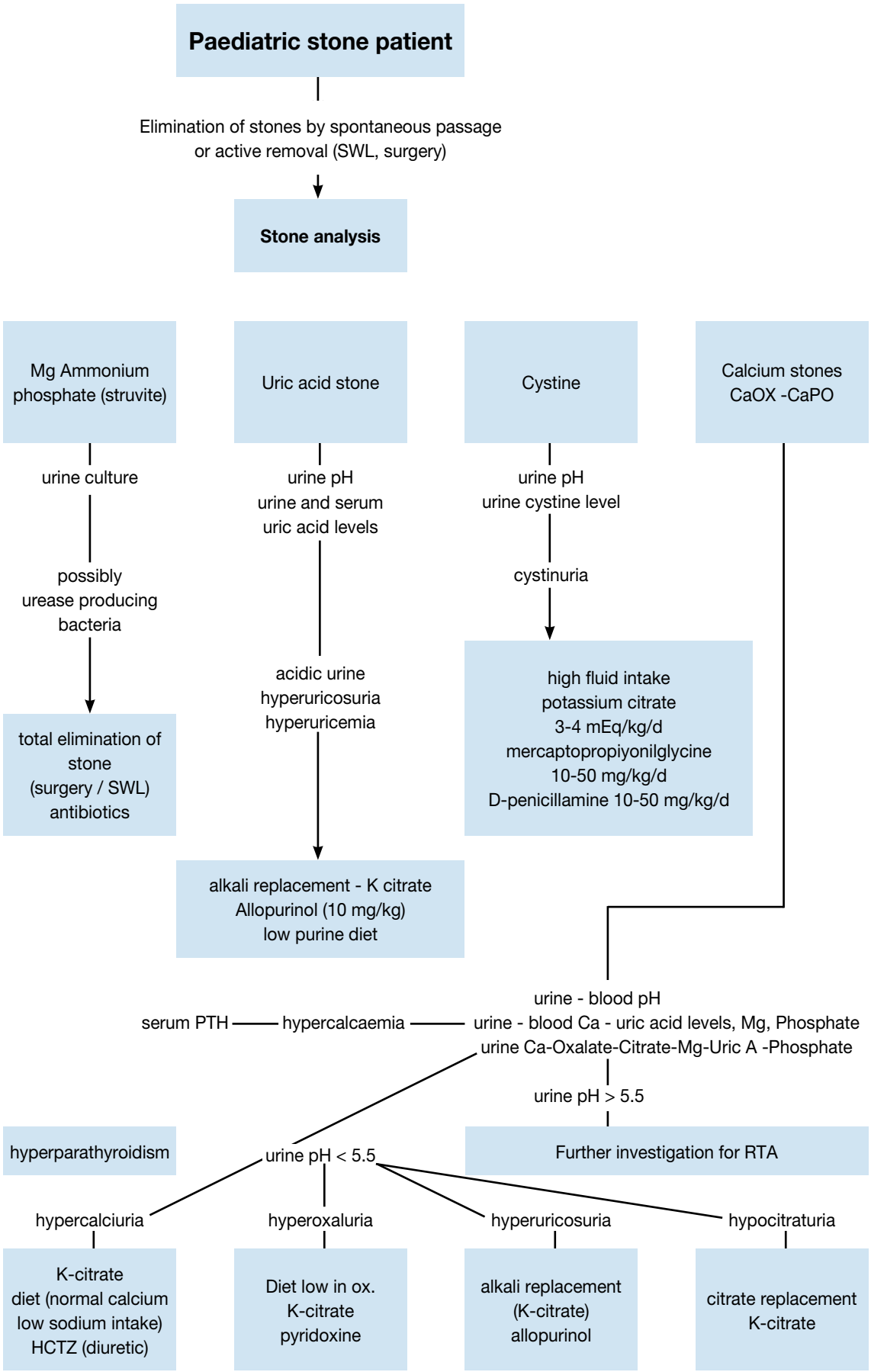
Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in renal pelvis and upper ureter seem to respond better to SWL. In these mentioned sites, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% (37-40).

SWL treatment 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 (37,39,40-42).

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 (35).

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient (34,35). 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 (20,36).

Figure 4: Algorithm for metabolic investigations in urinary stone disease in children



SWL = extracorporeal shockwave lithotripsy; HCTZ = hydrochlorothiazide; PTH = parathyroid hormone; RTA = renal tubular acidosis.

SWL in children may have complications, but these are often self-limiting and transient. The most frequently observed 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 the infectious complications is not recommended (43). However, every effort should be made to sterilise the urine before performing ESWL, ureteroscopy (URS), or percutaneous nephrolithotomy.

16.5.2 ***Percutaneous nephrolithotomy***

SWL 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. PCNL 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 the blood loss. However, small-calibre instruments have now been developed and there are some advantages for PCNL in 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 (43,44). Now that appropriate-size instruments are available, age is no longer a limiting factor for PCNL.

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 (45-48,50,51).

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion is reported in 0.4% to 23.9% and is closely associated with stone burden, operative time, sheath size and number of tracts. Post-operative fever and infection has been reported up to 29.3% and 5.5%, respectively; the origin of fever is not thought to be the infection (49-56).

The mean post-operative hospital stay is similar to adults. It is reported as 3 to 4 days in all the previously mentioned studies 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).

16.5.3 ***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 done less and less and only in selected cases. The general tendency is to use hydrodilation more as it is shown to be as effective (57-60,43,61-63) (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 (50,58,60,64-70).

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 (71).

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 (72-76). 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 (74,75). 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 (72-74,76). The need for additional procedures was related to stone size (72). Although the use of flexible instruments seems feasible for the present time, more data are needed for comparison with other endourological modalities in children.

*16.5.4 **Open stone surgery***

Most stones in children can be managed by SWL and endoscopic techniques. Yet 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. Severe orthopaedic deformities may limit positioning for endoscopic procedures. Open surgery would also be a necessity for such children.

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 11: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	LE	Secondary treatment options	Comment
Staghorn stones	PCNL	2b	Open/SWL	Multiple sessions and accesses with PCNL maybe needed Combination with SWL may be useful
Pelvis < 10 mm	SWL	1a	RIRS/PCNL	
Pelvis 10-20 mm	SWL	2b	PCNL/Open	Multiple sessions with SWL may be needed PCNL has similar recommendation grade
Pelvis > 20 mm	PCNL	2b	SWL/Open	Multiple sessions with SWL may be needed
Lower pole calix < 10 mm	SWL	2c	RIRS/PCNL	Anatomical variations are important for complete clearance after SWL
Lower pole calix > 10 mm	PCNL	2b	SWL	Anatomical variations are important for complete clearance after SWL
Upper ureteric stones	SWL	2b	PCNL/URS/ Open	
Lower ureteric stones	URS	1a	SWL/Open	Additional intervention need is high with SWL
Bladder stones	Endoscopic	2b	Open	Open is easier and with less operative time with large stones

** Cystine and uric acid stones excluded.*
PCNL = percutaneous nephrolithostomy; SWL = shock-wave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

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17. OBSTRUCTIVE PATHOLOGY OF RENAL DUPLICATION: URETEROCELE AND ECTOPIC URETER

17.1 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).

17.1.1 ***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).

17.1.2 ***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).

17.2 Definition and classification

17.2.1 ***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 uretereocele 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.

17.2.1.1 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.

17.2.1.2 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.

17.2.2 ***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%).

17.3 Diagnosis

17.3.1 ***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.

17.3.2 ***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. MRI). 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).

17.4 Treatment

17.4.1 ***Ureterocele***

The management is controversial with a choice between a conservative approach, endoscopic decompression, 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).

17.4.1.1 Early treatment

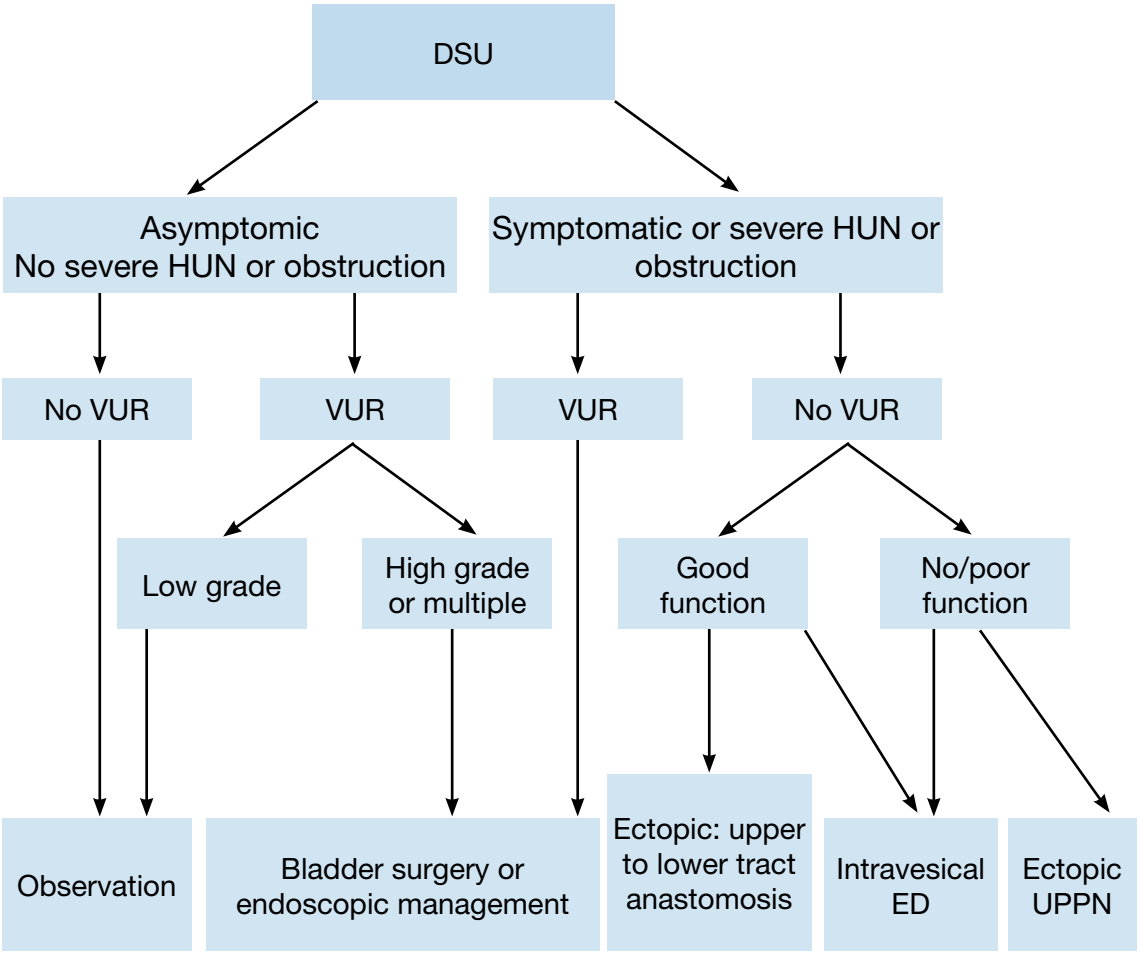
In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non- or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated.

17.4.1.2 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 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)



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. Endoscopic management includes decompression of ureterocele and endoscopic or conservative management of VUR.

17.4.2 ***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).

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18. DISORDERS OF SEX DEVELOPMENT

18.1 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 exstrophy, 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.

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.

18.2 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.

18.2.1 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)

Apparent male
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
Apparent female
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

Table 13: Diagnostic work-up of neonates with ambiguous genitalia

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure
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.

18.2.2 ***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 congential 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.

18.3 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.

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits.

18.4 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

Diagnostic role

- Clinical examination
- Ultrasound
- Genitography
- Cystoscopy
- Diagnostic laparoscopy

Therapeutic role

- Masculinising surgery
- Feminising surgery
- Gonadectomy

18.4.1 ***Diagnosis***

18.4.1.1 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 (3).

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?

18.4.1.2 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 Mülllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utriculur structure visible? (4,5).

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 (6,7).

18.5 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 (8).

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.

18.5.1 ***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 (9,10). Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown (11).

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 (12,13).

Vaginoplasty should be performed during the teenage years. Every technique (self dilatation, skin or bowel substitution) has its specific advantages and disadvantages (14). 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.

18.5.2 ***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 (15) (GR: A).

18.6 References

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19. POSTERIOR URETHRAL VALVES

19.1 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 35% of cases. PUV are found in 1 in 1,250 in a population undergoing foetal ultrasound screening (1). An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated (2,3). In one report, up to 46% of foetuses with a PUV diagnosis were terminated (4), indicating a possible decrease in incidence.

19.2 Classification

*19.2.1 **Urethral valve***

Despite recent attempts to introduce new classification terms, such as 'congenital obstructive posterior urethral membrane (COPUM)' (5), the original classification by Hugh Hampton Young remains the most commonly used (6).

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 this point a slight separation of the folds exist' (6).

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 urethra, with a small opening in the centre' (6).

The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane (7). The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca (8).

19.3 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 bladder neck is hypertrophied and rigid.
- 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 uretereovesical 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 echogenity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

A voiding cysturethrography (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 (9). 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 (10). Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites (11). However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV (12,13).

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 (14).

19.4 Treatment

19.4.1 ***Antenatal treatment***

About 40-60% of PUV are discovered before birth (15). The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amnion 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 (16).

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% (16-18). Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and longterm results of patients with PUV (17,18).

19.4.2 ***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. 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.

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 (19). 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 (20-22).

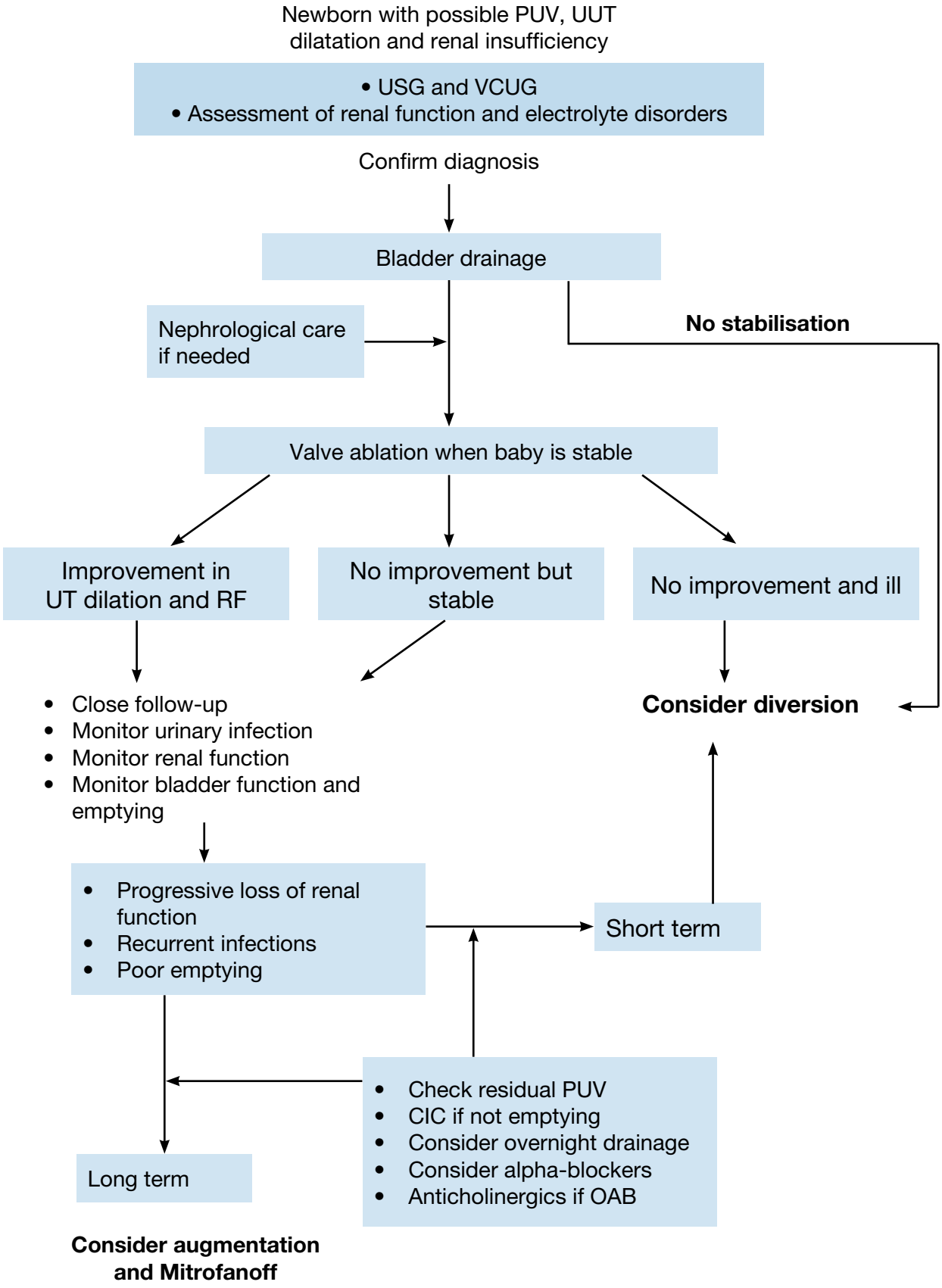
High diversion. If bladder drainage is insufficient to drain the upper urinary tract, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate 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 (23-25). 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% (26).

High-grade reflux is mostly associated with a poor functioning kidney. 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 (27).

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 (9, 14). Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. Between 10% and 47% of patients may develop end-stage renal failure (14,28). Renal transplantation in these patients can be performed safely and effectively. Deterioration of the graft function is mainly related to lower urinary tract dysfunction (29,30).

Figure 6: An algorithm providing information on assessment, treatment and follow up of newborns with possible PUV



PUV = posterior urethral valve; UUT = upper urinary tract; USG = urinary specific gravity; VCUG = voiding cystourethrogram; UT = urinary tract; RF = renal function; CIC = clean intermittent catheterisation; OAB = overactive bladder.

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20. POST-OPERATIVE FLUID MANAGEMENT

20.1 Background

It is often stated that children are not simply small adults, and have specific metabolic features. Children are growing and developing organisms that have a different total body fluid distribution, changing renal physiology, different electrolyte requirements and weaker cardiovascular compensation mechanisms as compared to adults (1). Additionally, developing children have a high metabolic rate and low body stores of fat and other nutrients, and are therefore, susceptible to metabolic disturbances due to 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. Current guidelines of pre-operative fasting for elective surgery are indicated in Table 15 (4,5).

Table 15: Preoperative fasting times for elective surgery

Ingested material	Minimum fasting period (h)
Clear liquids	2
Breast milk	4
Infant formula	4 (< 3 months old) to 6 (> 3 months old)
Non-human milk	6
Light meal	6

Although hypoglycaemia is considered to be an important issue for children, later studies have demonstrated that hypoglycaemia is uncommon if children are fed until 4 h before anaesthesia induction (6). Low glycogen

stores and impaired gluconeogenesis are common problems in newborns. Limiting the period of preoperative starvation and use of glucose-containing solutions are recommended. Therefore, monitoring of blood glucose and continuous adjustment of glucose supply appear to be necessary in neonates and children who are small for their age, to avoid excessive fluctuations in blood glucose levels (7).

20.3 Maintenance therapy and intraoperative fluid therapy

Typically, intraoperative management is the responsibility of the anaesthetist, whereas surgeons write the postoperative instructions. The goal of intraoperative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid to maintain adequate intravascular volume, cardiac output and oxygen delivery to tissues at a time when normal physiological functions are altered by surgical stress and anaesthetic agents (7).

The fluids for maintenance therapy do not take into account blood loss or third-space loss of fluid into the interstitial space or gut, and replaces losses from two sources: insensible (evaporative) and urinary loss. The principle formulae for calculating the daily maintenance water requirement has not changed for the past 50 years (Table 16) (8). Previous calculations have shown that there is good agreement in fluid requirements between non-operated and anaesthetised children (9). Thus, the combination of maintenance fluid and electrolyte requirements results in a hypotonic electrolyte solution. Conventionally, the usual intravenous maintenance fluid given to children by paediatricians is a quarter to a third strength saline (4,10).

Table 16: Hourly and daily fluid requirements according to body weight

Body weight	Hourly	Daily
< 10 kg	4 mL/kg	100 mL/kg
10-20 kg	40 mL + 2 mL/kg; > 10 kg	1000 mL + 50 mL/kg; > 10 kg
>20 kg	60 mL + 1 mL/kg; > 20 kg	1500 mL+ 20 mL/kg; > 20 kg

Fasting deficit is calculated by multiplying the hourly maintenance fluid requirement by the number of hours of restriction. Replacement of 50% of the fasting deficit in the first hour and 25% in the second and third hours is recommended (11). However, Berry et al. have proposed simplified guidelines for fluid administration according to the child's age and severity of surgical trauma (12) (Table 17).

Table 17: Intraoperative fluid management adapted for children fasted for 6-8 h following the classical recommendation "nil per oral after midnight"

The amount of fluid given during the first hour should be reduced if children are fasting for a shorter period of time, or if the child is already receiving intravenous fluid before surgery.

Furman (11)			
Hour of fluid replacement	**Maintenance fluid**	**Fasting deficit replacement**	**Persistent losses**
First hour	As Table 16	50%	Third space + blood loss replacement
Second hour	As Table 16	25%	Third space + blood loss replacement
Third hour	As Table 16	25%	Third space + blood loss replacement
Berry (12)			
First hour	≤ 3 years: 25 mL/kg ≥ 4 years: 15 mL/kg		Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids
All other hours	Maintenance volume = 4 mL/kg/h Maintenance + mild trauma = 6 mL/kg/h Maintenance + moderate trauma = 8 mL/kg/h Maintenance + severe trauma = 10 mL/kg/h		Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids

Five percent dextrose with a quarter- to half-normal saline is frequently used as maintenance fluid, and balanced salt solution or normal saline as replacement fluid. Blood losses are replaced with either 1:1 ratio of blood or colloid, or 3:1 ratio for crystalloid. However, the administration of a large volume of normal saline can cause dilutional acidosis or hyperchloraemic acidosis, whereas 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. Albumin, plasma, synthetic colloids, and blood are administered where appropriate (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 for replacing fasting deficit or third-space losses. Both losses consist mainly of extracellular fluids. Thus, hydrating solutions should contain high sodium and chloride and a low concentration of bicarbonate, calcium and potassium. Intraoperative 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. The present recommendations include the use of low-dextrose-containing solutions for maintenance fluid therapy (except for patients who are at greatest risk for hypoglycaemia) (1,10). Intraoperative 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 1% or 2% dextrose in lactated Ringer's solution is appropriate (4).

20.4 Post-operative fluid management

During the postoperative period, the basic principle is to estimate the function of the gut and to continue oral or enteral nutrition as much as possible (2). However, it should be taken into consideration that withholding oral fluids postoperatively from children undergoing day surgery reduces the incidence of vomiting (13). For minor surgical procedures, the intraoperative administration of large volumes of crystalloids is associated with a reduced incidence of postoperative nausea and vomiting after anaesthesia in paediatric and adult patients (14). Thus, Berry's guidelines seem appropriate for minor surgical cases provided that either lactated ringer polyionique B66, which has an osmolarity similar to plasma (15) is administered during surgery. It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal preoperative renal and hepatic functions. However, if oral intake is postponed for > 24 h (e.g. intestinal surgery), there is an increased risk for electrolyte abnormalities that require further assessment and subsequent management, particularly for potassium. Postoperative findings such as decreased bowel movements and ileus may be signs of hypokalemia, which might be corrected with a solution including 20 mmol/L potassium with an infusion rate not more than 3 mmol/kg/day. In these cases, fluid therapy should be administered 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.

Fluid therapy should provide basic metabolic requirements, and compensate for gastrointestinal and additional losses. If hypovolemia is present, it should be treated rapidly. Hyponatremia is the most frequent electrolyte disorder in the postoperative period (15,16). Therefore, hypotonic fluid should not be routinely administered to hospitalised children because they have several stimuli for AVP production, and are 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. Moreover, it is advised to administer isotonic fluids intraoperatively and also immediately postoperatively, albeit at two-thirds of the calculated maintenance rate in the recovery room. Fluid composition should balance high sodium requirements, energy requirements and osmolarity of the solution. The extra losses from gastric or chest tubes should be replaced with lactated Ringer's solution. Fluid administration to dilute the medications also should be taken into account (4).

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention. The risk of polyuria due to post-obstructive diuresis has to be assessed. In cases in which polyuria develops, fluid intake and urine output should be followed, as well as renal function and serum electrolytes. When necessary, clinicians should not feel any hesitation in consulting with a paediatric nephrologist.

20.5 Post-operative fasting

Although some previous studies have reported that fasting reduces the risk of vomiting by up to 50% (13,21,22), a recent study has revealed that, if children were freely allowed to drink and eat when they felt ready or requested, the incidence of vomiting did not increase, the children felt happier, and were significantly less bothered by their pain than those in the fasting group (23). The mean times until first drink and eating in the free group were 108 and 270 min, respectively, which were 4 and 3 h earlier than in the fasting group.

Previous studies have implied that gastric motility returns to normal 1 h after emergence from anaesthesia in children who have undergone non-abdominal surgery (24), and first oral intake in children 1 h after emergence from anaesthesia for minor surgery does not appear to cause an increase in the incidence of vomiting, as long as the fluid ingested is at body temperature (25). Therefore, panel members recommend encouraging early fluid intake for children who undergo minor or non-abdominal urological surgery.

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21. POST-OPERATIVE PAIN MANAGEMENT IN CHILDREN: GENERAL INFORMATION

21.1 Introduction

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 postoperative pain in children (2). The authors emphasise the need for a postoperative pain management protocol in children, and state that the frequency of pain assessment, use of parenteral opioids, introduction of regional anaesthesia, and application of rescue analgesics are far from what they should be (3).

The recent understanding of maturation of the pain system, pain assessment methods, clinical consequences of pain in neonates, and the traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned (4-8). Many studies have shown that deficiency or insufficiency in proper analgesia might be the cause of future behavioural and somatic sequelae (9-13). The current understanding fully depends on the belief that all children irrespective of age deserve adequate treatment.

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 selecting the appropriate pain assessment technique is important. There are several pain assessment tools that 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 patient and parents during this process. Parents and patients can manage postoperative 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, even in patient-family-controlled analgesia applications (16-21).

21.3 Drugs and route of adminstration

Pre-emptive analgesia is an important concept that aims to induce suppression of pain before neural hypersensitisation occurs (22), and local anaesthetics or non-steroidal analgesics are given intraoperatively to delay postoperative pain and decrease postoperative 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) might 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 with respect to their age, body weight and individual medical status.

Table 18: List of several drugs used in postoperative pain management in children (5,13,19,25-27)

Name	Route of administration	Dose	Side effects	General remarks	Caution
Non-narcotics					
Acetaminophen	Rectal Oral Intravenous	40 mg/kg loading, 20 mg/kg/dose 4 times/day 15-40 mg/kg, followed by 30 mg/kg/8 h Propacetamol (prodrug)	Nephrotoxicity, hepatotoxicity (neonates)	Most common used analgesic, Antipyretic effect Opioid sparing effect Wide safety range	Slow onset time and variable absorption via rectal route, dividing the vehicle 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 > 32 weeks post-conceptual age; and 40 mg/kg for preterm neonates < 32 weeks post-conceptual age
Ibuprofen	Oral, rectal	4-10 mg/kg/dose 3-4 times/day		Better analgesic that paracetamol	Safety not established for infants < 6 months old
Diclofenac	Tablet, syrup, suppository	1-1.5 mg/kg 2-3 times/day	Nephrotoxicity, GI disturbances	Better than ibuprofen	> 6 years old
Ketorolac	Oral IV, IM	0.2-0.5 mg/kg every 6 h (48 h) Total dose < 120 mg/day		Opioid sparing effect	
Ketamine	Oral, rectal, IM, SC, IV and intraspinal	< 2 mg/kg (IM) < 1 mg/kg (IV, epidural)			
Metamizole, dipyrone	Oral IM drop	10-15 mg/kg/dose (max 40 mg/kg total) 10-15 mg/kg 1 drop/kg/dose, max 4 times	Risk of agranulocytosis, not clarified definitely	Very effective antipyretic	Not approved in some countries including USA, Sweden, Japan and Australia
Narcotics					
Opioids			Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria		
Tramadol (weak opioid)	Oral, rectal, IV, IM (dose can be repeated 4-6 times/day)	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)	nausea, vomiting, pruritus and rash	Does not inhibit prostaglandin synthesis	IM injection not recommended, Slow IV infusion, Be careful in patients under psychoactive medications and with seizures

Codeine	Oral	1 mg/kg, single dose	Respiratory depression not seen after single dose	Both antitussive and analgesic effect	
Morphine	IM, IV	6-12 months: 0.1 mg/kg (IM), 0.05 mg/kg (IV)		Most common used but not the most suitable opioid for pain relief in children	IM injection not recommended < 2 months old: be careful
Nalbuphine	IV	< 3 months old: 0.05 mg/kg/dose > 3 months old: 0.05-0.10 mg/kg/ dose (4-6 times/day)			
Piritramide	IV	0.05-0.10 mg/kg/dose (4-6 times/ day)			
Dextromethorphan	Oral, syrup	1 mg/kg			
Pethidine/ meperidine	IM, IV	1.5-2 mg/kg IM as premedicant 1 mg/kg IV analgesic	No advantage over morphine		
Fentanyl	IV	1-2 µg/kg	Not so popular		
Buprenorphine	IV	3-5 mg/kg			
Pentazocine	IV, IM	1 mg/kg IM or 0.5-0.75 mg/kg IV	In small infants, observe respiration after IV administration		
Regional (local) anaesthetics					
bupivacaine		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, and 0.2-0.25 mg/kg/h (5-6 mg/kg/day) in neonates	Cardiotoxicity, convulsion		
Levobupivacaine	IV, IM	0.2-0.25% 1-2.5 mg/kg for single shot epidural intravenous continuous administration 0.2-0.4 mg/kg/h		Less toxic than bupivacaine	
Ropivacaine	IV,IM	0.2-0.25% 1-2.5 mg/kg for single shot epidural intravenous continuous administration 0.2-0.4 mg/kg/h		Less toxic than levobupivacaine	

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. Postoperative management should be based on sufficient intraoperative 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 postoperative analgesia. A proposed strategy for postoperative analgesia may be as follows:

1. Intraoperative 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 and it needs proper pain management (28). Despite this, adequate pain management is still below expectations (29). Potential analgesic interventions during circumcision include use of 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 postoperative analgesic affect, 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 postoperative motor weakness and micturition problems (38-43).

21.5 Penile, inguinal and scrotal surgery

Caudal block is the most studied method for post-hypospadias surgery analgesia. Several agents with different doses, concentrations and adminstration techniques have been used with similar outcomes (44-58). Both single and combined use of these agents has been shown to be effective (46,48,53,54,56,57).

Penile blocks can be used for postoperative analgesia and have similar postoperative analgesic properties as caudal blocks (59). Two penile blocks at the beginning and conclusion of surgery seems better (60). Severe bladder spasms due to the presence of the bladder catheter may sometimes cause more problems than pain, which necessitates antimuscarinic medications.

For inguinoscrotal surgery, all anaesthetic methods, such as caudal blocks (61-65), nerve block (66,67), wound infiltration or instillation, as well as irrigation with local anaesthetics (68-70), have been shown to have adequate postoperative analgesic properties. Combinations may improve the results (71).

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 underutilised although effective agent that has been shown to decrease frequency and severity of bladder spasms, as well as the length of postoperative hospital stay and costs (76-81).

Open kidney surgery is particularly painful because all three muscle layers are cut during conventional loin incision. Dorsal lumbotomy incision may be a good alternative because of the shorter postoperative hospital stay and earlier return to oral intake and unrestricted daily activity (82).

Caudal blocks plus systemic analgesics (83), and continuous epidural analgesia have been shown to be effective in terms of decreased postoperative 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 intraoperative and postoperative 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 perirenal fascia may be beneficial (88).

Table 19: A simple pain management strategy for paediatric urological surgery

Intensity of surgery	First step	Second step	Third step
Mild (inguinal, scrotal, penile)	Paracetamol and wound infiltration with local anaesthetics	NSAIDs	Regional block/weak opioid or intravenous strong opioid with small increments as rescue analgesia (nalbuphine, fentanyl, meperidine, morphine etc.)
Moderate (lower abdominal)			Peripheral nerve block (single shot or continuous infusion)/opioid injection (IV PCA)
Severe (upper abdominal or lombotomy)			Epidural local/major peripheral nerve/plexus block/opioid injection (IV PCA)

IV PCA = intravenous patient-controlled analgesia.

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22. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AGS	adrenogenital syndrome
ACTH	adrenocorticotropic hormone
AMH	anti-Müllerian hormone
ARM	anorectal malformation
CAH	congenital adrenal hyperplasia
CIC	clean self-intermittent catheterisation
CNS	central nervous system
COPUM	congenital obstructive posterior urethral membrane
CRP	C-reactive protein
DDAVP	desmopressine
CT	computed tomography
DHTST	dihydrotestosterone
DMSA	dimercaptosuccinic acid
EMG	electromyography
ESR	erythrocyte sedimentation rate
FSH	follicle stimulating hormone
GnRH	gonadotrophin-releasing hormone
hCG	human chorionic gonadotrophin
IC	intermittent catheterisation
ICCS	International Children's Continence Society
IVU	intravenous urogram
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LUTD	lower urinary tract dysfunction
LUT(S)	lower urinary tract (symptoms)
MRI	magnetic resonance imaging
NDSD	neurogenic detrusor-sphincter dysfunction
OAB	overactive bladder
PNL	percutaneous litholapaxy
RCT	randomised controlled trial
RN	reflux nephropathy
RNC	radionuclide cystography
RTA	renal tubular acidosis
SWL	(extracorporeal) shockwave lithotripsy
Tc-MAG3 (99m)	technetium-99m mercaptoacetyltriglycine (MAG3)
TIP	tubularised incised plate urethroplasty
TST	testosterone
UPJ	ureteropelvic junction
URS	ureterorenoscopy
US	ultrasound
UTIs	urinary tract infections
VCUG	voiding cystourethrography
VR	vesicorenal reflux
VUR	vesicoureteral reflux
VUS	voiding urosonography

Conflict of interest

All members of the Paediatric Urology Guidelines writing 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 kept on file in the European Association of Urology Central Office database. 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 Urological Trauma

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1. INTRODUCTION

1.1 Background

The European Association of Urology (EAU) Guidelines Group for Urological Trauma prepared this guidelines document to assist medical professionals in the management of urological trauma.

The Urological Trauma guidelines are based on a review of the literature, using on-line searches of MEDLINE and other source documents published between 2005 and 2008. A critical assessment of the findings was made, not involving a formal appraisal of the data. There is a paucity of high-powered randomised controlled trials in this area and considerable available data are based on retrospective studies. The panel recognises this limitation.

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 history information: The Urological Trauma Guidelines were first published in 2003, with a partial update in 2006 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

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

Table 2: Grade of recommendation

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

**modified from Sackett et al. (1).*

1.2 Reference

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.. http://www.cebm.net/index.aspx?o=1025 [Access date January 2012].

2. RENAL TRAUMA

2.1 Background

Renal trauma occurs in approximately 1-5% of all trauma cases (1,2). The kidney is the most commonly injured genitourinary and abdominal organ. There is a 3:1 male to female ratio in kidney trauma patients (3-5). Renal trauma can be acutely life-threatening, but the majority of renal injuries can be managed conservatively. Advances in imaging and treatment strategies during the past 20 years have decreased the need for surgical intervention and increased renal preservation (6-8).

2.2 Mode of injury

Renal injuries are classified by their mechanism: blunt or penetrating. In rural settings, blunt trauma can account for the largest percentage (90-95%) (9), while in urban settings the percentage of penetrating injuries can increase to 20% (6) or higher.

Blunt trauma is usually caused by motor vehicle accidents, falls, vehicle-associated pedestrian accidents, contact sports, and assault. Traffic accidents are the major cause of almost half the blunt renal injuries (10). Renal injury in frontal and side-impact collisions appears to occur after direct impact from objects in the vehicle compartment. For frontal crashes, occupant acceleration 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 (11). A 20-year review of renal injuries following free falls found a rate of 16% (12).

Renal lacerations and renal vascular injuries make up only 10-15% of all blunt renal injuries. Isolated renal artery injury following blunt abdominal trauma is extremely rare, and accounts for less than 0.1% of all trauma patients (13).

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.

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 (14).

In wartime, the kidney is the most commonly injured urogenital organ. Most are found to be associated with major abdominal injuries, and the rate of wartime nephrectomies is relatively high (25-33%) (15-17).

*2.2.1 **Injury classification***

Classifying renal injuries helps to standardise different groups of patients, select appropriate therapy, and predict results. A total of 26 classifications for renal injuries have been presented in the literature in the past 50 years (18), but the committee on organ injury scaling of the American Association for the Surgery of Trauma (AAST) has developed a renal-injury scaling system that is now widely used (19). Renal injuries are classified as grade 1 to 5 (Table 3). Abdominal computed tomography (CT) or direct renal exploration is used to classify injuries. Most recent publications in the field of renal trauma have adopted this classification. In a retrospective review, the AAST scaling system was determined as the most important variable predicting the need for kidney repair or removal (20,21). It also predicts for morbidity after blunt or penetrating injury, and for mortality after blunt injury (22).

Table 3: AAST renal injury grading scale (17)

Grade*	Description of injury
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 3.*

2.3 Diagnosis: initial emergency assessment

Initial assessment of the trauma patient should include securing the airway, controlling external bleeding, and resuscitation of shock, as required. In many cases, physical examination is carried out during the stabilisation of the patient. When renal injury is suspected, further evaluation (CT scan, laparotomy) is required for a prompt diagnosis.

2.3.1 History and physical examination

A direct history is obtained from conscious patients. Witnesses and emergency personnel can provide valuable information about unconscious or seriously injured patients. Possible indicators of major renal injury include a rapid deceleration event (fall, high-speed motor vehicle accidents) or a direct blow to the flank. In assessing trauma patients after motor vehicle accidents, the history should include the vehicle's speed and whether the patient was a passenger or pedestrian.

In penetrating injuries, important information includes the size of the weapon in stabbings, and the type and calibre of weapon used in gunshot wounds, as high-velocity projectiles have the potential to cause more extensive damage.

The medical history should be as detailed as possible, as pre-existing organ dysfunction can have a negative effect on trauma patient outcome (23). In the early resuscitation phase, special consideration should be given to pre-existing renal disease (24). Another point of interest is the functioning renal mass of the trauma patient, as there are numerous case reports in the literature about complicated renal trauma in solitary kidneys (25).

Pre-existing renal abnormality makes renal injury more likely following trauma. Pre-existing renal pathology should be noted. Hydronephrosis due to ureteropelvic junction abnormality, renal calculi, cysts, and tumours are the most commonly reported entities that may complicate a minor renal injury (26). The overall percentage of these cases varies from 4% to 22% (27,28).

Haemodynamic stability is the primary criterion for the management of all renal injuries. Shock is defined as a systolic blood pressure of less than 90 mmHg found at any time during an adult patient's evaluation. 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 could indicate possible renal involvement:

- haematuria;
- flank pain;
- flank ecchymoses;
- flank abrasions;
- fractured ribs;
- abdominal distension;
- abdominal mass;
- abdominal tenderness.

2.3.2 Recommendations

	GR
Haemodynamic stability should be decided upon admission.	B
History should be taken from conscious patients, witnesses and rescue team personnel with regard to the time and setting of the incident.	C
Past renal surgery, and known pre-existing renal abnormalities (ureteropelvic junction obstruction, large cysts, lithiasis) should be recorded.	B
A thorough examination should be made of the thorax, abdomen, flanks, and back for penetrating wounds.	B
Findings on physical examination such as haematuria, flank pain, flank abrasions and ecchymoses, fractured ribs, abdominal tenderness, distension, or mass could indicate possible renal involvement.	B

2.3.3 Laboratory evaluation

The trauma patient is evaluated by a series of laboratory tests. Urinalysis, haematocrit, and baseline creatinine are the most important tests for evaluating renal trauma.

Urinalysis is considered the basic test in the evaluation of patients with suspected renal trauma. Haematuria

is the presence of an abnormal quantity of red blood cells in the urine and is usually the first indicator of renal injury. Microscopic haematuria in the trauma setting may be defined as greater than 5 red blood cells per high-power field (rbc/hpf), while gross haematuria is demonstrated by urine in which blood is readily visible.

Haematuria is a hallmark sign of 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 (29). Major renal injury, such as disruption of the ureteropelvic junction, renal pedicle injuries or segmental arterial thrombosis may occur without haematuria (30). In a study by Eastham *et al.*, 9% of patients with stab wounds and resultant proven renal injury did not manifest haematuria (31). Haematuria that is out of proportion to the history of trauma may suggest pre-existing renal pathology (32). 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 (33).

Serial haematocrit determination is a method of continuous evaluation of the trauma patient. Initial haematocrit in association with vital signs implies the need for emergency resuscitation. 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.

As most trauma patients are evaluated within 1 hour of injury, creatinine measurement reflects renal function prior to the injury. An increased creatinine usually reflects pre-existing renal pathology.

2.3.4 ***Recommendations***

	GR
Urine from a patient with suspected renal injury should be inspected grossly and then by dipstick analysis.	B
Serial haematocrit measurement indicates blood loss. However, until evaluation is complete, it will not be clear whether it is due to renal trauma and/or associated injuries.	B
Creatinine measurement could highlight patients who had impaired renal function prior to injury.	C

2.3.5 ***Imaging: criteria for radiographic assessment in adults***

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 (34).

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 (35). The indications for radiographic evaluation are gross haematuria, microscopic haematuria and shock, or the presence of major associated injuries (36). 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 (12).

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 (37).

2.3.5.1 Ultrasonography

Ultrasonography (US) is a popular imaging modality in the initial evaluation of abdominal trauma. It provides a quick, non-invasive, low-cost means of detecting peritoneal fluid collections without exposure to radiation (38). However, the usefulness of conventional US in the radiographic evaluation of renal trauma has been widely questioned. Its limitations stem from the difficulty in obtaining good acoustic windows on trauma patients who have sustained numerous associated injuries. The results are also highly dependent on the operator.

Ultrasound scans can detect renal lacerations but cannot definitely assess their depth and extent and do not provide functional information about renal excretion or urine leakage. Despite the drawbacks of the method, US scans can be conveniently used during the primary assessment of renal injuries. During the evaluation of blunt trauma patients, US scans were more sensitive and specific than standard intravenous pyelography (IVP) in minor renal trauma (39). In a study comparing the results of US scans and IVP, the sensitivity of US decreased as the severity of the trauma increased, while that of IVP remained high for all degrees of severity (40).

Another possible role for US may be for serially evaluating stable renal injuries for the resolution of urinomas and retroperitoneal haematomas (41). Ultrasound might be considered suitable for the routine follow-up of renal parenchymal lesions or haematomas in the intensive care unit. Contrast-enhanced sonography is more sensitive than conventional US in the detection of renal injuries. In haemodynamically stable patients, it is

a useful tool in the assessment of blunt injuries (42).

In conclusion, since US 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 (43,44). Ultrasound findings do not provide sufficient evidence for a definite answer on the severity of renal injuries.

2.3.5.2 Standard IVP

Standard IVP is no longer the study of choice for the evaluation of renal trauma. In some centres it may be the only study available, in which case IVP should establish the presence or absence of one or both of the kidneys, clearly define the renal parenchyma, and outline the collecting system. In order to stage renal trauma, the IVP should include nephrotomograms, delineate the renal contour, and visualise the excretion of contrast material from both kidneys into the renal pelvis and ureter. Non-visualisation, contour deformity, or extravasation of contrast implies a major renal injury and should prompt further radiological evaluation with CT or, less commonly, angiography if available.

The most significant findings on 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, calyceal distortion, and obscuring of the renal shadow. The sensitivity of IVP is high (> 92%) for all degrees of trauma severity (45).

2.3.5.3 One-shot intraoperative IVP

Unstable patients selected for immediate operative intervention (and thus unable to have a CT scan) should undergo one-shot IVP in the operating theatre. 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 the majority of cases. It 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).

While the majority of experts advocate its use, not all studies have shown one-shot IVP to be necessary. In cases of penetrating abdominal trauma, the positive predictive value of one-shot IVP was only 20% (80% of patients with normal one-shot IVP findings had renal injuries not detected by the IVP) (47). One-shot IVP is of no significant value in assessing penetrating abdominal trauma patients who undergo exploratory laparotomy for associated intra-abdominal injuries, and should be reserved only for patients with a flank wound or gross haematuria following penetrating trauma (48).

2.3.5.4 Computed tomography (CT)

Computed tomography is the gold standard method for the radiographic assessment of stable patients with renal trauma. CT is more sensitive and specific than IVP, ultrasonography or angiography. In a retrospective study, the positive rate during evaluation of 298 patients was 96% by CT, 91% by double-dose intravenous IVP and 79% by US (45).

Computed tomography 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 (49). Computed tomography is particularly useful in evaluating traumatic injuries to kidneys with pre-existing abnormalities (50).

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 (51).

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. Newer ‘spiral’ CT provides shorter scanning time and thus fewer artefacts in the examinations of patients who cannot co-operate adequately (52). 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. 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).

2.3.5.5 Magnetic resonance imaging (MRI)

Although MRI is not used in the majority of renal trauma patients, Leppäniemi *et al*. investigated the use of high-field strength MRI (1.0 T) in the evaluation of blunt renal trauma (56). MRI scans were accurate in finding peri-renal haematomas, assessing the viability of renal fragments, and detecting pre-existing renal abnormalities, but failed to visualise urinary extravasation on initial examination. The authors concluded that MRI could replace CT in patients with iodine allergy and could be used for initial staging if CT were not available (56).

In a recent study comparing CT and MRI findings, the latter clearly revealed renal fracture with non-viable fragment, and was able to detect focal renal laceration not detected on CT due to peri-renal haematoma (57).

However, MRI is not the first choice in managing patients with trauma because it requires a longer imaging time, increases the cost, and limits access to patients when they are in the magnet during the examination. MRI 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.

2.3.5.6 Angiography

Computed tomography has largely replaced the use of angiography for staging renal injuries, as angiography is less specific, more time-consuming and more invasive. Angiography is, however, more specific for defining the exact location and degree of vascular injuries and may be preferable when planning selective embolisation for the management of persistent or delayed haemorrhage from branching renal vessels (50).

Angiography can define renal lacerations, extravasation, and pedicle injury. Additionally, it is the test of choice for evaluating renal venous injuries. The most common indication for arteriography is non-visualisation of a kidney on IVP after major blunt renal trauma when a CT is not available. Common causes for non-visualisation are:

- total avulsion of the renal vessels (usually presents with life-threatening bleeding);
- renal artery thrombosis;
- severe contusion causing major vascular spasm.

Angiography is also indicated in stable patients to assess pedicle injury if the findings on CT are unclear, and for those who are candidates for radiological control of haemorrhage (31).

2.3.5.7 Radionuclide scans

Radionuclide scans might be helpful for documenting renal blood flow in trauma patients with severe allergy to iodinated contrast material (50), but are not generally used or required.

2.3.6 ***Recommendations***

	GR
Blunt trauma patients with macroscopic or microscopic haematuria (at least 5 rbc/hpf) with hypotension (systolic blood pressure < 90 mmHg) should undergo radiographic evaluation.	B
Radiographic evaluation is also recommended for all patients with a history of rapid deceleration injury and/or significant associated injuries.	B
All patients with any degree of haematuria after penetrating abdominal or thoracic injury require urgent renal imaging.	B
Ultrasonography can be informative during the primary evaluation of polytrauma patients and for the follow-up of recuperating patients, although more data is required to suggest this modality universally.	C
A CT scan with enhancement of intravenous contrast material is the best imaging study for the diagnosis and staging of renal injuries in haemodynamically stable patients.	B
Unstable patients who require emergency surgical exploration should undergo a one-shot IVP with bolus intravenous injection of 2 mL/kg contrast.	C
Formal IVP, MRI, and radiographic scintigraphy are acceptable second-line alternatives for imaging renal trauma when CT is not available.	C
Angiography can be used for diagnosis and simultaneous selective embolisation of bleeding vessels.	B

2.4 Treatment

*2.4.1 **Indications for renal exploration***

The goal in managing patients with renal injuries is to minimise morbidity and to preserve renal function. The need for renal exploration can be predicted with accuracy with a nomogram, which uses the type of injury, transfusion requirements, blood urea nitrogen (BUN), creatinine, and injury grade (58). However, the management of renal injury is usually influenced by the decision to explore or observe associated abdominal injuries (59).

A life-threatening haemodynamic instability due to renal haemorrhage is an absolute indication for renal exploration, irrespective of the mode of injury (60,61). Other indications include an expanding or pulsatile peri-renal haematoma identified at exploratory laparotomy performed for associated injuries (this finding heralds a grade 5 vascular injury and is quite rare). A one-shot intraoperative IVP can provide valuable information. Poor visualisation or any other abnormality of the injured kidney is an indication for exploration.

Grade 5 vascular renal injuries are, by definition, regarded as an absolute indication for exploration, although a single report has suggested that patients who are haemodynamically stable at presentation but with a grade 5 parenchymal injury (shattered kidney) after blunt trauma might be safely treated conservatively (62).

The management of major renal injuries with urinary extravasation and devitalised fragments is controversial. Since these injuries are very uncommon, published series report on small numbers of patients. In recent years, it seems to have been recognised that most major injuries heal with non-operative treatment (63). Moudouni *et al*. suggest that an initially conservative approach is feasible in stable patients with devitalised fragments (64). These injuries are, however, associated with an increased rate of complications and late surgery (65).

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 (32).

*2.4.2 **Operative findings and reconstruction***

The overall exploration rate for blunt trauma is less than 10% (60), and may be even lower as more centres adopt a very conservative approach to the management of these patients (66). The goal of renal exploration following renal trauma is control of haemorrhage and renal salvage. Most experienced authors suggest the transperitoneal approach for surgery (67,68). 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 (69). It tends to lower blood loss and the nephrectomy rate, and appears not to increase post-operative azotaemia or mortality (70). 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, injury severity scores, and mortality (71). Other intra-abdominal injuries also slightly increase the need for nephrectomy (72). Mortality is associated with the overall severity of the injury and is not often a consequence of the renal injury itself (73). In gunshot injuries caused by a high-velocity bullet, reconstruction can be difficult and nephrectomy is often required (14).

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 peri-renal fat bolster may be used for coverage (74). In a review by Shekarriz and Stoller, the use of fibrin sealant in traumatic renal reconstruction proved to be helpful (75). Newly developed haemostatic agents that have proven useful in open and laparoscopic partial nephrectomy, might also be helpful, but are largely unproven in the trauma setting. In all cases, drainage of the ipsilateral retroperitoneum is recommended to provide an outlet for any temporary leakage of urine.

Renovascular injuries are uncommon. They are associated with extensive associated trauma and increased peri- and post-operative mortality and morbidity. Blunt renal artery injury is rare. Non-operative management should be considered as an acceptable therapeutic option (76).

Following blunt trauma, repair of grade 5 vascular injury is seldom if ever effective (77). Repair could be attempted in those very rare cases in which there is a solitary kidney or the patient has sustained bilateral injuries (78). In all other cases, nephrectomy appears to be the treatment of choice (79). In a recent review, it appears that nephrectomy for main renal artery injury has outcomes similar to those of vascular repair, and it does not worsen post-treatment renal function in the short term. Non-operative management for segmental renal artery injury results in excellent outcomes (80).

Angiography with selective renal embolisation for haemorrhage control is a reasonable alternative to laparotomy provided that no other indication for immediate surgery exists (81). Cure of haematuria after superselective transarterial embolisation is reported as high as 98% (82). Successful haemostasis by

embolisation is reported to be identical in blunt and penetrating injuries (83,84). The complication rate is minimal, and it has been proven effective for grade 4 injuries where conservative therapy failed (85). In our series, embolisation failed when applied to grade 5 injuries (85).

*2.4.3 **Non-operative management of renal injuries***

As the indications for renal exploration become clearer, non-operative management has become the treatment of choice for the majority of renal injuries. In stable patients, supportive care with bed-rest, hydration, and antibiotics is the preferred initial approach (7). Primary conservative management is associated with a lower rate of nephrectomy without any increase in the immediate or long-term morbidity (86). The failure of conservative therapy is low (1.1%) (6).

All grade 1 and 2 renal injuries can be managed non-operatively, whether due to blunt or penetrating trauma. Therapy of grade 3 injuries has been controversial, but recent studies support expectant treatment (87-89). Patients diagnosed with urinary extravasation in solitary injuries can be managed without major intervention and a resolution rate of > 90% (90). Persistent bleeding is the main indication for a reconstruction attempt (91).

The majority of patients with grade 4 and 5 renal injuries present with major associated injuries, and consequently experience high exploration and nephrectomy rates (92), although emerging data indicate that many of these patients can be managed safely with an expectant approach. Although almost all grade 4 patients with penetrating injury require renal exploration, only 20% of those with blunt trauma do (93). Isolated grade 4 renal injuries represent a unique situation to treat the patient based solely on the extent of the renal injury, thus non-operative management is used more frequently. 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 (91).

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 (94).

Low-velocity gunshot and stab wounds of minor degree may be managed conservatively with an acceptably good outcome (95). Tissue damage from high-velocity gunshot injuries, on the other hand, might be more extensive and nephrectomy could be required. Non-operative management of renal gunshot wounds in selected stable patients is associated with a high rate of success (96-98).

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 (99). 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 missed injury (61). 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 (100).

*2.4.4 **Recommendations***

	GR
Following grade 1-4 blunt renal trauma, stable patients should be managed conservatively with bed-rest, prophylactic antibiotics, and continuous monitoring of vital signs until haematuria resolves.	B
Following grade 1-3 stab and low-velocity gunshot wounds, stable patients, after complete staging, should be selected for expectant management.	B
Indications for surgical management include: - haemodynamic instability; - exploration for associated injuries; - expanding or pulsatile peri-renal haematoma identified during laparotomy; - grade 5 injury.	
Incidental finding of pre-existing renal pathology requiring surgical therapy.	B
Renal reconstruction should be attempted in cases where the primary goal of controlling haemorrhage is achieved and a sufficient amount of renal parenchyma is viable.	B

*2.4.5 **Post-operative care and follow-up***

Patients who are successfully treated conservatively carry some risk of complications. This risk correlates with increasing grade. Repeat imaging 2-4 days after trauma minimises the risk of missed complications, especially in grade 3-5 blunt renal injuries (101). However, the utility of frequent CT scanning after injury has never been

satisfactorily proven. CT scans should always be performed on patients with fever, unexplained decreasing haematocrit, or significant flank pain.

Nuclear renal scans are useful for documenting and tracking functional recovery in patients following renal reconstruction before discharge from hospital (97). To detect many of the delayed complications, an excretory urogram is recommended within 3 months of major renal injury, although benefit to the patient has not yet been proven in the literature. Follow-up should involve physical examination, urinalysis, individualised radiological investigation, serial blood pressure measurement and serum determination of renal function (60, 64). 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 (102).

The literature is generally inadequate on the subject of the long-term consequences of trauma on renal tissue. It appears that on histopathological evaluation, renal tissue may appear dystrophic following some cases of conservative management of minor renal injuries (103).

2.4.6 ***Recommendations***

	GR
Repeat imaging is recommended for all hospitalised patients within 2-4 days of significant renal trauma (although no specific data exists). Repeat imaging is always recommended in cases of fever, flank pain, or falling haematocrit.	B
Nuclear scintigraphy before discharge from the hospital is useful for documenting functional recovery.	C
Within 3 months of major renal injury, patients' follow-up should involve: 1. physical examination; 2. urinalysis; 3. individualised radiological investigation; 4. serial blood pressure measurement; 5. serum determination of renal function.	C
Long-term follow-up should be decided on a case-by-case basis but should at the very least involve monitoring for renovascular hypertension.	C

2.4.7 ***Complications***

Early complications occur within the first month after injury and can be bleeding, infection, peri-nephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation, and urinoma. Delayed complications include bleeding, hydronephrosis, calculus formation, chronic pyelonephritis, hypertension, arteriovenous fistula, hydronephrosis, and pseudoaneurysms.

Delayed retroperitoneal bleeding usually occurs within several weeks of an injury or procedure and may be life-threatening. Selective angiographic embolisation is the preferred treatment (104). Peri-nephric abscess formation is usually best managed by percutaneous drainage, although open drainage may sometimes be required (60). 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.

Renal trauma is a rare cause of hypertension, mostly in young men. The frequency of post-traumatic hypertension is estimated to be less than 5% in all published series (105,106). Hypertension may occur acutely as a result of external compression from peri-renal haematoma (Page kidney), or chronically because of compressive scar formation (Goldblatt kidney). 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 arteriovenous fistulae. Arteriography is informative in cases of post-traumatic hypertension (107). Treatment is required if the hypertension persists, and could include medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or total nephrectomy (108).

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 (109). Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage as necessary (63).

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating trauma. Percutaneous embolisation is often effective for symptomatic arteriovenous fistulae, but larger ones may require surgery (110).

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 (111,112).

Acute renal colic from a retained missile has been reported, and can be managed endoscopically if

possible (113). Other unusual late complications, such as duodenal obstruction, may result from retroperitoneal haematoma following blunt renal trauma (114).

2.4.8 ***Recommendations***

	GR
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
Renal salvage should be the surgeon's aim for patients in whom surgical intervention is necessary.	C

2.4.9 ***Paediatric renal trauma***

Blunt renal trauma is the most common injury seen in children and accounts for more than 90% of renal injuries in the paediatric population (115,116). Children are more susceptible to renal trauma than adults. Differences in anatomy and physiology, as well as the higher incidence of pre-existing renal disease, make children more likely to sustain injury. The kidneys are lower in the abdomen, less well-protected by the lower ribs and muscles of the flank and abdomen, more mobile, have less protective peri-renal fat and are proportionately larger in the abdomen than in adults (117-119).

History and physical examination are very important factors in the evaluation of the paediatric patient with suspected renal trauma. Unlike adults, hypotension is an unreliable sign in children, as an outpouring of catecholamines can maintain blood pressure despite a significant volume of blood loss. Hypotension is less common in children, and significant injury can be present despite stable blood pressures (120). Another important difference from adults is that children with microscopic haematuria or normal urinalyses and stable vital signs may have sustained significant renal injury (121). Haematuria is an important clinical sign of paediatric renal injury and is directly related to the severity of that renal injury and the presence of associated injuries (122).

The radiographic evaluation of children with suspected renal trauma is still controversial. Stein *et al*. proposed that all paediatric patients with any degree of haematuria should be evaluated for renal trauma (123). In contrast, Morey *et al*. concluded that significant injuries are unlikely in the absence of gross or significant microscopic haematuria (> 50 rbc/hpf) (124). Nguyen and Das proposed a low threshold for renal imaging following renal trauma. The instances of its use should include patients with blunt abdominal trauma with any level of haematuria, patients with associated abdominal injury regardless of the findings of urinalysis, and patients with normal urinalyses but in whom the mechanism of injury has a high index of suspicion for renal trauma (i.e. rapid deceleration event, direct flank trauma, falls from a height) (125). After studying 720 paediatric trauma cases, Santucci *et al*. concluded that the decision for imaging based on the adult criteria of gross haematuria, shock and significant deceleration injury is appropriate (126).

Ultrasound is considered a reliable method of screening and following the course of renal injury in paediatric patients with blunt renal trauma in Europe, although it is used much less frequently in the USA (127, 128). Ultrasound is used in some centres, mostly in stable cases with abnormal urinalyses and/or findings suggestive of a major injury (129). The diagnostic accuracy of IVP is superior to that of US, and should be performed as an emergency procedure if CT scan is not available (130).

Computed tomography is the best imaging modality, however, and those with multiple injuries or suspected renal trauma should be evaluated by contrast-enhanced CT if possible (131,132). The use of MRI in paediatric patients with vesicoureteral reflux found that MRI at 1.5 T was better than dimercaptosuccinic acid (DMSA) scans in detecting small renal parenchymal lesions (133), although MRI has little proven use in the acute management of the trauma patient.

Conservative treatment for grade 1-2 renal injuries is clearly defined, and these injuries should be managed expectantly (134). Non-operative management results in an excellent long-term outcome in the majority of cases (135). Non-operative management of high grade renal injuries is effective and is recommended for stable children, but requires close clinical observation, serial CT, and frequent reassessment of the patient's overall condition (136).

The length of hospital stay does not increase with worsening severity of renal injury, but is determined by the severity of non-renal injuries (137). Haemodynamic instability and a diagnosed grade 5 injury are the strongest indications for operative management (59,120,136). Stable patients with urinary extravasation can also be managed expectantly since most urinomas resolve spontaneously. In cases where there is persistent leakage, the placement of a ureteral stent or percutaneous drainage is feasible and curative in most cases. Early placement of a ureteral stent can be considered for paediatric patients with blunt renal trauma who demonstrate an absence of contrast material in the ipsilateral ureter, as clinical indications for stent placement will likely develop (138).

Major kidney trauma has significant consequences on the opposite side. Post-traumatic functional

evaluation by DMSA scintigraphy 8 days after major injury is a valid prognostic indicator of later function, but its clinical utility has never been established.

Children with renal injuries that fail with non-surgical therapy appear to do so in a median time of 4 hours, but the majority of patients fail within the first 24 hours (139). The failure rate of non-surgical management for renal injuries is 3% (140). Buckley and McAninch presented an algorithm for the management of paediatric renal injuries based on the 25 year experience of the San Francisco General Hospital, which is highly recommended (135) (Figure 1).

Mild renal injuries do not require follow-up imaging. Follow-up is only recommended for patients with major injuries as there is an increased risk of delayed complications and loss of renal function (139).

The majority of patients with severe renal injuries develop parenchymal scars. Radionuclide scans such as DMSA can be useful in the early diagnosis of scars and consequent hypertension (141).

2.4.10 ***Recommendations***

	GR
Indications for radiographic evaluation of children suspected of renal trauma include: 1. blunt and penetrating trauma patients with any level of haematuria; 2. patients with associated abdominal injury regardless of the findings of urinalysis; 3. patients with normal urinalysis who sustained a rapid deceleration event, direct flank trauma, or a fall from a height.	B
Ultrasonography is considered a reliable method of screening and monitoring blunt renal injuries by some researchers, but is not universally accepted.	B
CT scanning is the imaging study of choice for staging renal injuries.	B
Haemodynamic instability and a diagnosed grade 5 injury are absolute indications for surgical exploration.	B

2.4.11 ***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 77-100%. Gunshot wounds are associated with organ injury more often than are stab wounds. The majority of 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 (142).

Blunt and penetrating trauma equally contributed to combined renal and pancreatic injury, as reported by Rosen and McAninch (143). Renal preservation was achieved in most patients, and the complication rate of the series was 15% (143). 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 (144).

Renal injuries seem to be rather rare in patients with blunt chest trauma. In a recent study of polytrauma patients, conservative management was safely attempted without increasing morbidity (145). In polytrauma patients undergoing partial or total nephrectomy, there is no increased mortality or renal failure rate (146).

2.4.12 ***Recommendations***

	GR
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 injuries should be evaluated simultaneously.	C
The decision for conservative management should consider all injuries independently.	C

2.5 Iatrogenic renal injuries

2.5.1 ***Iatrogenic vascular injuries***

Iatrogenic main renal artery injuries with perforation or rupture are rare. They are usually reported after renal artery angioplasty or stenting, and have an incidence of 1.6% (147). One case of an iatrogenic renal artery perforation as a complication of cardiac catheterisation has also been reported (148). Since most iatrogenic renal artery lesions occur during endovascular procedures, there are no reports on the clinical symptoms, but

only on the angiographic findings. Arteriovenous fistulae, pseudoaneurysms, arterial dissection, or contrast extravasation are the possible radiological findings in these traumatic vascular lesions.

Traditional therapy for renal perforation has been renal artery ligation followed by bypass grafting or nephrectomy, but nowadays the treatment for acute iatrogenic rupture of the main renal artery is balloon tamponade. However, in case of failure, the immediate availability of a stent graft is vital.

Patients with iatrogenic operative injuries are strikingly different from those with penetrating, blunt, or catheter-related vascular trauma. Renal vessels are vulnerable during oncological procedures. Factors that increase technical difficulty are previous operation, tumour recurrence, radiation exposure, and chronic inflammatory changes.

Renal vein injuries during elective abdominal operations represent a serious complication with significant morbidity. Most patients with operative venous injuries have partial lacerations that can be managed with relatively simple techniques, such as venorrhaphy. Patch angioplasty with autologous vein or polytetrafluoroethylene (ePTFE) graft may be required if venorrhaphy is not possible (149).

Some renal vascular injuries, such as pseudoaneurysms following nephron-sparing surgery, can be managed by transcatheter embolisation (150).

2.5.2 ***Renal transplantation***

The orthotopic kidney is protected from external force by muscles, Gerota's fascia, and peri-nephric fat. A renal graft is located in the lower pelvis in the iliac fossa and is therefore more susceptible to injury, especially from direct blows to the abdomen. The transplanted kidney, unlike the native kidney, is fixed in position by a thick fibrotic capsule that develops post-transplant. Also, the transplant kidney is not suspended by the renal vessels, so deceleration events that cause pedicle injury to a native kidney are less likely to affect a transplanted kidney (151). As transplant recipients return to more active lifestyles, including a significant risk of becoming a trauma victim, a renal graft is liable to be severely affected by trauma that might not cause any injury to a native kidney.

In transplant recipients it is very important to know patients' baseline renal function (152). The knowledge of an abnormal renal baseline may prevent unnecessary extensive diagnostic evaluation. Radiographic evaluation should proceed as for the native kidney. The increased risk for contrast nephrotoxicity can be minimised with adequate hydration.

A CT scan is the test of choice for a stable injured transplant recipient, as it will identify renal and associated intra-abdominal injuries and will also indirectly assess renal blood flow and function. A renal duplex examination can be also very helpful for identifying isolated trauma to the transplanted kidney and for identifying renal blood flow. Radionuclide scans might reveal urine leaks and are good for assessing overall blood flow and renal function, while angiography can assess blood flow and identify specific arterial injuries.

The surgical management of an injured transplanted kidney is complex. A very short vascular pedicle and ureter, dense scarring, and a fibrous capsule may prevent any attempt at the direct repair of the parenchymal, collecting system and vascular pedicle injuries. Grade 1-3 injuries can be managed non-operatively. Grade 4-5 injuries might require exploration with debridement and drainage. Major injuries could require a subcapsular nephrectomy. Renovascular injuries have a poor prognosis. Renal arteriography may be helpful with embolisation of the main artery to stop bleeding, or with more selective embolisation to salvage part of the kidney. When renal graft injury occurs, saving the patient's life is the first priority, but saving the graft is also very important to maintain renal function.

Iatrogenic vascular injuries of renal transplants can be managed by embolisation. Angiographic embolisation often fails, and is associated with a high complication rate and high eventual nephrectomy rate (153). On the other hand, transcatheter embolisation is highly effective for biopsy-related vascular injury in the transplanted kidney.

2.5.3 ***Percutaneous renal procedures***

Percutaneous nephrostomy is achieved in nearly all patients without major complications. Haematuria is common for a few days, but massive retroperitoneal haemorrhage is rare. Small subcapsular renal haematomas resolve spontaneously, while arteriovenous-calyceal fistulae are best managed by angiographic embolisation.

If a nephrostomy catheter is seen to transfix the renal pelvis, the possibility of injury to a large renal artery must be considered. The misplaced nephrostomy catheter should be withdrawn over a guidewire, and renal artery embolisation might enable rapid arrest of a life-threatening haemorrhage (154). In more complex cases, CT could be used to detect possible catheter malposition and successfully guide catheter repositioning into the renal collecting system (155).

Renal pelvis injuries can occur during percutaneous nephrostomy placement. Haemorrhage can be prevented by avoiding puncture in anticoagulated or coagulopathic patients, careful puncture on to target calyceals, and avoidance of medial punctures. A pelvic injury is less likely to happen if the dilator is not

advanced further than the calyx, the peelaway sheaths are handled with care, especially when advanced around the pelviureteric junction, and kinking of the guidewires is avoided (156).

Percutaneous renal biopsy is a relatively safe procedure. Haemorrhage, arteriovenous fistula and renal capsular artery pseudoaneurysm might occur. Arteriovenous fistula might present with severe hypertension and is managed by embolisation (157). A pseudoaneurysm should be suspected if the patient presents with flank pain and decreasing haematocrit without haematuria. Arteriography and transarterial embolisation is the appropriate therapy (158).

Percutaneous nephrolithotomy (PCNL) is a popular procedure in which stones in the renal pelvis are removed via a nephroscope, often after ultrasonic or electrohydraulic disruption. The complications include haemorrhage, extravasation, and absorption of large volumes of irrigation fluid, fever, infection, colonic perforation, arteriovenous fistulae, and pneumothorax.

Extravasation of fluid is often due to a tear in the pelvicalyceal system. A close watch on irrigation fluid input and output is required for early recognition of the complication. Termination of the procedure if the renal pelvis is torn or ruptured is a safe choice. Apart from intraoperative evaluation of serum electrolytes, acid-base status and oxygenation, the monitoring of airway pressure is a good indicator of this complication. Metabolic acidosis, hyponatraemia, hypokalaemia, peritonism, and ileus are due to absorption of large volumes of irrigation fluids. Management of this complication requires close monitoring, placement of an abdominal or retroperitoneal drain, correction of acidosis and supportive measures (159).

The diagnosis of a colon injury during or after percutaneous renal surgery can be elusive because symptoms are often variable. An unrecognised or untreated colon injury can result in abscess formation, septicaemia, and/or nephrocolic or colocutaneous fistula. Surgical exploration is inevitable when the patient experiences haemorrhage, pneumoperitoneum, and peritonitis.

The majority of these cases can be successfully managed conservatively. The consistent application of proper techniques, avoidance of puncturing the kidney lateral to the posterior axillary line, and puncture of the upper pole calyx when feasible, will help prevent the injuries.

Vascular injuries with renal bleeding are quite frequent and can occur at any stage of the percutaneous procedure, requiring transfusion in 1-11% of cases. A high number of punctures and incorrect choice of puncture site (access that is too medial or direct puncture of the renal pelvis) have been suggested as the cause of vascular lesions after percutaneous procedures. Renal bleeding can arise from both venous and arterial lesions. Bleeding from venous vessels could be profuse at the end of a procedure, but is generally controlled by simple measures, such as placing the patient supine to reduce abdominal compression, positioning a nephrostomy catheter, and forcing diuresis through hydration and parenteral administration of mannitol after clamping of the nephrostomy catheter. In the case of major venous trauma with massive haemorrhage, patients with concomitant renal insufficiency can be treated without open exploration or angiographic embolisation using a Council balloon catheter (160).

Arterial lesions may induce acute or late post-operative bleeding. Severe acute bleeding usually arises from injury to the anterior or posterior segmental arteries. Delayed bleeding is usually caused by interlobar and lower pole artery lesions, often arteriovenous fistulae and post-traumatic aneurysms. Duplex US and CT angiography can diagnose vascular injuries.

Hyperselective renal embolisation is considered the most appropriate technique for the treatment of iatrogenic vascular lesions. It is essential to identify the precise site of the lesion so as to be as selective as possible and reduce the risk of renal dysfunction. Hyperselective catheterisation of the renal artery branches is achieved by means of either hydrophilic 5 French catheters or coaxial systems with low profile microcatheters (2.6 French). The use of an embolic agent helps in performing a distal and irreversible occlusion with complete haemostasis. A variety of embolic materials have been used; microcoils, homologous clots, detachable balloons, polyvinyl alcohol particles, gelfoam, silicone rubber, cotton pellets, and silk filaments. The choice of the embolic agent is dependent mainly on the blood flow entity at the level of the lesion, the vessel size and the operator's experience.

Finally, complications of endopyelotomy can be classified as major (vascular injury) and minor (infection, urinoma) (161). Preventive steps, along with proper patient selection, minimise the risk for these complications.

2.5.4 *Recommendations*

	GR
Iatrogenic rupture of the main renal artery should be treated with balloon tamponade and, in case of failure, with a stent graft.	C
Surgical venous injuries should be managed with venorrhaphy or patch angioplasty.	C
The transplanted kidney should be evaluated on the basis of renal function, type of injury and the patients' condition.	C
Hyperselective embolisation may control arterial bleeding during percutaneous procedures.	C

2.6 Suggestions for future research studies

Among the topics that would be useful subjects for future research studies are:

- blunt trauma grade 5 patients, as it appears that some of them may benefit from non-surgical management;
- the necessity and nature of follow-up imaging;
- the value of the administration of antibiotics in low-grade renal injuries selected for conservative management.

2.7 Algorithms

Figure 1 is an algorithm for the management of renal trauma in children. Figures 2 and 3 show the suggested treatment of blunt and penetrating renal injuries in adults.

Figure 1: Algorithm for the management of paediatric renal trauma (119)

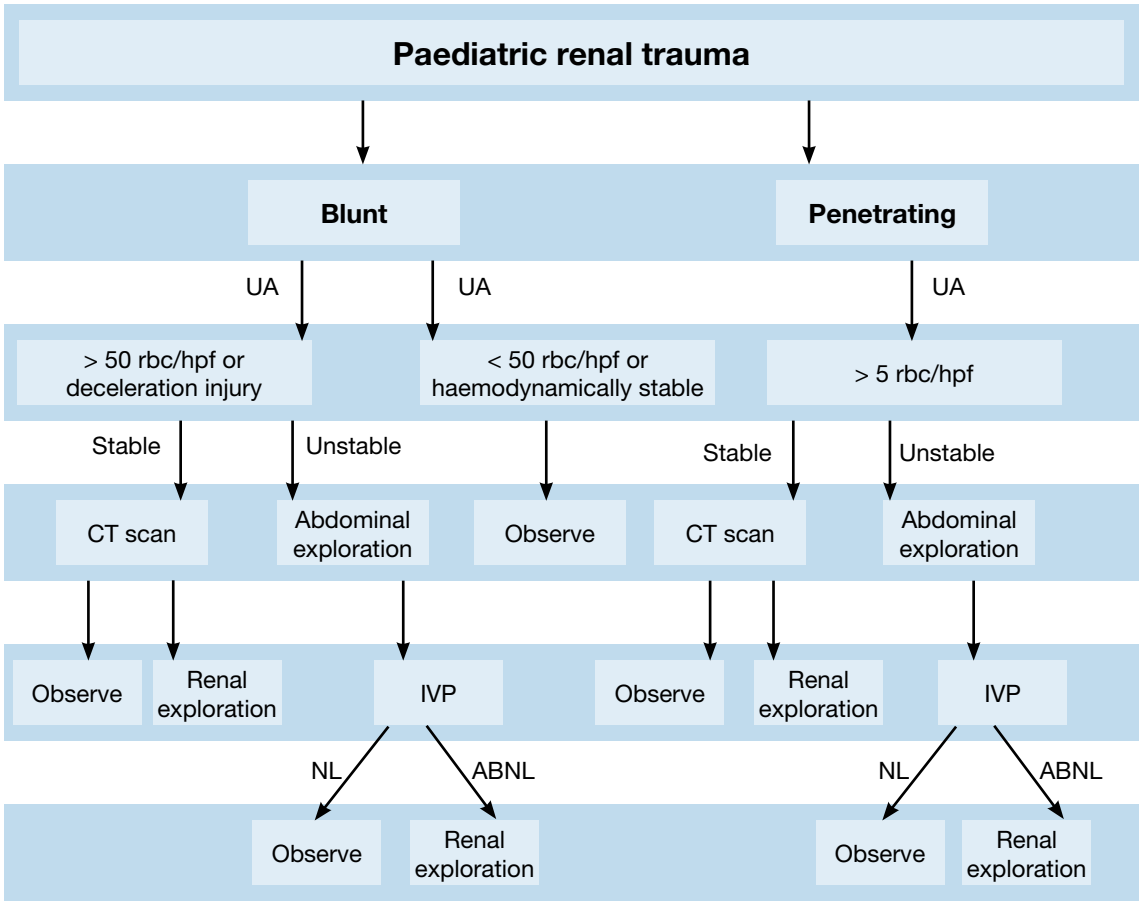
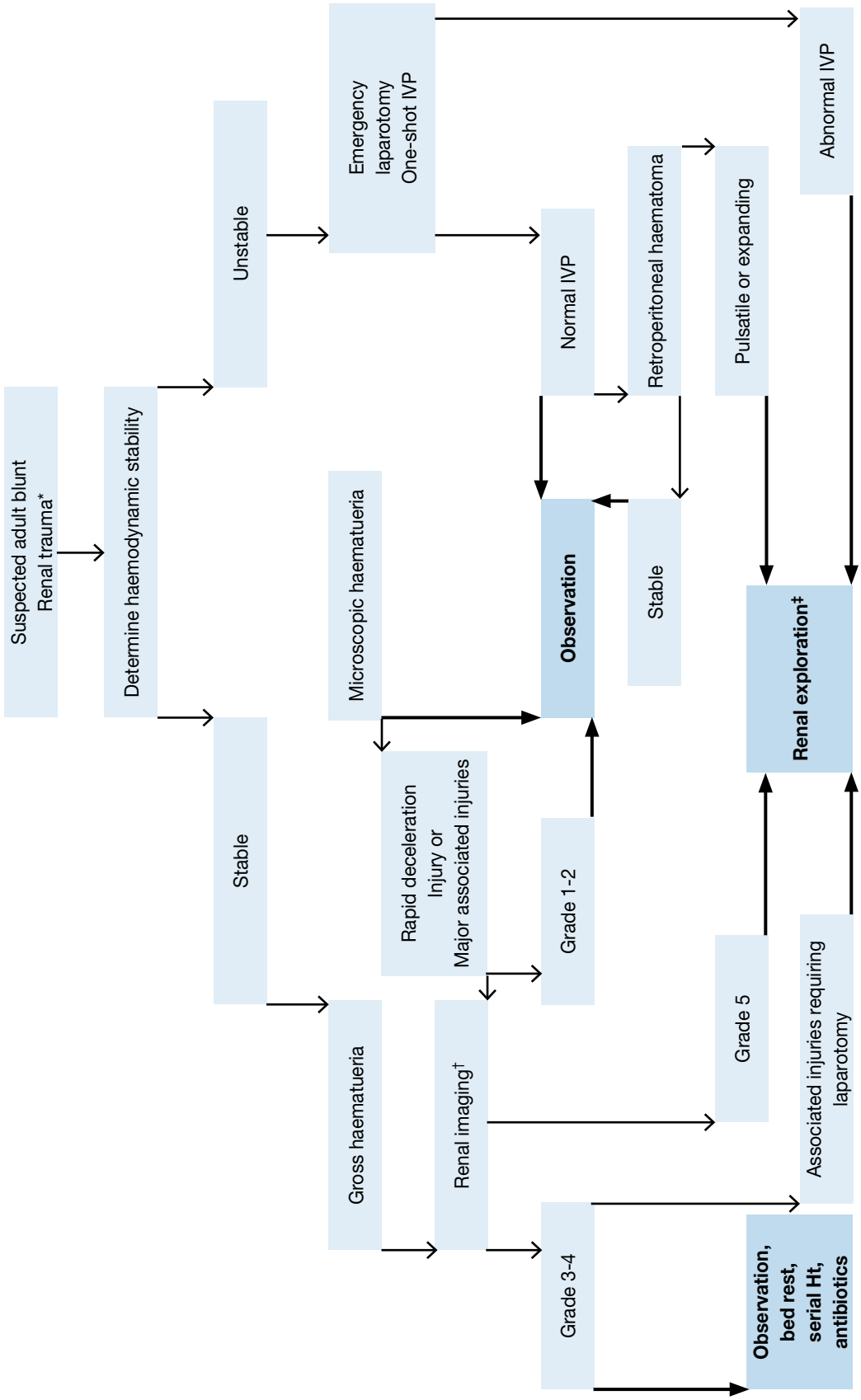


Figure 2: Evaluation of blunt renal trauma in adults

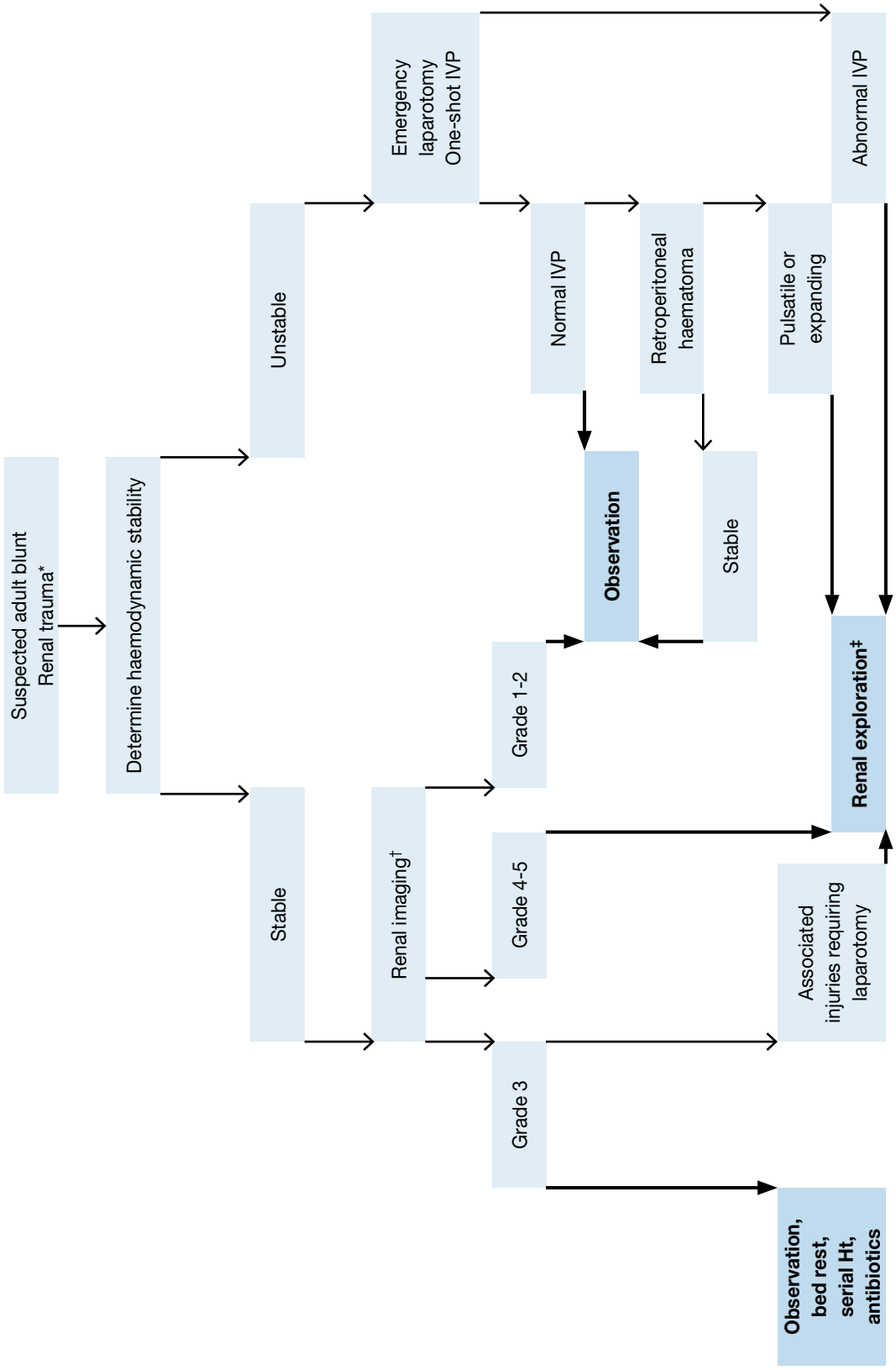


**Suspected renal trauma results from reported mechanism of injury and physical examination.*

† 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 3: Evaluation of penetrating renal trauma in adults



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3. URETERAL TRAUMA

3.1 Introduction

The ureter is the sole conduit for urinary transport between the kidney and the bladder. Thus, any ureteral injury can threaten the function of the ipsilateral kidney. This small, mobile, worm-like, peristalsing, urothelial-lined tube runs inferiorly from the renal pelvis in the retroperitoneal space. It lies anterior to the muscles of the posterior abdominal wall and lateral to the vertebral column, before descending into the bony ring of the pelvis to enter the bladder. Any external injury to the flank or back and any calamity within the bony pelvis therefore places the ureter at risk. Perhaps because of its protected location, its small size, and its mobility, trauma to the ureter is relatively rare and accounts for only 1% of all urinary tract trauma. Thus, there is a relatively small volume of published clinical experience upon which to base recommendations of management.

3.2 Aetiology

The largest and most contemporary review of ureteral trauma in the European literature is from Dobrowolski *et al*. in Poland (1). These authors retrospectively analysed the records of patients with upper urinary tract injuries presenting to 61 urology departments between 1995 and 1999. They identified 452 ureteral injuries. Of these, 340 (75%) were iatrogenic, 81 (18%) were from blunt trauma, and 31 (7%) were from penetrating trauma. Of the 340 iatrogenic injuries, 247 (73%) were gynaecological in origin, 46 (14%) were general surgical, and 47 (14%) were urological. It is therefore important to note that ureteral injury is much more likely to occur from activity within a hospital rather than from injuries sustained outside. Dobrowolski *et al*. estimate the frequency of ureteral injury during gynaecological pelvic surgical procedures to be 1.6 per 1000 (1). Of the total ureteral injuries identified, the injury was in the upper third in 60 cases (13%), in the middle third in 61 cases (13%), and in the lower third in 331 (74%). The median time to diagnosis was 3.3 h.

The most common diagnostic investigation was intravenous urography (IVU), which was used in 244 patients; retrograde ureteropyelography was used in 98 patients; and ureteral catheterisation was used in 125. The diagnosis was also established at open surgery in 104 patients. This snapshot of ureteral trauma in a modern European setting is similar to that seen in the USA (2).

3.3 Diagnosis

*3.3.1 **Clinical diagnosis***

There are no classic clinical symptoms and signs associated with acute ureteral trauma caused by external injury (3). In view of this, the diagnosis must be one of suspicion. Ureteral trauma should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, and also in cases of blunt deceleration

trauma, in which the kidney and renal pelvis can be torn away from the ureter. This deceleration injury is more likely to occur in children because of their hyperextensible vertebral column (4). Haematuria is also a poor indicator of injury, as it is present in only half of those with ureteral trauma (5).

It is possible for isolated ureteral injuries to be missed. Such patients tend to present with subsequent evidence of upper tract obstruction, urinary fistula formation and sepsis (6). After gynaecological pelvic surgery, any woman who complains of flank pain, develops vaginal leakage of urine or becomes septic should also be suspected of having injury to the ureter or bladder and should be investigated appropriately. At surgery, when the ureter is explored to exclude injury, the use of intravenous indigo carmine or methylene blue is to be recommended. This will help reveal the site of injury by leakage of blue-stained urine. This is especially important in partial tears.

*3.3.2 **Radiological diagnosis***

Ureteral injury may cause radiological signs of upper urinary tract obstruction but the sine qua non of ureteral injury is extravasation of radiological contrast material (3). This sign can be produced by the use of IVP, giving 2 mg of contrast material per kilogram of body weight. However, because of the increasing use of CT scanning in polytraumatised patients, the diagnosis is increasingly made with this modality.

If a high suspicion of ureteral injury exists and the CT scan is non-diagnostic, then a 'poor man's IVP' can be obtained by taking a plain kidney-ureter-bladder (KUB) film 30 minutes after intravenous injection of CT contrast medium. If this is also non-diagnostic and a suspicion of injury still exists, then retrograde pyelography should be undertaken as the gold standard investigation.

3.4 Classification

The AAST has classified ureteral injuries as shown in Table 4 (7).

Table 4: Classification of ureteral injury

Grade	Description of injury
I	Haematoma only
II	Laceration < 50% of circumference
III	Laceration > 50% of circumference
IV	Complete tear < 2 cm of devascularisation
V	Complete tear > 2 cm of devascularisation

3.5 Management

*3.5.1 **Partial injuries***

These can be defined as grade I to II lesions. Once recognised, they can be managed with ureteral stenting or by placement of a nephrostomy tube to divert urine (3). There is no prospective clinical trial comparing outcomes between these techniques. We believe that ureteral stenting is probably superior because a stent across the injury will allow secure drainage of the kidney, as well as providing canalisation and stabilisation of the injury. We believe that this will reduce the subsequent risk of stricture. The stent may be placed in an antegrade or retrograde fashion. In all cases, fluoroscopy and ureteropyelography with radio-opaque contrast should be used to guide stent placement.

The procedure should commence with the passage of a hydrophilic atraumatic guidewire across the damaged segment of ureter. Once across the site of the injury, an access catheter can be backloaded over the wire and passed across the injury. The hydrophilic wire can then be exchanged for a 0.038-inch wire, and the stent deployed. If this technique is utilised, a bladder catheter should be left in place for 2 days to limit stent reflux during voiding until mucosal healing has begun. The stent should be left in place for at least 3 weeks. The patient should have a follow-up dynamic renogram and IVP between 3 and 6 months, or sooner if lateralising flank pain develops. If there is evidence of stricture, then this should be managed by endo-urological or open surgical techniques, as appropriate.

If a grade II or III injury is encountered during immediate surgical exploration of an iatrogenic injury, then primary closure of the ureteral ends over a stent may be recommended, with placement of an external, non-suction drain adjacent to the injury.

3.5.2 Complete injuries

These are grade III to V injuries. Successful repair should utilise the principles outlined in Table 5.

Table 5: Principles of repair of complete injury

Debridement of ureteral ends to fresh tissue
Spatulation of ureteral ends
Placement of internal stent
Watertight closure of reconstructed ureter with absorbable suture
Placement of external, non-suction drain
Isolation of injury with peritoneum or omentum

The type of reconstructive repair procedure chosen by the surgeon depends on the nature and site of the injury (3). The options are depicted in Figure 4.

Figure 4: Diagram of the options for repair of complete injuries, based on the site of the injury

Upper third: Uretero-ureterostomy
Transuretero-ureterostomy
Ureterocalycostomy

Middle third: Uretero-ureterostomy
Transuretero-ureterostomy
Boari flap and reimplantation

Lower third: Direct reimplantation
Psoas hitch
Blandy cystoplasty

Complete: Ileal interposition
Autotransplantation

3.5.3 ***Sterile surgery***

3.5.3.1 Uretero-ureterostomy

Using the principles outlined above, the ureteral ends are debrided and freshened. The ends are spatulated. An internal double J-stent is inserted and the ends are closed over the stent using an interrupted 4/0 vicryl suture. An external, non-suction drain is placed at the site of the injury, and a catheter is left in the bladder. The bladder catheter can be removed after 2 days. The wound drain can be removed 2 days later if drainage is low. The stent should be removed after 6 weeks, and a follow-up renogram and IVP should be obtained after 3 months to assess the patency of the repair.

3.5.3.2 Ureterocalycostomy

In cases were the pelvi-ureteral junction has been destroyed, the lower pole of the affected kidney can be amputated to expose the lower pole infundibulum and calyces. The distal ureteral end can then be debrided and spatulated, and anastomosed to the lower pole calyx, over an internal stent, using an interrupted 4/0 vicryl suture. An external, non-suction drain is placed at the site of the injury and a catheter is left in the bladder. The bladder catheter can be removed after 2 days. The wound drain can be removed 2 days later if drainage is low. The stent should be removed after 6 weeks and a follow-up renogram and IVP should be obtained after 3 months to assess the patency of the repair.

3.5.3.3 Transuretero-ureterostomy

The distal end of the injured ureter is ligated with an absorbable suture. The proximal end is debrided and spatulated. This end is then transposed across the midline through a retroperitoneal window above the level of the inferior mesenteric artery. A 1.5 cm ureterotomy is made on the medial aspect of the contralateral ureter. A stent is placed from the ipsilateral kidney, through the anastomosis, and down the distal contralateral ureter into the bladder. A watertight anastomosis is fashioned using an interrupted 4/0 vicryl suture. An external, nonsuction drain is placed at the site of the injury, and a catheter is left in the bladder. The bladder catheter can be removed after 2 days. The wound drain can be removed 2 days later if drainage is low. The stent should be removed after 6 weeks, and a follow-up renogram and IVP should be obtained after 3 months to assess the patency of the repair.

3.5.3.4 Ureteroneocystostomy with Boari flap

The proximal ureteral end is debrided and spatulated. A traction suture is placed. The distal ureteral end is ligated with an absorbable suture. The bladder is filled with 200-300 ml of normal saline via a urethral catheter, and controlling stay sutures are placed on the bladder. The L-shaped flap is raised, its base being approximately four times wider than the width of the ureter to be implanted. The ureter is pulled through a submucosal tunnel in the flap and secured to the bladder mucosa using an interrupted 4/0 vicryl suture. Anchoring sutures can be placed at the serosal aspect of the ureter to secure it to the bladder. A stent is placed across the neo-ureterocystostomy, and a suprapubic catheter is placed in the bladder. The bladder is then closed in two layers with 2/0 vicryl sutures. An external, non-suction drain should be placed at the site of the reimplant; it can be removed after 2 days. The urethral catheter can be removed at the same time. The suprapubic catheter can be removed after a cystogram at 2 weeks, and the stent can be removed after 6 weeks. An IVP and renogram should be obtained 3 months thereafter to confirm the patency of the neocystostomy.

3.5.3.5 Ureterocystostomy and psoas hitch

The proximal ureteral end is debrided and spatulated. A traction suture is placed. The distal ureteral end is ligated with an absorbable suture. The fundus of the bladder is mobilised, and the contralateral superior vesical pedicle may be divided to improve fundal mobility. The bladder is filled with 200-300 ml of normal saline via a urethral catheter, and controlling stay sutures are placed. A cystotomy (Blandy) is performed perpendicular to the line of the ureter. Two fingers are placed inside the bladder to stretch it gently towards the ipsilateral psoas tendon. Three non-absorbable 2/0 sutures are placed between the bladder wall and the tendon, with care being taken to avoid the genitofemoral nerve.

Ureteroneocystostomy is then undertaken using either the Leadbetter-Politano or Lich-Gregoire techniques. A double J-stent is placed across the reimplant, and a suprapubic catheter is placed in the bladder. The bladder is then closed in two layers with 2/0 vicryl in the line of the ureter, thus providing extra length to the hitch. The anastomosis is thus under no tension. An external, non-suction drain should be placed at the site of the reimplant, and can be removed after 2 days. The urethral catheter can be removed at the same time. The suprapubic catheter can be removed after a cystogram at 2 weeks, and the stent can be removed after 6 weeks. An IVP and renogram should be obtained 3 months thereafter to confirm the patency of the neocystostomy.

3.5.3.6 Ileal interposition graft

In cases of long segment ureteral destruction, the ureter can be totally replaced using the distal ileum. This should be avoided in patients with coincidental gastrointestinal disease, such as Crohn's disease, and in patients with impaired renal function. A 25-cm length of ileum is taken out of bowel continuity about 20 cm proximal to the ileocaecal valve. Gastrointestinal continuity is restored with an ileo-ileal anastomosis using interrupted 3/0 seromuscular vicryl. The mesenteric is repaired using 2/0 vicryl. The ileal segment is placed in the isoperistaltic orientation between the renal pelvis and the bladder. Ileo-pelvic and cysto-ileal end-to-end anastomoses are fashioned using 2/0 vicryl. A nephrostomy tube should be inserted into the ipsilateral kidney to decompress the affected upper tract. A catheter should be placed in the bladder. External, non-suction drains should cover the proximal and distal anastomoses. Lastly, the reconstruction should be wrapped in omentum.

The wound drains can be removed after 2 days. A nephrostogram should be performed after 3 weeks; if no leakage is demonstrated, the nephrostomy can be clamped and then removed. Finally, the urinary catheter can be removed. Follow-up should include IVP and renography at 3 months, together with testing for the levels of serum creatinine, chloride, bicarbonate, and base excess, looking for evidence of hyperchloraemic metabolic acidosis.

3.5.3.7 Autotransplantation

If complete ureteral disruption should occur in the presence of coincidental gastrointestinal disease or impaired renal function, then autotransplantation of the affected renal unit can be undertaken. The renal artery and vein are divided long at the aorta and cava. The kidney is moved to the pelvis, and vascular continuity is restored using 5/0 prolene for the artery and 4/0 prolene for the vein. A Lich-Gregoire extravesical neoureterocystostomy can then be fashioned to re-establish urinary drainage. This need not be stented. A covering external, non-suction drain should be placed, and a catheter inserted in the bladder. The drain can be removed after 2 days, if dry, and the catheter removed after a cystogram at 2 weeks. Again, follow-up at 3 months with IVP and renogram is recommended.

3.5.3.8 Nephrectomy

There is one circumstance in which immediate nephrectomy should be undertaken. This is when ureteral injury complicates the repair of an abdominal aortic aneurysm or other vascular procedure in which a vascular prosthesis is to be implanted. We feel that immediate excision of the corrupted renal unit and its damaged ureter leads to less chance of urinary leak, urinoma, sepsis, and graft infection.

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4. BLADDER TRAUMA

4.1 Background

Among abdominal injuries that require surgical repair, 2% involve the bladder (1). Blunt or penetrating trauma account for 67-86% and 14-33% of bladder ruptures, respectively (2-4). Motor vehicle accidents are the most common cause (90%) of bladder rupture by blunt trauma (5-7). In the setting of blunt trauma, bladder rupture may be classified as either extraperitoneal with leakage of urine limited to the perivesical space, or intraperitoneal, in which the peritoneal surface has been disrupted, with concomitant urinary extravasation.

Bladder trauma: facts and figures

- 70-97% of patients with bladder injuries caused by blunt trauma have associated pelvic fractures (3,8,9).
- Pubic symphysis diastasis, sacroiliac diastasis, and sacral, iliac, and pubic rami fractures are significantly associated with bladder rupture, whereas isolated acetabular fractures are not (10,11).
- > 50% of the associated pelvic fractures are of the pubic ramus (12).
- Up to 30% of patients with pelvic fractures will have some degree of bladder injury (13).
- Major bladder injury occurs in only 5-10% of patients who have pelvic fracture(s) (7,14).
- > 85% of patients with pelvic fractures have associated injuries in other organ systems (8), with a mortality rate of 22-44% (12,13,15).
- Approximately 25% of intraperitoneal bladder ruptures occur in patients who do not have pelvic fracture(s) (7).

During a motor vehicle accident, traumatic forces can be transferred to the bladder by the seatbelt; injuries usually occur in patients with a full bladder. The degree of distension of the bladder with urine determines its shape and, to some degree, the injury it sustains. A fully distended bladder can be ruptured by a light blow; however, an empty bladder is seldom injured, except by crushing or penetrating wounds. Pelvic scars or pre-existing pelvic pathology can influence susceptibility to injury (16).

Combined intra- and extraperitoneal rupture may occur in 2-20% of cases (7,17-19). Simultaneous bladder and prostate-membranous urethra ruptures occur in 10-29% of male patients (10). Several studies investigating pelvic fractures and associated injuries in paediatric patients reported a lower incidence of urogenital injury (7-14%) (20-23), than in comparative adult series (7,13,14). In seven paediatric series (20-26), the average rate of bladder injury in patients with pelvic fractures was 4%. Motor vehicle accidents were the cause of the trauma in 97% of cases (26).

4.1.1 ***Iatrogenic trauma***

During lower abdominal operations, the bladder is the most frequently injured genitourinary organ (27). Most iatrogenic injuries occur during:

- open abdominal or pelvic surgery (85%);
- anterior vaginal surgery (9%);
- laparoscopy (6%).

The majority (92%) of these injuries are graded as III-IV, using the AAST scale (27). Most injuries occur during obstetric and gynaecological procedures (52-61%), followed by urological (12-39%) and general surgical (9-26%) interventions (27,28). Of the general surgical operations that result in iatrogenic injury to the bladder, most involve resection of bowel as a result of malignancy, diverticulitis, or inflammatory diseases (27,28).

Bladder injury occurs during gynaecological operations in 0.3-8.3% of cases (29-34). Concurrent anti-incontinence surgery significantly increases the risk of injury to the bladder (13% vs 3%; P= 0.049) (34). Most cases of urological iatrogenic trauma occur during vaginal operations and laparoscopy (27,28). The incidence of bladder wall perforation is generally low (1%) during transurethral resection of bladder tumours, and most (88%) can be managed by catheter drainage (35,36). Transurethral resection of the prostate is also associated with low injury rates (37).

Routine cystoscopy is an important adjunct to the major gynaecological procedures, and its omission may result in underestimation of iatrogenic bladder injury. An extensive review of the literature indicated that in studies not involving routine cystoscopy, the frequency of bladder injury varied from 0.2/1000 to 19.5/1000, with an overall frequency of 2.6/1000. Only 52% of bladder injuries were identified and managed intraoperatively (31). In studies involving routine cystoscopy, the frequency of bladder injury varied from 0.0/1000 to 29.2/1000, with an overall frequency of 10.4/1000. Up to 85% of unsuspected bladder injuries were identified with the use of cystoscopy and were managed successfully intraoperatively (31). Routine cystoscopy is recommended after any type of incontinence surgery as it enables identification of unsuspected bladder injury in 85% of patients (31,32,34,38).

Surgical procedures for the correction of stress urinary incontinence can also result in bladder trauma. The rate of bladder injury is below 3% in Burch colposuspension (39-41). Bladder injury is the most common complication of the tension-free vaginal tape (TVT) procedure, with an incidence of 2.0-11.5% (42-47) and up to 19% in patients with prior failed incontinence surgery (48).

The transobturator tape (TOT) procedure minimises the retropubic needle passage, and the incidence of bladder injury is expected to be low. Although during early experience with this technique rates of injury were similar to those associated with the TVT procedure (39), a recent meta-analysis indicated a lower incidence of bladder injuries (odds ratio: 0.12; 95% confidence interval: 0.05-0.33) with TOT procedures (49).

4.2 Classification

Table 6: Bladder injury scale[1]

Grade*	Description	
I	Hematoma	Contusion, intramural hematoma
	Laceration	Partial thickness
II	Laceration	Extraperitoneal bladder wall laceration < 2 cm
III	Laceration	Extraperitoneal (> 2 cm) or intraperitoneal (< 2 cm) bladder wall laceration
IV	Laceration	Intraperitoneal bladder wall laceration > 2 cm
V	Laceration	Intraperitoneal or extraperitoneal bladder wall laceration extending into the bladder neck or ureteral orifice (trigone)

**Advance one grade for multiple injuries up to grade III.*
[1] Adapted from the AAST.

4.3 Risk factors

Individuals who are driving under the influence of alcohol are likely to have a distended bladder and a motor vehicle accident. Driving after drinking alcohol is therefore a risk factor for bladder injury (19) (LE: 3).

Concurrent anti-incontinence surgery during gynaecological procedures results in a fourfold increased risk of bladder injury, and is therefore a risk factor for iatrogenic bladder trauma (34) (LE: 3).

4.4 Diagnosis

The most common signs and symptoms in patients with major bladder injuries are gross haematuria (82%) and abdominal tenderness (62%) (3). Other findings may include inability to void, bruises over the suprapubic region, and abdominal distension (6). Extravasation of urine may result in swelling in the perineum, scrotum, and thighs, as well as along the anterior abdominal wall within the potential space between the transversalis fascia and the parietal peritoneum.

*4.4.1 **Macroscopic (gross) haematuria***

Gross haematuria indicates urological trauma (LE: 3). Traumatic bladder rupture is strongly correlated with the combination of pelvic fracture and gross haematuria. Morey *et al*. reported gross haematuria in all their patients with bladder rupture, and 85% had pelvic fractures (50). Thus, the classic combination of pelvic fracture and gross haematuria constitutes an absolute indication for immediate cystography in patients who have blunt trauma (3,7,13,50) (LE: 3).

The presence of gross blood at the urethral meatus is diagnostic of a urethral injury (LE: 3). A Foley catheter should not be inserted before a retrograde urethrogram has been carried out to ensure urethral integrity (51). Although grossly clear urine in a trauma patient without a pelvic fracture virtually eliminates the possibility of bladder rupture, 2-10% of patients with bladder rupture may have only microhaematuria or no haematuria at all (5,51).

In a retrospective review of more than 8000 paediatric trauma patients, of those cases with pelvic fractures, only one patient (0.5%) had an extraperitoneal bladder rupture (26). Lower urogenital injury occurred in six patients (2.8%). The absence of gross haematuria ruled out serious injury in this cohort.

Based on this data, no further work-up was recommended in paediatric patients with pelvic fractures without gross haematuria. It is recommended that patients with gross haematuria, multiple associated injuries, or significant abnormalities found on physical examination should be further evaluated with retrograde urethrography and cystography (LE: 3).

*4.4.2 **Microscopic haematuria***

In the trauma patient with a pelvic ring fracture, microscopic haematuria might indicate bladder laceration, and further investigation is warranted (LE: 3). However, the exact quantity of blood in the urine that should trigger investigation is controversial.

- Morgan *et al*. reported that no ruptures were seen in patients with < 25 red blood cells/high-power field (rbc/hpf) (10).
- Werkman *et al*. (52) concluded that if cystography had been restricted to patients with > 35-50 rbc/hpf, no perforation would have been missed in their series.
- Fuhrman *et al*. (53) believe that cystography in blunt trauma should be restricted to patients with gross haematuria, which they defined as > 200 rbc/hpf. They also thought that a retrograde urethrogram should be carried out first.

Existing data do not support lower urinary tract imaging in all patients with pelvic fracture or microscopic haematuria alone. Hochberg and Stone (54) concluded that cystography might be safely reserved for those patients with pelvic fracture considered to be high risk for bladder injury (significant pubic arch involvement, gross haematuria and/or haemodynamic instability), as 90% of patients in their series with pelvic fracture did not have a bladder rupture.

These observations do not appear to be valid for paediatric trauma patients. Abou-Jaoude *et al*. (55) reported a threshold for radiological evaluation of ≥ 20 rbc/hpf would miss 25% of cases with bladder injury. In contrast with other reported series (26), they suggested that lower urogenital tract evaluation in paediatric trauma patients, especially in the presence of pelvic fractures, should be based as much on clinical judgment as on the presence of haematuria (55) (LE: 3).

4.4.3 ***Cystography***

Retrograde cystography is the standard diagnostic procedure in the evaluation of bladder trauma (7,13,56-58) (LE: 3). This is the most accurate radiological study to identify bladder rupture. When bladder filling and post-void images are obtained, cystography has an accuracy rate of 85-100% (5,7,59,60). Bladder rupture is usually diagnosed when the contrast is identified outside the bladder. Adequate distension of the urinary bladder is crucial to demonstrating perforation, especially in cases of penetrating trauma, as most instances of a false-negative retrograde cystography were found in this situation (56).

Cystography requires plain film, filled film, and post-drainage films (as a minimum) (LE: 3); half-filled film and obliques are optional. For the highest diagnostic accuracy, the bladder must be distended using instillation of at least 350 mL of contrast medium by gravity. Bladder injury may be identified only on the post-drainage film in approximately 10% of cases (7). False-negative findings may result from incorrectly performed studies with less than 250 mL of contrast instillation or omission of a post-drainage film (61) (LE: 3). Only a correctly performed cystography should be used to exclude bladder injury (7).

4.4.4 ***Excretory urography IVP***

An IVP is inadequate for evaluation of the bladder and urethra after trauma, not only because of dilution of the contrast material within the bladder, but also because resting intravesical pressure is simply too low to demonstrate a small tear (16,62). An IVP has a low accuracy (15-25%) (15), and clinical studies have indicated that IVP has an unacceptably high false-negative rate (64-84%), which precludes its use as a diagnostic tool in bladder injuries (52,59,63) (LE: 3).

4.4.5 ***Ultrasound (US)***

Although, the use of US in bladder rupture has been described (64), it is not routine for evaluation of bladder injury. Free peritoneal fluid in the presence of normal viscera, or failure to visualise the bladder after transurethral saline instillation, are highly suggestive of bladder rupture (66) (LE: 3). Practically, however, US is not definitive in bladder or urethral trauma and is almost never used.

4.4.6 ***Computed tomography (CT)***

Computed tomography is clearly the method of choice for the evaluation of patients with blunt or penetrating abdominal and/or pelvic trauma (LE: 3). However, routine CT is not reliable in the diagnosis of bladder rupture, even if an inserted urethral catheter is clamped. CT demonstrates intraperitoneal and extraperitoneal fluid, but cannot differentiate urine from ascites.

As with IVP, the bladder is usually inadequately distended to reveal extravasation through a bladder laceration or perforation during routine abdominal and pelvic studies. Thus, a negative study cannot be entirely trusted, and routine CT cannot exclude bladder injury (12,16,65).

In a review of the cystograms and CT scans (CT cystography) of 25 patients who underwent both investigations during the initial evaluation of blunt abdominal trauma, five patients were found to have bladder rupture, three of which were extraperitoneal and two intraperitoneal (66); all of the injuries were detected by both studies. It was concluded that delayed imaging or contrast instillation could provide the adequate bladder distention needed to demonstrate contrast extravasation from the injury site. Similarly, in a series of 316 patients, 44 cases were diagnosed with bladder ruptures (60). In patients who underwent a formal surgical repair, 82% had operative findings that exactly matched the CT cystography interpretation. Either retrograde cystography or CT cystography are diagnostic procedures of choice for suspected bladder injury (51).

Computed tomography cystography can be used in place of conventional cystography (overall sensitivity 95% and specificity 100%) (LE: 3), especially in patients undergoing CT scanning for other associated injuries (60). However, this procedure should be performed using retrograde filling of the bladder with a minimum of 350 mL of dilute contrast material (7,66,67).

In conclusion, CT cystographic features may lead to accurate classification of bladder injury and allow prompt, effective treatment without further radiation exposure and the additional cost of conventional cystography (70) (LE: 3).

4.4.7 *Angiography*

Angiography is seldom, if ever, indicated. It can be useful in identifying an occult source of bleeding and can guide its subsequent therapeutic embolisation (16).

4.4.8 *Magnetic resonance imaging (MRI)*

It is extremely difficult to monitor a seriously injured patient in a strong magnetic field; MRI therefore has little place in the evaluation of acute bladder (16). The use of MRI has been described for later evaluation of urethral injury (69-71).

4.4.9 *Cystoscopy*

Mainly useful in iatrogenic trauma, routine cystoscopy identifies 85% of the unsuspected injuries to the bladder that would otherwise go unnoticed (31,34,39). Thus, it must be used as an adjunct to major gynaecological operations as well as surgical interventions for incontinence (LE: 3).

4.5 Treatment

The first priority in the treatment of bladder injuries is stabilisation of the patient and treatment of associated life-threatening injuries (LE: 3).

4.5.1 *Blunt trauma: extraperitoneal rupture*

Most patients with extraperitoneal rupture can be managed safely by catheter drainage alone, even in the presence of extensive retroperitoneal or scrotal extravasation (61) (LE: 3). Obstruction of the catheter by clots or tissue debris must be prevented for healing to occur. A success rate of 90% was reported with this approach in extraperitoneal rupture (5): 87% of the ruptures were healed in 10 days, and virtually all were healed in 3 weeks (57). However, bladder neck involvement (2), the presence of bone fragments in the bladder wall, or entrapment of the bladder wall will necessitate surgical intervention (19) (LE: 3).

4.5.2 *Blunt trauma: intraperitoneal rupture*

Intraperitoneal ruptures occurring after blunt trauma should always be managed by surgical exploration (LE: 3). This type of injury involves a high degree of force and, because of the severity of associated injuries, carries a high mortality (20-40%) (72). Lacerations are usually large in these cases, with the potential risk of peritonitis due to urine leakage if left untreated (61). Abdominal organs should be inspected for possible associated injuries and urinoma must be drained, if present.

4.5.3 *Penetrating injuries*

All bladder perforations resulting from penetrating trauma should undergo emergency exploration and repair (61) (LE: 3).

4.5.4. *Iatrogenic injuries*

Iatrogenic bladder perforations can occur during any pelvic, abdominal, or vaginal procedure (27). Prompt intraoperative recognition is extremely important to ensure a successful repair. Generally, suture repair is satisfactory, limiting unnecessary extravesical dissection (LE: 3). Most (> 95%) of urinary bladder injuries sustained during gynaecological operations are detected and can be managed during surgery (73). Repair can be performed either transvaginally or abdominally. Simple catheter drainage is sufficient in most cases of bladder perforation during transurethral resection of prostate or bladder tumours (36-38) (LE: 3).

4.6 Recommendations

4.6.1 *General*

	GR
Stabilisation of the patient is always the priority in cases with associated injuries.	B

4.6.2 *Diagnosis*

	GR
Immediate cystography is required in the presence of haematuria and pelvic fracture.	B
Diagnosis should be made with retrograde cystography with a minimum of 350 mL of gravity-filled contrast medium.	B
For cystography, the minimum requirement includes a plain film, filled film, and post-drainage film. Half-filled film and obliques are optional.	B
CT cystography can be used with equal efficacy if the patient is undergoing CT scanning for associated injuries.	B
Routine cystoscopy is recommended after major gynaecological operations and/or incontinence surgery.	B

4.6.3 *Treatment*

	GR
In the absence of bladder neck involvement and/or associated injuries that require surgical intervention, extraperitoneal bladder ruptures caused by blunt trauma are managed by catheter drainage alone.	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.	B
The technique of surgical repair used depends on the surgeon's preference, but a two-layer closure with absorbable sutures achieves a safe repair of the bladder wall.	B

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5. URETHRAL TRAUMA

5.1 Anatomical and aetiological considerations

The male urethra is divided into the anterior and posterior sections by the urogenital diaphragm. The posterior urethra consists of the prostatic and the membranous urethra. The anterior urethra consists of the bulbar and penile urethra. Only the posterior urethra exists in the female; the anterior urethra corresponds to the labia minora, which results from persistent separation of the urethral folds on the ventral surfaces of the genital tubercle.

*5.1.1 **Posterior urethral injuries***

Road traffic accidents, falls, and crush injuries can cause pelvic fractures, which result in injuries to the posterior urethra. About two-thirds (70%) of pelvic fractures occur because of motor vehicle accidents. The incidence of pelvic fracture is 20% in survivors of motor accidents where fatalities have occurred. The incidence is nearly 50% in fatal pedestrian accidents. Twenty-five per cent of cases result from a fall from a height (1,2).

Altogether, blunt trauma accounts for more than 90% of urethral injuries (3). Overall, the male posterior urethra is injured in 4-19% and the female urethra in 0-6% of all pelvic fractures (2,4-12). The female urethra is rarely injured, except by contusion or laceration by bone fragments.

During crush or deceleration impact injury, the severe shearing forces necessary to fracture the pelvis are transmitted to the prostatomembranous junction, resulting in disruption of the prostate from its connection to the anterior urethra at the prostatic apex. Retrograde urethrography and MRI correlates to this location of the injury (13,14). Cadaveric studies suggest that in most cases the membranous urethra is torn distally to the urogenital diaphragm (15).

An accurate knowledge of the functional anatomy of the sphincter mechanism is essential to the success of posterior urethral surgery. Continence after anastomotic reconstruction of subprostatic pelvic fracture urethral distraction defects depends upon the function of the bladder neck and of the distal urethral sphincter mechanism, each of which is competent and independently capable of maintaining continence in the absence of the other (16).

Unstable pelvic fractures (8,11,17-21), bilateral ischiopubic rami fractures ('straddle fracture'), and symphysis pubis diastasis have the highest likelihood of injuring the posterior urethra. 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 7 times higher than for either straddle injuries or sacroiliac ('Malgaigne') fractures alone (Table 7) (2).

Table 7: Odds ratio of suffering urethral injury with different types of pelvic fracture

Type of fracture	Odds ratio
Single ramus	0.6
Ipsilateral rami	0.8
Malgaigne's (vertical shear)	3.4
Straddle	3.9
Straddle plus sacroiliac	24.0

Lower urinary tract injury has been reported in about 16% of patients with unilateral rami fractures and in 41% of patients with bilateral rami fractures (22). Anteroposterior compression injuries from frontal crushes produce more severe pelvic fractures, major retroperitoneal bleeding and more frequent injury to the lower urinary tract than do lateral crashes (23).

Prostatomembranous urethral injuries can vary from simple stretching (25%) to partial rupture (25%) or complete disruptions (50%) (2). The more severe injuries result in prostatourethral displacement, with progressive scar formation encompassing the rupture defect. The incidence of double injuries involving the urethra and the bladder ranges between 10% and 20% in males, and may be intraperitoneal (17-39%), extraperitoneal (56-78%), or both (2,7).

Urethral injuries, by themselves, 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. Initially, the assessment and management of other associated injuries is usually more important than the assessment and management of the urethral injury (24).

The American Association for Surgery of Trauma has proposed the classification given in Table 8.

Table 8: Organ injury scaling III classification of urethral injuries (25)

Grade	Description	Appearance
I	Contusion	Blood at the urethral meatus; Normal urethrogram
II	Stretch injury	Elongation of the urethra without extravasation on urethrography
III	Partial disruption	Extravasation of contrast at injury site with contrast visualised in the bladder
IV	Complete disruption	Extravasation of contrast at injury site without visualisation in the bladder; < 2 cm of urethral separation
V	Complete disruption	Complete transection with > 2 cm urethral separation or extension into the prostate or vagina

New classifications provide an anatomical classification and a means of comparing treatment strategies and outcomes (26,27). The classification shown in Table 9 combines the best of previous classifications and has direct implications in clinical management.

Table 9: Classification of blunt anterior and posterior urethra

Grade	Description	Appearance
I	Stretch injury	Elongation of the urethra without extravasation on urethrography
II	Contusion	Blood at the urethral meatus No extravasation on urethrography
III	Partial disruption of anterior or posterior urethra	Extravasation of contrast at injury site with contrast visualised in the proximal urethra or bladder
IV	Complete disruption of anterior urethra	Extravasation of contrast at injury site without visualisation of proximal urethral or bladder
V	Complete disruption of posterior urethra	Extravasation of contrast at injury site without visualisation of bladder
VI	Complete or partial disruption of posterior urethra with associated tear of the bladder neck or vagina	

Clinical management is according to the injury grade:

- grade I no treatment required;
- grades II and III can be managed conservatively with suprapubic cystostomy or urethral catheterisation;
- grades IV and V will require open or endoscopic treatment, primary or delayed;
- grade VI requires primary open repair.

5.1.1.1 Urethral injuries in children

Urethral injuries in children are similar to those in adults. The only significant difference is that straddle pelvic fractures, Malgaigne's fractures or the association of straddle plus sacroiliac joint fracture is more common in children than in adults. In addition, posterior urethral injuries can involve the prostatic urethra and the bladder neck, as well as the membranous urethra. The tear is often in the prostatic urethra or at the bladder neck because of the rudimentary nature of the prostate, and is more likely to be a complete rupture (69% versus 42%). Urethral stretching is less common than in adults. The more proximal the injury, the greater the risk of incontinence, impotence, and stricture (2,24,28,29).

5.1.1.2 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 usually occur in children. They are often accompanied by severe pelvic fractures, where bony fragments of the fractured pelvis can lacerate the urethra. Urethral injuries in females frequently extend into the bladder neck or vagina, and often disrupt the normal continence mechanism (4,12). 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 (29).

5.1.1.3 Penetrating injuries to the perineum

These can occur after external violence such as 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 occur quite often as a result of ischaemic injury during obstructed labour.

5.1.2 ***Anterior urethral injuries***

Anterior urethral injuries result from blunt trauma more frequently than from penetrating trauma (Table 10).

Table 10: Aetiology of anterior urethral injuries

Cause	Example
Blunt trauma	• Vehicular accidents • Fall astride (straddle) • Kicks in the perineum • Blows in the perineum from bicycle handlebars, tops of fences, etc.
Sexual intercourse	• Penile fractures • Urethral intraluminal stimulation
Penetrating trauma	• Gunshot wounds • Stab wounds • Dog bites • External impalement • Penile amputations
Constriction bands	• Paraplegia
Iatrogenic injuries	• Endoscopic instruments • Urethral catheters/dilators

5.1.2.1 Blunt trauma

Vehicular accidents, falls, or blows cause most anterior urethral injuries. In contrast to posterior urethral trauma, they are rarely associated with pelvic fractures. They are usually straddle-type injuries caused by blows of blunt objects against the perineum, such as bicycle handlebars or the top of a fence. In this type of accident, the relatively immobile bulbar urethra is trapped and compressed by a direct force on it against the inferior surface of the symphysis pubis. These injuries are more common in children than in adults (28).

5.1.2.2 Intercourse-related trauma

A less common cause of blunt anterior urethral trauma is penile fracture. This rupture of the corpus cavernosum usually occurs during intercourse. In these injuries, the urethra is involved in 20% of the cases (30). Intraluminal stimulation of the urethra with foreign objects has also been reported to cause anterior urethral trauma. Most are short and incomplete, and occur in the distal penile urethra.

Surgery is rarely indicated and depends on the degree and extent of injury to the urethra.

5.1.2.3 Penetrating trauma

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 can involve the rectum, which may result in pelvic abscesses and the formation of fistulae (31,32). Other less frequent causes of external anterior urethral injuries include stab wounds, penile amputation, and impalement.

5.1.2.4 Constriction band-related trauma

Individuals with paraplegia who use a constriction device for urinary incontinence and forget to release the band because of the lack of sensation can cause severe ischaemic injuries involving the penis and urethra.

5.1.2.5 Iatrogenic trauma

Iatrogenic urethral injuries caused by instruments are by far the most common cause of urethral trauma. Urethral ischaemic injuries related to cardiac bypass procedures are not infrequent and can result in long and fibrotic strictures. A separate section in this chapter discusses iatrognic trauma in more detail (see section 4.6).

5.2 Diagnosis: initial emergency assessment

*5.2.1 **Clinical assessment***

The initial management of urethral injury is resuscitation of the patient. In the absence of blood at the meatus or genital haematoma, a urological injury is very unlikely and is excluded by catheterisation. Maintain airway and respiratory function, secure the cervical spine if necessary, and address blood loss if present. This is particularly important in posterior urethral injuries because of their close association with pelvic fractures.

The next step includes taking a complete history and carrying out physical, laboratory, and radiographic evaluations in order to identify all injuries accurately. A diagnosis of acute urethral trauma should be suspected from the history. A pelvic fracture, or any external penile or perineal trauma, can be suggestive of urethral trauma (33,34).

For penetrating injuries, the type of weapon used, including the calibre of the bullet, is helpful in assessing potential tissue damage. In a conscious patient, a thorough voiding history should be obtained to establish the time of last urination, the force of the urinary stream, whether urination is painful and whether haematuria is present. The following clinical indicators of acute urethral trauma warrant a complete urethral evaluation.

5.2.1.1 Blood at the meatus

This is present in 37-93% of patients with posterior urethral injury, and in at least 75% of patients with anterior urethral trauma (35,36). When blood is present at the urethral meatus, do not attempt urethral instrumentation until the entire urethra is imaged. In an unstable patient, attempt to pass a urethral catheter, but if there is any difficulty, place a suprapubic catheter and perform a retrograde urethrogram when appropriate.

It is extremely unlikely that gentle passage of a urethral catheter will do any additional damage (37,38), although it has been suggested that this may convert a partial tear into one that is complete (39). There are no convincing data indicating a higher rate of infection or urethral stricture after a single attempt at catheterisation (3). Indeed, if a urethral injury is suspected, urethrography prior to attempted catheterisation is the most prudent approach.

5.2.1.2 Blood at the vaginal introitus

This is present in more than 80% of female patients with pelvic fractures and co-existing urethral injuries (4).

5.2.1.3 Haematuria

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, as a mucosal contusion or small partial tear may be accompanied by copious bleeding, while total transection of the urethra may result in little bleeding (40).

5.2.1.4 Pain on urination or inability to void

The inability to void suggests urethral disruption.

5.2.1.5 Haematoma or swelling

With anterior urethral trauma, the pattern of the haematoma can be useful in identifying the anatomical boundaries violated by the injury. Extravasation of blood or urine in a sleeve distribution along the penile shaft indicates that the injury is confined by Buck's fascia. Disruption of Buck's fascia results in a pattern of extravasation limited only by Colles' fascia, and can extend to the coracoclavicular fascia superiorly and the fascia lata inferiorly. This results in a characteristic butterfly pattern of bruising in the perineum. In female

patients with severe pelvic fractures, the presence of labial swelling may be an indicator of urethral injury. It can be caused by urinary extravasation and warrants immediate attention.

5.2.1.6 High-riding prostate

This is a relatively unreliable finding in the acute phase since the pelvic haematoma associated with pelvic fractures often precludes the adequate palpation of a small prostate, particularly in younger men (3). A boggy mass is usually palpated without recognition of a prostate gland (41). Rectal examination is more important as a tool to screen for rectal injuries, which can be associated with pelvic fractures. Blood on the examination finger is suggestive of a rectal injury. Assessment of concomitant genital injuries is mandatory in every case of external urethral trauma.

*5.2.2 **Radiographic examination***

Retrograde urethrography is the gold standard for evaluating urethral injury (5,29). A scout film should be performed first to assess the radiographic technique, and to detect pelvic fractures and foreign bodies, such as bullets. This is performed using a Foley catheter in the fossa navicularis, with the balloon inflated using 1-2 mL of saline to occlude the urethra. Then, 20-30 mL of contrast material is injected while films are taken in a 30° oblique position. When severe pelvic fractures and associated patient discomfort are present, the oblique position may not always be possible. The radiographic appearance of the urethra permits classification of the injury and facilitates the subsequent management.

If posterior urethral injury is suspected, a suprapubic catheter is inserted. Later on, a simultaneous cystogram and ascending urethrogram can be carried out to assess the site, severity and length of the urethral injury. This is usually done after 3 months if a delayed repair is considered.

When the proximal urethra is not visualised in a simultaneous cystogram and urethrogram, either MRI of the posterior urethra (42) or endoscopy through the suprapubic tract is used to define the anatomy of the posterior urethra. Since manipulation in the bladder can cause the bladder neck to open and give the false impression of incompetence, the endoscopic appearance of the bladder neck should be noted immediately on placing the scope into the bladder (43).

After assessing the endoscopic appearance of the bladder neck, the flexible endoscope can be advanced through the bladder neck into the posterior urethra to the level of obstruction. If there is a question about the length of the distraction, a simultaneous retrograde urethrogram can be performed while the endoscope is in the posterior urethra. The radiographic appearance of the bladder neck is important, but is not as reliable an indicator of continence as the endoscopic appearance is. Furthermore, there are patients who, despite evidence of an open or scarred bladder neck, will have acceptable continence after reconstruction. For this reason, the need for concomitant bladder neck surgery at the time of urethral reconstruction is debatable (43,44).

Ultrasonography is not a routine investigation in the initial assessment of urethral injuries but can be very useful in determining the position of pelvic haematomas, or the exact location of the bladder when a suprapubic catheter is indicated.

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 penile crura, bladder, kidneys, and intra-abdominal organs (14,45).

*5.2.3 **Endoscopic examination***

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 (46).

5.3 Management

The management of urethral injuries remains controversial because of the variety of injury patterns, associated injuries and treatment options available. In addition, urethral injuries are relatively uncommon, hence the limited experience of most urologists worldwide and the absence of randomised prospective studies.

*5.3.1 **Anterior urethral injuries***

5.3.1.1 Blunt injuries

Partial tears can be managed with a suprapubic catheter or with urethral catheterisation (29,37,47). Suprapubic cystostomy has the advantage that it not only diverts the urine away from the site of injury, but also avoids urethral manipulation (48), as well as allowing for a simultaneous study to be carried out at a later date.

If the bladder is not easily palpable suprapubically, transabdominal sonography should be used to guide the placement of the catheter. The cystostomy tube is maintained for approximately 4 weeks to allow urethral healing. Voiding cystourethrography is then performed. Remove the suprapubic tube if normal voiding

can be re-established and neither contrast extravasation nor stricture is present.

The potential early complications of acute urethral injuries include strictures and infections.

Extravasated blood or urine from the urethral tear produces an inflammatory reaction that can progress to the formation of an abscess. The extent of the infection depends on the fascial planes violated (see section 4.2). The potential sequelae of these infections include urethrocutaneous fistulae, peri-urethral diverticulae and, rarely, necrotising fasciitis. Prompt urinary diversion coupled with the appropriate administration of antibiotics decreases the incidence of these complications.

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.

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 (47,49). 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 urethroplasty is indicated. Almost all complete ruptures of the anterior urethra require anastomotic or patch urethroplasty at 3-6 months. The only exception to this is urethral injury associated with penile fracture; this usually results in partial urethral disruption and can be repaired at the time of cavernosal closure.

5.3.1.2 Open injuries

5.3.1.2.1 Male urethral injuries

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 surgically evaluated and repaired as needed. Urethral strictures form in fewer than 15% of these patients (50).

Primary urethral suturing involves direct visualisation of the severed urethral ends and creation of a watertight, tension-free repair. The patient should be in a supine position. Use a circumferential subcoronal incision to deglove the penis.

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 14 French Foley catheter. Suture small lacerations with fine absorbable material. Careful overclosure of the corpus spongiosum and skin prevents the subsequent formation of fistulae (24). Keep urethral debridement to a minimum since the spongiosum is well vascularised and will usually heal well.

As with any surgery, give pre-operative antimicrobial prophylaxis. Some experts recommend the post-operative continuation of prophylactic antibiotics, but we are not aware of any data that prove that they help. After 10-14 days, obtain a peri-catheter retrograde urethrogram with the urethral catheter in situ. Provided there is no leakage at the anastomotic site, remove the urethral catheter. If there is leakage, leave the catheter in and repeat the cystourethrogram 1 week later.

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. One should marsupialise the urethra preparatory to a two-stage urethral repair, and consider a suprapubic urinary diversion. Perform a delayed elective procedure 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 contamination or decreased blood supply can compromise such a repair (33).

5.3.1.2.2 Female urethral injuries

Most female urethral disruptions can be sutured primarily. These injuries often occur together with bladder ruptures. Frequently, if the bladder injury is going to be repaired primarily, the urethral disruption can be repaired at the same time. For proximal urethral injuries, urethral exposure is best obtained transvesically. Distal urethral injuries can be approached vaginally (29). Early repair of post-traumatic urethral fistulae can also be accomplished transvaginally (4,12).

5.3.2 ***Posterior urethral injuries***

It is important to distinguish between inflammatory or iatrogenic posterior urethral strictures and true pelvic fracture urethral distraction defects as the principles of their surgical management are entirely different. Urethral stricture indicates a narrowing of the urethral lumen. In urethral distraction defects, there is a gap between the two otherwise normal ends of the urethra. The dismembered ends of the urethra retract, and the

space between them fills with fibrous tissue. There is no urethral wall in the scarred space, and any lumen represents merely a fistulous tract between the urethral stumps. A further difference between inflammatory strictures and distraction defects is that the urethral stumps are usually not fibrotic and can be re-anastomosed without tension after distraction injury. Once anastomosed, they usually heal without stricture (51).

Erectile dysfunction occurs in 20-60% of patients after traumatic posterior urethral rupture (51-55). The most important determining factor associated with impotence is the severity of the initial injury. The incidence of erectile dysfunction being caused by the open surgical repair itself is 5% or less (51,56). Erectile dysfunction seems to be a direct result of the pelvic fracture plus urethral injury. King reported an incidence of 42% in cases of pelvic fracture and urethral injury, but only 5% when the urethra was not injured (53). Barbagli *et al*. reported an incidence of 60% in patients with posterior urethral injury, compared with 14% in patients with bulbar injury (57).

Factors that correlate with the development of impotence are age, defect length, and the type of fracture. 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 (58,59). Associated vasculogenic erectile failure may occur in up to 80% of cases (60). Dixon *et al*. presented evidence that impotence may also be a consequence of avulsion of the corporus cavernosum from the ischium (14). In this series, five out of six patients with avulsion of the corpus cavernosum off the inferior pubic ramus, were impotent. Spontaneous return of potency may occur up to 2 years after injury (42). Gibson reported an incidence of improved sexual function after 18 months in 21% of patients (52).

5.3.2.1 Partial urethral rupture

Manage partial tears of the posterior urethra with a suprapubic or urethral catheter. Perform urethrography at 2-weekly intervals until healing has occurred (29,37). They may heal without significant scarring or obstruction if managed by diversion alone (48,61). Manage residual or subsequent stricture with urethral dilatation or optical urethrotomy if short and flimsy, and with anastomotic urethroplasty if dense or long (24,37).

5.3.2.2 Complete urethral rupture

Acute treatment options 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).

Delayed treatment options include:

- 'delayed primary urethroplasty' (which implies primary repair 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).

5.3.2.3 Primary realignment

The management of complete posterior rupture of the urethra has changed in recent years. There is now more active orthopaedic management of pelvic fractures with immediate external and internal fixation. This has led to the option of early repair of urethral injuries (37).

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 it will also ensure that it is easily treated if it does occur (62).

Open realignment has been described (63), 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 point 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:

1. Unrepaired bladder neck injury risks incontinence and infection of the pelvic fractures.
2. Unrepaired rectal injury carries the obvious risk of sepsis and fistula, and early exploration is indicated to evacuate contaminated haematomas and perform colostomy.
3. Urethral realignment over a stenting catheter is appropriate in such cases (29,40,64-66).

The overall condition of the patient and the extent of the associated injuries greatly affect the decision to proceed with primary realignment. Most patients with pelvic crush injuries have multiple organ injuries.

Associated lower extremity fractures can prevent placement in the lithotomy position, which may be required for primary realignment (although bedside flexible cystoscopy can be used). Head injuries increase the adverse risks of anaesthesia. If these conditions are controlled, such that a haemodynamically stable patient can safely undergo a lengthier anaesthesia and can be placed in the lithotomy position, endoscopic urethral realignment could be considered during the first 2 weeks after trauma.

The proposed benefits of primary alignment are:

1. A lower stricture rate than with suprapubic catheter placement alone (69% versus 10%) (6), which avoids a second operation for urethral reconstruction in about one-third of patients (3).
2. If scarring occurs, restoration of urethral continuity is simplified and may be accomplished by endoscopic procedures or dilatation.
3. If urethroplasty is required later, it is technically easier when the prostate and urethra are well aligned; the disadvantage might be a higher incidence of erectile dysfunction and incontinence when compared with delayed reconstruction (6,67).

The great variation of techniques used for primary realignment procedures confuses any comparison with delayed repair procedures (68-71). Primary realignment techniques include:

- simple passage of a catheter across the defect (70);
- catheter realignment using flexible/rigid endoscopes and biplanar fluoroscopy (72,73);
- use of interlocking sounds ('railroading') or magnetic catheters to place the catheter (71,74);
- 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 (75).

Realignment may be insufficient to join the margins of the severed urethra completely, and 1.5-4.0 cm defects have been observed even after catheter realignment (76). This finding agrees with experimental animal data, which show that when the urethra is transacted and an apparently good urethral junction is achieved by catheter traction, there is no evidence of epithelialisation of the mucosal gap, but rather that the intervening area is filled with fibrous tissue (77).

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 (3,64). Series that use immediate urethral realignment with minimal traction without suture repair bolsters report the most favourable results (Table 11).

Endoscopic primary realignment fulfils these criteria and should be used when a primary procedure is contemplated. Open primary realignment in the absence of bladder neck injury or rectal injury has no place in the treatment of posterior urethral injuries because of its higher morbidity.

Table 11: Results of immediate realignment in complete urethral disruption (68,70,72,74,77-91)

Series	Ref.no.	No. of patients	Follow-up months (range)	Erectile dysfunction	Incontinence	Restricture rate
Gibson (1974)	77	35†	n/a	12 (34%)	1 (3%)	26 (74.3%)
Crassweller et al. (1977)	78	38	– (24-240)	19/42 (45%)	n/a	12 (31.6%)
Malek et al. (1977)‡	79	7	168 (96-264)	0	0	1 (14.3%)
Gelbard et al. (1989)	72	7	10.2 (2-24)	1/6 (16.7%)	0	2 (33%)
Cohen et al. (1991)	80	4	28 (17-35)	2 (50%)	0	2 (50%)
Melekos et al. (1992)	81	4	n/a	0	0	4 (100%)
Follis et al. (1992)	68	20	42 (1-360)	4 (20%)	2 (10%)	12 (60%)
El-Abd (1995)	82	44	n/a	35 (79.5%)	0	44 (100%)
Gheiler and Frontera (1997)	83	3	6 (5-9)	0	0	1 (33.3%)
Londergan et al. (1997)	84	4	20.2 (12-35)	1 (25%)	0	3 (75%)

Elliott and Barrett (1997)	85	53	126 (1->120)	11 (21%)	2 (3.8%)	36 (68%)
Porter et al. (1997)	70	10	10.9 (2-31)	1/7 (14%)	0	5 (50%)
Rehman et al. (1998)	86	3	– (11-26)	1 (16.7%)	0	2 (66.7%)
Sahin et al. (1998)	87	5	31 (21-53)	1 (20%)	1 (20%)	4 (80%)
Tahan et al. (1999)	88	13	29 -	3 (23%)	0	5 (38.5%)
Jepson et al. (1999)	89	8	50.4 (35-85)	3 (37.5%)	1 (12.5%)	5 (62.5%)
Asci et al. (1999)	90	20	39 (19-78)	4 (20%)	2 (10%)	9 (45%)
Ying-Hao et al. (2000)	91	4	56 (39-85)	0	0	1 (25%)
Moudouni et al. (2001)	92	23	68 (18-155)	4/29 (14%)	0	16 (69.5%)
Mouraviev et al. (2005)	74	57	< 24 (2-15)	19/57 (34%)	10/57 (10%)	28/57 (49%)
Total		362		130/368 (35.3%)[§]	19/362 (5.2%)	218/362 (60.2%)

**Stricture that requires internal urethrotomy, or open urethroplasty, or more than one dilatation;*
[†]5 patients with partial rupture;
[‡]children;
[§]some partial ruptures included.

This type of summary of the literature suggests that immediate realignment is associated with an impotence rate of approximately 35%, an incontinence rate of 5%, and a restricture rate of 60%.

5.3.2.4 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 hampers adequate mobilisation and subsequent surgical apposition (24). Incontinence and impotence rates are higher than with the other techniques described in these guidelines (impotence 56%, incontinence 21%, restricture 49%) (6,29,48,62,65,93,94).

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 (29,40,64-66). In children, similar results have been reported with delayed repair and immediate open urethroplasty (63).

5.3.2.5 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 7 days. Fewer than 50 cases have been reported, and most of these are individual case reports only (12).

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 (29).

5.3.2.6 Delayed urethroplasty

Delayed 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 these 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 bulbar urethra at the distal point of obliteration, mobilisation of a normal bulbar 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 (24).

This technique has the advantage that associated injuries, damaged skin and tissues, and pelvic haematoma have resolved by the time it is performed. The only problem with this approach would be the length of time that the patient must have a suprapubic catheter in place before definitive treatment.

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' (95):

- 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 is 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 12 (96,97).

Table 12: Circumstances that might preclude successful perineal anastomotic repair as either initial or salvage therapy (96,97)

Circumstance	Alternative procedure
Distraction defects longer than 7-8 cm	A tubed interposition flap of penile or peri-neoscrotal 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 (see section 4.3.2.7).
Fistulae	These might require a combined abdominoperineal approach to secure adequate closure.
Synchronous anterior urethral stricture	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.
Urinary incontinence	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. The most common cause of bladder neck incompetence is the circumferential tethering of the uninjured bladder neck by scarring. In such cases, it is usually possible to restore functional competence of the bladder neck by mobilising it meticulously. This can be accomplished by removal of the dense haematoma-fibrosis anchoring the bladder neck to the pubis, anteriorly and laterally. Secondary rescarring is prevented by placement of a local omental flap (44, 98).

The results of various techniques are reviewed by Koraitim (66) 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 stricture. Urethroplasty was ultimately necessary 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% (28,38,43,51,55,99-102), and the risk of impotence caused by delayed urethroplasty was about 5% (37,51,55,56,65,103-105).

The gold standard remains delayed urethral repair at a minimum of 3 months after trauma, using a one-stage perineal approach.

The results obtained in children are similar to those in adults. The higher incidence of abdominal surgery simply reflects the greater propensity to damage of the bladder neck in children (105-106).

5.3.2.7 Reconstruction of failed repair of posterior urethral rupture

Restenosis 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 (38).

The principles of salvage repair are similar to those of the initial procedure. Progressive perineal anastomotic repair alone can be successful in 85% of salvage urethroplasties. If an anastomotic repair cannot be performed, a one-stage substitution urethroplasty using a pedicle island of penile skin might be possible

and could be more desirable than the final alternative, a two-stage scrotourethral inlay procedure or mesh split-thickness skin graft urethroplasty (63,107,108).

The main indications for a combined abdominoperineal surgical approach are:

- the presence of fistulous tracts to the bladder base, abdominal wall or rectum;
- peri-urethral epithelialised cavities;
- an ability to achieve the lithotomy position (97).

Restenosis to a luminal calibre of 12 French Foley catheter or smaller is required before a reduction in the urinary flow is perceived as abnormal (109). A wide calibre stricture may be observed or gently dilated. Optical urethrotomy is an alternative, particularly for a short, narrow stricture.

5.3.2.8 Delayed endoscopic optical incision

The principles of the procedure were described by Sachse in 1974 (109). 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: suprapubic passage of a cystoscope for transillumination of the thin perineal membrane and transurethral 'cutting-to-the-light' with an electrode (110). 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 the suprapubic drainage for an additional 2 weeks to confirm consistent voiding (111).

The results of several small series have been reported and are summarised in Table 13.

Table 13: Results of optical urethrotomy for traumatically obliterated pelvic urethra (82,112-116,118-123)

Series	Ref. no.	n	Follow-up months (range)	No. (%) requiring repeat urethrotomy	Erectile dysfunction
Gupta and Gill (1986)	112	10	15.1 (6-24)	10 (100%)	0
Chiouet et al. (1988)	113	8	43 (12-79)	7 (87.5%)	0
Marshall (1989)	114	10	n/a	10 (100%)	0
Barry (1989)	115	12	22 (1.5-85)	6 (50%)	0
DeVries and Anderson (1990)	116	4	< 4	1 (25%)	0
Kernohan et al. (1990)	118	7	35 (21-84)	7 (100%)	0
Yasuda et al. (1991)	119	17	44 (12-96)	7 (41.2%)	0
Quint and Stanisic (1993)	120	10	43 (7-108)	6 (60%)	0
El-Abd (1995)	82	284	n/a	272 (95.8%)	0
Goel et al. (1997)	121	13	17.7 (11-24)	10 (76.9%)	n/a
Levine and Wessells (2001)	122	6	60	6 (100%)	n/a
Dogra and Nabi (2002)*	123	61	30 (9-44)	11 (18%)	n/a
Total		445		354 (79.5%)	

**Laser urethrotomy*

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 (116). Although immediate restoration of urethral continuity is commonly possible, failure is common. Urethral dilatation, optical urethrotomy, and transurethral resection of stricture will be needed in about 80% of patients. 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 (124). Urethral false passage and rectal perforation have been reported (112,116,119). Stents are not currently recommended for patients with strictures following pelvic trauma, as fibrotic tissue tends to grow though into the lumen of the stent (43,125-127).

5.4 Recommendations for treatment: algorithms

The optimal management of patients with prostatomembranous disruptions should not be thought of as delayed repair versus other types of treatment modalities. Each patient should be assessed and managed according to the initial clinical circumstances. It is impractical to suggest that all patients be managed by one single method because of the variability of each case and the severity of associated injuries. The intervention should be guided by the clinical circumstances. The following algorithms are suggested for the treatment of urethral injuries in males and females (Figures 5-7).

Figure 5: Management of posterior urethral injuries in men

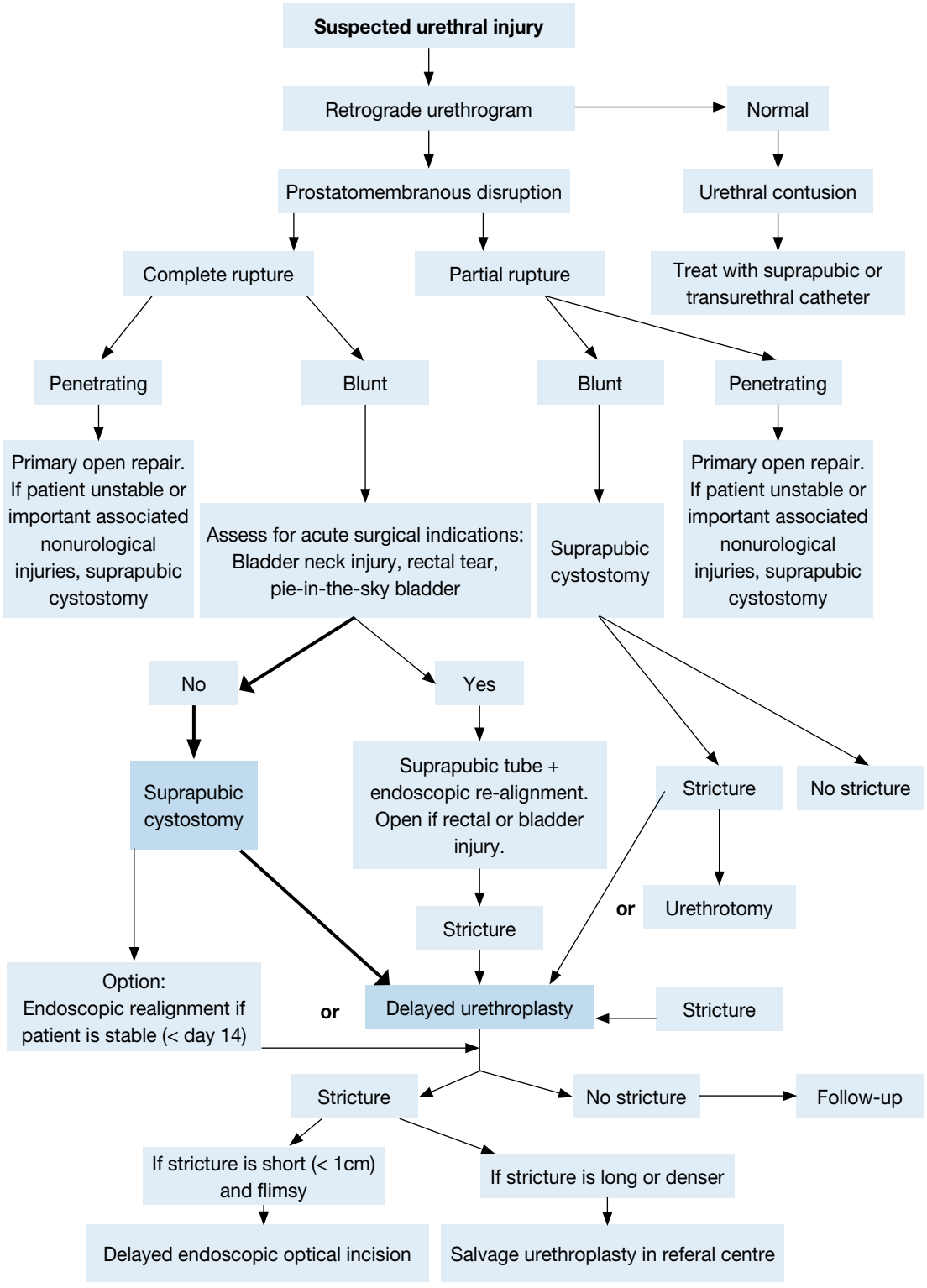


Figure 6: Management of anterior urethral injuries in men

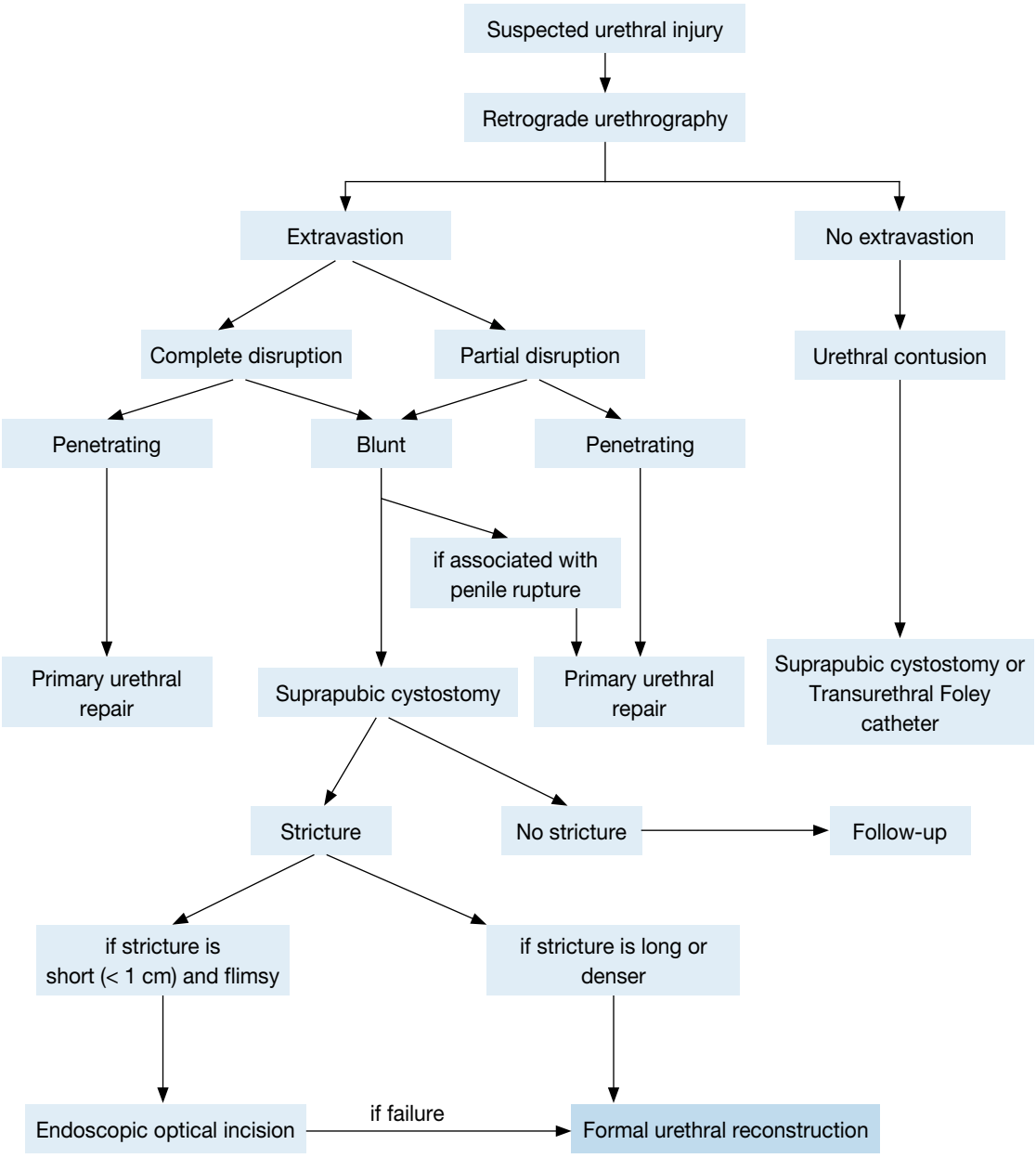
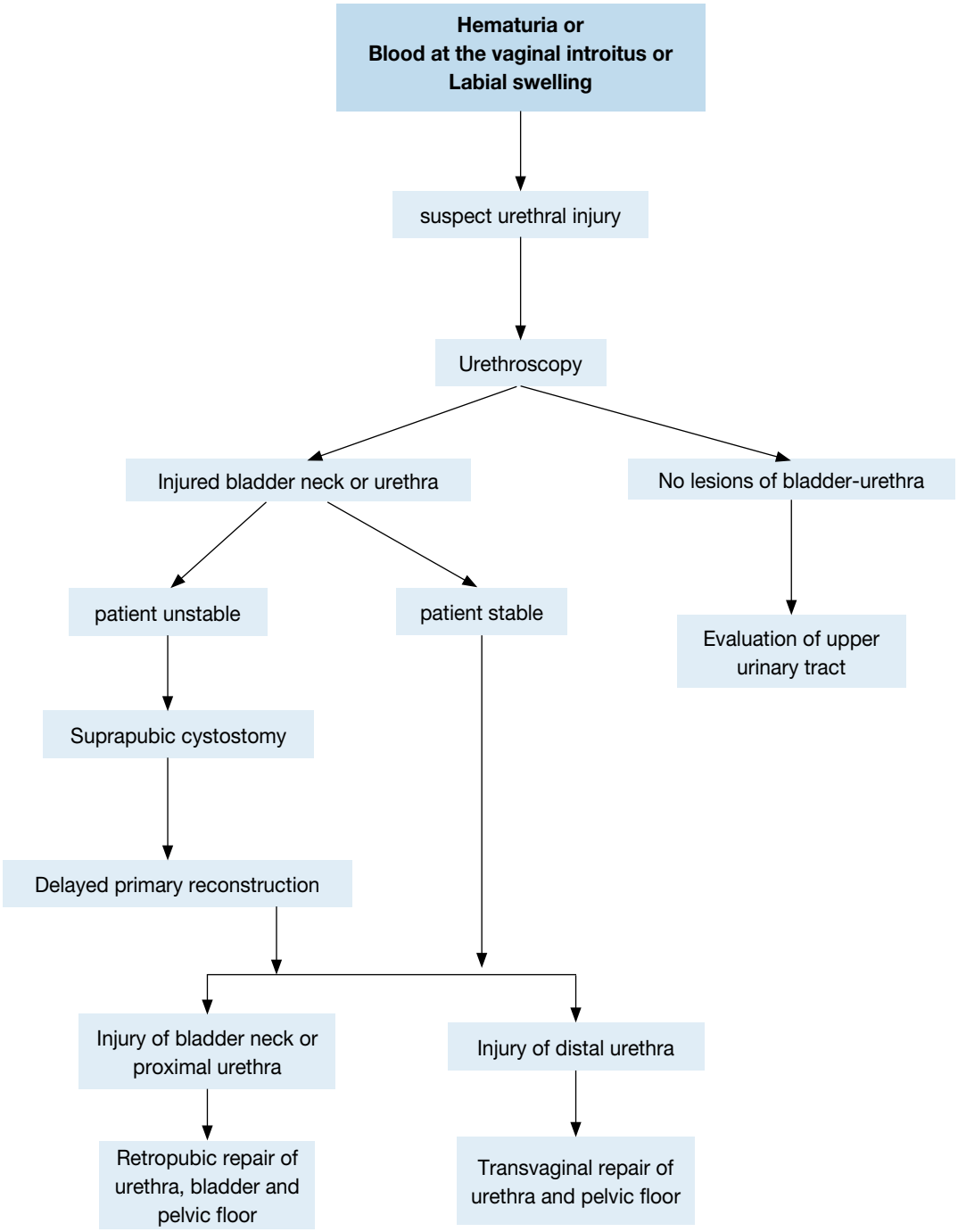


Figure 7: Management of urethral injuries in women



5.5 Iatrogenic urethral trauma

5.5.1 ***Introduction***

The most common form of iatrogenic urethral trauma is that caused by instruments. Most of the relevant urethral lesions caused by iatrogenic trauma are strictures. These strictures are of variable location and severity. They often require different management strategies (128,129).

5.5.2 ***Iatrogenic urethral trauma caused by catheterisation***

The majority of iatrogenic lesions are the result of improper or prolonged catheterisation. They are surprisingly common and account for 32% of urethral strictures. Of these, 52% affect the bulbar and/or prostatic urethra (129) (LE: 3).

Improper insertion of a urethral catheter is a preventable cause of urethral trauma in male patients (130) (LE: 4). The incidence of this type of urethral injury, especially weighed against the total number of urethral catheterisations performed in the same period of time, is difficult to evaluate, and there have been no statistical

data published on this matter so far. However, the risk to an individual patient of a urethral injury caused by improper catheterisation during a hospital stay has been estimated to be 3.2:1000 (129).

Prolonged catheterisation contributes to stricture formation (129). The anterior urethra is primarily affected. The bladder neck is rarely affected (131) (LE: 1b). Iatrogenic urethral injuries can be prevented by the implementation of educational programmes for medical practitioners that are designed to decrease the exposure of patients to catheter-related risk factors (such as prolonged catheterisation and improper catheterisation) (132) (LE: 2b).

*5.5.3 **Iatrogenic urethral trauma caused by transurethral surgery***

Transurethral procedures, especially transurethral resection of the prostate (TURP), are the second most common cause of iatrogenic urethral lesions. Electrical dispersion generated by unipolar electric current and direct urethral injury related to the diameter of the instruments used are factors (133) (LE: 1b). Risk factors include:

- large prostate volume;
- the presence of prostate cancer;
- inexperienced surgeon.

Another cause of stricture formation following transurethral procedures is the form of post-operative urinary drainage used. Urethral catheterisation following transurethral procedures such as TURP, and general post-operative urinary drainage with silicone Foley catheters, both result in a higher incidence of stricture development (134) (LE: 1b).

*5.5.4 **Iatrogenic urethral trauma related to surgical prostate cancer treatment***

A major source of iatrogenic urethral trauma is the treatment of prostate cancer. Urethral stricture after prostate cancer treatment can occur anywhere from the bladder neck to the meatus. The rate of bladder neck contracture after radical prostatectomy lies between 0.5% and 32%, varying according to the definition of stricture and individual practice (135,136) (LE: 2a).

The incidence of urethral stricture after multiple forms of prostate cancer therapy is determined from the CaPSURE database, a registry of men with biopsy-proven prostate cancer. The incidence varies from 1.1-8.4%, depending on the form of cancer treatment. The risk is highest after radical prostatectomy or brachytherapy plus external beam radiotherapy. Stricture formation after prostatectomy occurred within the first 24 months, whereas onset was delayed after radiation therapy. In a multivariate analysis, the type of primary treatment, age and obesity were found to be significant predictors for stricture development (135) (LE: 2b).

New surgical methods, such as robot-assisted prostatectomy can also cause iatrogenic trauma. In a recent study, bladder neck contracture was found in 2% of these patients. This correlates to the stricture rate found after conventional radical prostatectomy (137) (LE: 2b).

*5.5.5 **Iatrogenic urethral trauma related to radiotherapy for prostate cancer treatment***

Prostate brachytherapy (BT), external beam radiotherapy (EBRT), or a combination of the two are options for selected patients as the primary treatment for prostate cancer. Any of these options can cause urinary fistulas, with an incidence of 0.3-3% for patients after BT, and 0.0-0.6% of those treated with EBRT. Most fistulas will involve the rectum (138,139) (LE: 3).

*5.5.6 **Iatrogenic urethral trauma related to major abdominal surgery***

Iatrogenic injuries to the urethra can occur after abdominal and pelvic procedures. Pre-procedure bladder catheterisation must be performed to prevent or to reveal these complications (140) (LE: 2).

*5.5.7 **Symptoms of iatrogenic urethral injury***

The symptoms of urethral injury caused by improper catheterisation or use of instruments are:

- penile and/or perineal pain (100%);
- urethral bleeding (86%) (4) (LE: 2b).

Failure accurately to diagnose and treat urethral injuries may lead to significant long-term sequelae (141).

*5.5.8 **Diagnosis***

The diagnostic investigation of iatrogenic urethral trauma does not differ from that of other urethral injuries.

*5.5.9 **Treatment***

Temporary urethral stenting with an indwelling catheter is a good conventional therapeutic option for treating

acute false passage (142). The placement of a urethral catheter may be impossible, and endoscopic assistance or even placement of a suprapubic tube might be necessary (143) (LE: 3).

Iatrogenic prostatic urethral strictures after radical prostatectomy can be successfully treated by endoscopic management, either by incision or resection. Failure rates can be high, and repeat therapy might be necessary. The alternative is an indwelling catheter, urethral dilatation or open procedures. Open procedures might be required to salvage recurrent cases, but have increased morbidity (144) (LE: 2b).

Conservative treatment in patients with urethral lesions caused by radiotherapy is often ineffective. Major surgery or lifelong suprapubic diversion might ultimately be necessary (138,139) (LE: 3).

Table 14 details the most common causes of stricture, and Figures 8-10 show flow diagrams for the treatment of stricture after urethral injury due to improper insertion of a catheter, radical prostatectomy, and major abdominal surgery or radiotherapy, respectively.

Table 14 Aetiology of stricture

Causes of stricture
Improper catheterisation
Transurethral surgery
Prostate cancer surgery
Prostate cancer radiotherapy
Abdominal and pelvic surgery

5.5.10 Recommendations for treatment: algorithms

Figure 8: Flow diagram of treatment for iatrogenic urethral injury caused by improper insertion of a catheter

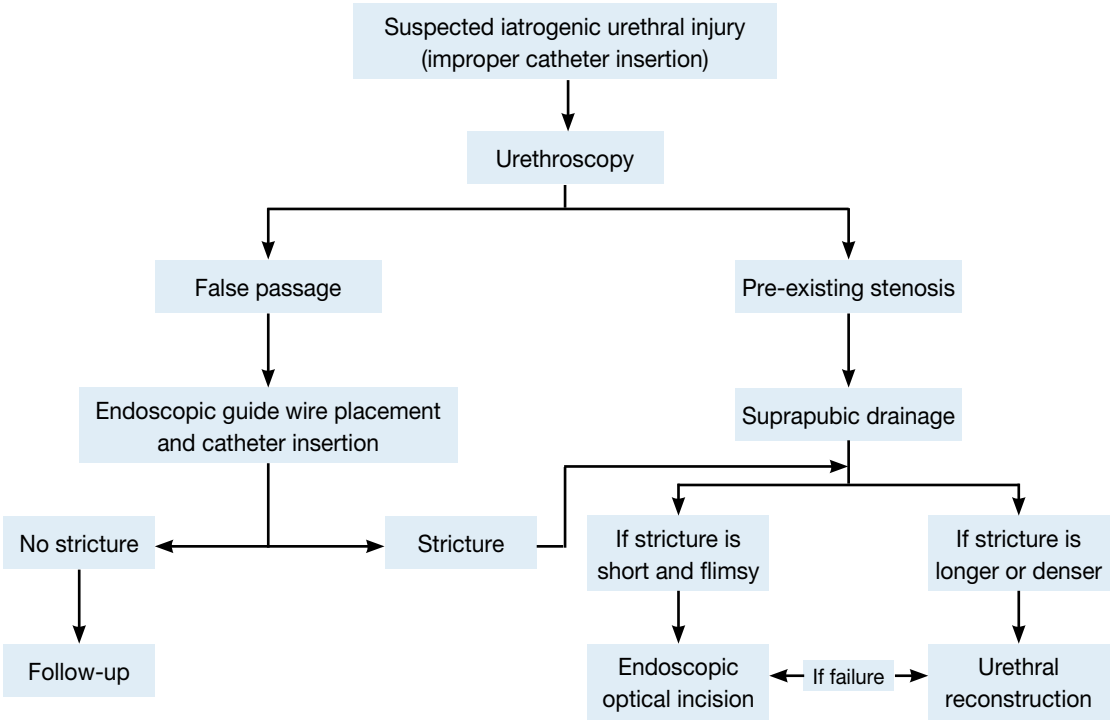


Figure 9: Flow diagram of treatment for stricture after radical prostatectomy

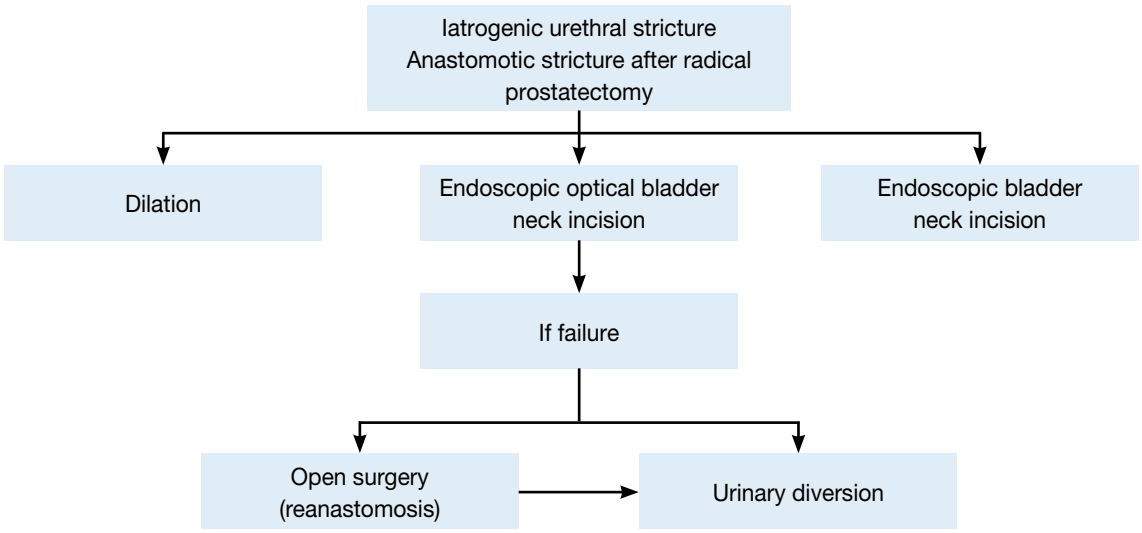
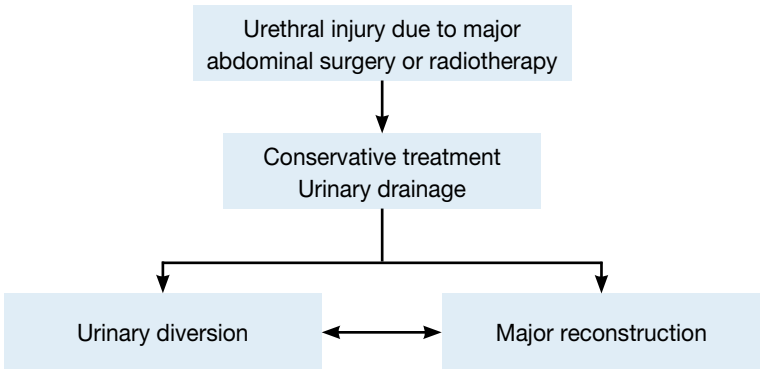


Figure 10: Flow diagram for treatment for stricture after major abdominal surgery or radiotherapy



5.5.11 ***Recommendations***

	GR
Avoid traumatic catheterisation.	A
Keep the length of time an indwelling catheter is present to a minimum.	B
Major abdominal and pelvic surgery should be undertaken with a catheter inserted.	B

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6. GENITAL TRAUMA

6.1 Background

Traumatic injuries to the genitourinary tract are seen in 2-10% of patients admitted to hospitals (1-5). Of these injuries, between one-third and two-thirds of cases are associated with injuries to the external genitalia (1). The

incidence of genital trauma is higher in men than in women, not only because of anatomical differences but also due to increased exposure to violence, the performance of aggressive sports, and a higher incidence of motor vehicle accidents. In addition, an increase in domestic violence has led to an increase in gunshot and stab wounds over the last several years (6-9). Approximately 35% of all gunshot wounds are affiliated with genital injuries (10).

Genitourinary trauma is seen in all age groups, most frequently in males between 15-40 years. However, 5% of patients are less than 10 years old (10). Genitourinary trauma is commonly caused by blunt injuries (80%) but the risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum, bowel) after blunt trauma is higher in females than in males.

Penetrating external genital trauma is seen in about 20% with 40-60% of all penetrating genitourinary lesions involving the external genitalia (11-13).

In men, blunt genital trauma frequently occurs unilaterally. Only 1% present as bilateral scrotal or testicular injuries (10). Penetrating scrotal injuries affect both testes in 30% of cases (10,14). In both genders, penetrating genital injuries occur with other associated injuries in 70% of patients.

The accurate diagnosis and treatment of patients with penetrating injuries are of utmost importance.

However, it is essential that physicians and nurses treating trauma patients are aware of an increased risk of hepatitis B and/or C infection in this cohort (7). Recently, a 38% infection rate with hepatitis B and/or C was reported in males with penetrating gunshot or stab wounds to the external genitalia (7). This was significantly higher compared to normal population, and exposes emergency staff to an increased risk.

6.2 Pathophysiology

Proper management of genital trauma requires information about the accident, involved persons, animals, vehicles, and weapons order to estimate the injury and potential risk of associated lesions.

6.2.1 ***Blunt trauma***

In males, a direct blow to the erect penis may cause penile fracture. Usually the penis slips out of the vagina and strikes against the symphysis pubis or perineum. This most frequently (60%) occurs during consensual intercourse (15). 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% (16,17).

Due to the thickness of the tunica albuginea in the flaccid state (approximately 2 mm), 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.

Blunt trauma to the scrotum can cause testicular dislocation, testicular rupture and/or subcutaneous scrotal haematoma. Traumatic dislocation of the testicle occurs rarely. It is most common in victims of motor vehicle accidents or auto-pedestrian accidents (18-21). Bilateral dislocation of the testes has been reported in up to 25% of cases (21). It can be classified as:

1. Subcutaneous dislocation with epifascial displacement of the testis;
2. Internal dislocation; in these cases, the testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity.

Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma (22). 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 50 kg is necessary to cause testicular rupture (23).

In females, blunt trauma to the vulva is rarely reported. The incidence of traumatic vulvar haematomas after vaginal deliveries has been reported as 1 in 310 deliveries (24). The frequency in non-obstetric vulvar haematomas is even lower, with only individual cases reported (25). 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% (26).

6.2.2 ***Penetrating trauma***

Penetrating trauma to the external genitalia is frequently associated with complex injuries of other organs. In children, penetrating injuries are most frequently seen after straddle-type falls or laceration of genital skin due to falls on sharp objects (10, 27).

Increasing civilian violence has led to a rising incidence of stab and/or gunshot injuries associated with injuries of the genitourinary tract. The extent of injuries associated with guns is related to the calibre and velocity of the missile (8). Handguns or pistols range from 0.22 to 0.45 calibre and produce bullet velocities of

200-300 meters/second (m/s). In addition, “magnum” handguns have larger gunpowder loads, and transmit 20-60% more energy than standard handguns due to the higher velocity of the missile. Injuries by rifles cause even more extensive lesions. Rifles have a calibre ranging from 0.17 to 0.460, with bullet velocities up to 1000 m/s.

Missiles with a velocity of approximately 200-300 m/s are considered “low velocity”. These bullets only induce a ‘permanent cavity’. The energy transmitted to the tissue along the projectile path is much less than in high-velocity missiles, so that tissue destruction in low-velocity guns is less extensive (8). High-velocity missiles (velocity of 800-1000 m/s) have an explosive effect with high-energy transmission to the tissue causing a ‘temporary cavity’ in addition to the permanent cavity. Due to the high-energy released, gaseous tissue vaporisation induces extensive damage often associated with life-threatening injuries.

Gunshot wounds are classified as penetrating, perforating or avulsive. Penetrating injuries are caused by low-velocity missiles, with bullets often retained in the tissue and a small, ragged entry wound. Perforating gunshot wounds are frequently seen in low to high-velocity missiles. In these cases, the missile passes through the tissue with a small entry wound, but larger, exit one. Serious injuries are associated with avulsive gunshot wounds caused by high-velocity missiles, with a small entry wound comparable to the calibre but a large tissue defect at the exit wound.

In any penetrating trauma, tetanus vaccination is mandatory and should be given using active (tetanus toxoid booster) and passive immunisation (250 IE human tetanus immunoglobulin) if the patient’s last immunisation was given more than 5 years ago (28). For current recommendations for tetanus vaccination, see information from the Robert Koch Institute, Germany (http://www.rki.de/cln_116/nn_504558/DE/Content/Infekt/Impfen/ImpfungenAZ/Tetanus/Tetanus_ImpfenA-Z_ges.html [Articles in German]).

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 *Pasturella Multicida*, which accounts for up to 50% of infections (28). Other commonly involved organisms are *Escherichia coli, Streptococcus viridans, Staphylococcus aureus, Eikenella corrodens, Capnocytophaga canimorsus, Veillonella parvula, Bacteroides* and *Fusobacterium spp*. (28-30).

The first choice of antibiotics is penicillin-amoxiclavulanic acid followed by doxycycline, cephalosporine or erythromycine for 10-14 days (31–33). 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 (34). 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 (34,35).

Genital bites from humans can rarely occur, but can also become infected. Wound infections in these cases may include *Streptococci, Staphylococcus aureus, Haemophilus spp., Bacteroides spp*. and other anaerobes. Transmission of viruses (e.g. hepatitis B, hepatitis C, human immunodeficiency virus [HIV]) following human bites is 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 (36).

Wound management should include cleaning with warm running water or disinfectants. Debridement should be conservative, due to the regenerative capacity of genital skin (36). Antibiotic therapy may be considered only in cases with infected wounds using amoxiclavulanic acid as first line therapy, or, alternatively clindamycin.

6.3 Risk factors

There are certain sports with an increased risk for genital trauma. Off-road bicycling and motorbike riding, especially on bikes with a dominant petrol tank, accidents from in-line hockey skating and rugby footballers have been associated with blunt testicular trauma (37-40). Any kind of full contact sports, without the use of necessary protective aids, may be associated with genital trauma.

Besides these risk groups, self-mutilation of the external genitalia have also been reported in psychotic patients and transsexuals (29).

6.4 Diagnosis

Investigating genital trauma requires information concerning the accident and a thorough history and physical examination, if possible. Trauma to external genitalia at any age may be due to abusive assault. In these cases, the extraordinary emotional situation of the patient must be considered and the privacy of the patient respected. In suspicious cases, a sexual assault forensic exam is necessary. Swabs or vaginal smears should be taken for detection of spermatozoa (27) and local legal protocols followed closely. A thorough history and

examination (in some cases under anaesthesia), photodocumentation, and identification of forensic material may be important. Genital injury is seen frequently (42%) after sexual abuse, and must be considered when such injuries present at any age (41). 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 (42-43).

In patients with gunshot wounds to the genitals several pieces of information will be useful: close or far range, calibre and type of weapon. Get a urinalysis. The presence or macro- and or microhaematuria requires a retrograde urethrogram in males (see above Chapter 4, Urethral trauma). In females, flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury (26,44). In women with genital injuries and blood at the vaginal introitus, further gynaecologic investigation to exclude vaginal injuries (44). 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.

6.4.1 ***Blunt penile trauma***

6.4.1.1 Penile fracture

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 if the hematoma is not too large. Physical exam and history usually confirm the diagnosis, but in rare cases imaging may be required.

Cavernosography or MRI (45-47) can identify lacerations of the tunica albuginea in unclear cases (48). In case of tunical laceration, surgical correction with suturing of the ruptured area is indicated.

6.4.2 ***Blunt testicular trauma***

Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting. The hemiscrotum is tender, swollen, and eccymotic. The testis itself may be difficult to palpate. High-resolution, real-time ultrasonography with a high resolution probe (minimum 7.5MHz or higher) should be performed to determine intra- and/or extratesticular haematoma, testicular contusion, or rupture (49-57). In children, scrotal ultrasonography must be performed with a 10-12MHz probe.

The literature is contradictory as to the real usefulness of US over exam alone. Some studies report convincing results with accuracy of 94% (29,49,54,55). Others reported poor specificity (78%) and sensitivity (28%) for differentiation of testicular rupture or haematocele, and accuracy as low as 56% (52).

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 (58). 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.

6.4.3 ***Blunt female trauma***

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 (27,44).

6.4.4 ***Penetrating trauma***

In penetrating trauma of the external genital in men, urethrography should be performed in all patients (irrespective of urinalysis). Associated pelvic or abdominal trauma may also require an abdominal CT. CT cystography should be performed in pelvic injuries associate with microhaematuria. In females, the use of diagnostic laparoscopy for identification of intraperitoneal injuries has been reported prior to explorative laparotomy (27). This approach is only reasonable in haemodynamic stable patients, in whom CT cannot exclude presence of associated bowel injuries or significant intra-abdominal bleeding.

6.5 Treatment

6.5.1 ***Penile trauma***

6.5.1.1 Blunt trauma

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 (13).

Benign penile injuries can be distinguished from penile fracture, because fracture is always associated with rapid post-traumatic detumescence. In penile fracture, surgical intervention with closure of the tunica albuginea is recommended. Closure can be obtained by using either absorbable or non-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% (15,59). 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 (59). Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% (15,59).

6.5.1.2 Penetrating trauma

In penetrating penile trauma, surgical exploration and conservative debridement of necrotic tissue is recommended in most severe injuries. Non-operative management is recommended in small superficial injuries with intact Buck's fascia (13). 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 (29). In extended loss of penile shaft skin, split-thickness grafts can be placed, either acutely or after the wound bed has been prepared by several days of wet/dry dressing changes and infection is under control. McAninch *et al*. recommended the use of a skin graft thickness of at least 0.015 inch in order to reduce the risk of contraction (29).

6.5.2 ***Testicular trauma***

6.5.2.1 Blunt trauma

Blunt trauma to the scrotum can cause significant haematocele even without testicular rupture. Conservative management is recommended in haematoceles smaller than three times the size of the contralateral testis (6).

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 (10,22,29,60,61).

Early surgical intervention resulted in > 90% preservation of the testis whereas delayed surgery necessitates orchiectomy in 45-55% (22). Additionally, non-operative management is associated with prolonged hospital stays. Large hematocoles 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 nonoperatively may need delayed surgery if they develop infection or undue pain.

In testicular rupture, surgical exploration with excision of necrotic testicular tubules and closure of the tunica albuginea is indicated. This results in a high rate of testicular preservation and normal endocrine function. Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.

6.5.2.2 Penetrating 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 (62). Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although there are only a few cases reported (62). 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 (13).

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 scrotum (29). Local wound management with extensive initial wound debridement and washout is important for scrotal convalescence.

6.5.3 ***Vulvar injuries***

Blunt trauma to the vulva is rare and commonly present as a large haematoma. 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 (25-27,44), 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 (63).

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 (44). 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.

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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;
- civilian terrorism.

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 **A**irway compromise, **B**reathing failure and/or **C**irculatory 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 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 over-triage, 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 (**A**irway, **B**reathing, **C**irculation, **D**isability or neurological status, **E**xposure) 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 injures 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. CT 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 ueretropyelography 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 post-operatively.

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 post-operatively (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).

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 (11,25). 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.

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8. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AAST	American Association for the Surgery of Trauma
ATLS	advanced trauma life support
BT	Transperineal, interstitial, permanent prostate brachytherapy
BUN	blood urea nitrogen
CT	computed tomography
DMSA	dimercaptosuccinic acid
EBRT	External beam radiotherapy
ePTFE	polytetrafluoroethylene
GR	grade of recommendation
HIV	human immunodeficiency virus
hpf	high-power field
ICU	intensive care unit
IVP	intravenous pyelography/pyelogram
IVU	intravenous urography
KUB	kidney-ureter-bladder
LE	level of evidence
MRI	magnetic resonance imaging
m/s	metres per second
PCNL	percutaneous nephrolithotomy
rbc/hpf	red blood cells per high-power field
TOT	transobturator tape
TURP	Transurethral resection of the prostate
TVT	tension-free vaginal tape
US	Ultrasonography

Conflict of interest

All members of the Urological Trauma Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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 Pain Management

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European Association of Urology

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1. INTRODUCTION

1.1 The Guideline

The European Association of Urology (EAU) Guidelines Working Group for Pain Management have prepared this guidelines document to assist medical professionals in appraising the evidence-based management of pain in urological practice. These guidelines include general advice on pain assessment, with a focus on treatment strategies relating to common medical conditions and painful procedures. No attempts have been made to exhaustingly cover the topic of pain.

The multidisciplinary panel of experts responsible for this document include three urologists, two radiotherapists and two anaesthesiologists.

*1.1.1 **Methodology***

The recommendations provided in the current guidelines are based on systematic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles.

It has to be emphasised that the current guidelines contain information for the treatment of an individual patient according to a standardised general approach.

1.2 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 “Peri-operative 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 2012 edition contains partial updates based on the available literature and two new topics were added, Section 3.4 “Denusomab” and Section 3.5 “Palliative care”. A quick reference document presenting the main findings of the General 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/.

1.3 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)*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	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, 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 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)*

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

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

1.4 References

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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 responsible for the perception of pain (2).

Acute pain - usually occurring in response to an identifiable noxious event with stimulation of the nociceptive system - 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 What is suffering?

Pain is a complex experience entailing physiological, sensory, affective, cognitive, and behavioural components. An individual's perception of the intensity of pain relates to the interactions of physical, psychological, cultural and spiritual factors (6).

Pain and suffering are closely identified, but are nevertheless distinct. Patients can experience severe pain without suffering (e.g. during childbirth), and suffering can include physical pain, but it is by no means limited to it. Patient distress also results from factors other than pain that add to suffering, such as anxiety, depression, nightmares, change in body perception, and changes in professional and social function.

The differences between pain and suffering are most pronounced in cancer pain patients. Cancer is one of the medical conditions patients fear most, because of the expectation that it will end in death, and that that death will be while in excruciating pain (7,8).

2.3 Nociception and innervation

Structure of the peripheral neural apparatus

Sensory information from the skin is transmitted to the central nervous system (dorsal horn of the spinal cord) via three different types of primary sensory neurones: Aβ-, Aδ-, and C-fibres.

These primary afferent neurones are responsible for transducing mechanical, chemical, and thermal information into electrical activity. Although all three classes can transmit non-nociceptive information, under physiological circumstances only C-fibres (dull pain) and Aδ-fibres (sharp pain) are capable of transmitting nociceptive information from the periphery to the dorsal horn of the spinal cord. Thus, under normal circumstances, Aβ-fibres are responsive only to non-noxious mechanical stimuli, including touch, vibration and pressure (9-12). Nociceptive information for the viscera reaches the central nervous system along the sympathetic chains and pelvic parasympathetic chain. However, the density of visceral afferents is low compared with the skin, which can explain the poor localisation of noxious stimuli in the viscera (responsible for the diffuse nature of visceral pain) (13).

2.4 Neuropathic pain

Definition of neuropathic pain

Neuropathic pain is defined by the IASP as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system' (2). While this definition has been useful in distinguishing some characteristics of neuropathic and nociceptive types of pain, a more precise definition has been developed (14): pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Where possible, neuropathic pain should be divided into peripheral or central neuropathic pain based on the anatomic location of the lesion or disease.

Both negative and positive sensory symptoms may be present. Positive signs include pain, paraesthesia, dysaesthesia, hyperalgesia, and allodynia. Negative signs involve sensory deficits (hypoaesthesia and hypoalgesia), weakness, and reflex changes. Clinically, patients may complain of spontaneous ongoing pain (stimulus-independent pain) that is burning, with intermittent shooting or electric shock-like (lancinating) sensations, and/or have pain hypersensitivity evoked in response to stimuli (stimulus-evoked pain) such as hyperalgesia and allodynia (15,16).

Mechanisms of neuropathic pain

A change in function, chemistry, and the structure of neurones (neural plasticity) leads to the production of the altered sensitivity characteristics of neuropathic pain. Peripheral sensitisation acts on the nociceptors, and central sensitisation takes place at various levels ranging from the dorsal horn to the brain. In addition, abnormal interactions between the sympathetic and sensory pathways contribute to mechanisms mediating neuropathic pain (17,18).

2.5 Innervation of the urogenital system

The differences between the mechanisms of nociception in the skin and viscera have been emphasised by studies of the response properties of visceral afferents from the urinary tract (19-21). (see also EAU Guidelines "Chronic Pelvic Pain", Chapter 2)

Ureter

The only sensation that can be evoked from the ureter is pain, whereas other organs such as the bladder can give rise to several sensations ranging from mild fullness to pain.

Ureteric afferents are thinly myelinated or unmyelinated, and respond to direct probing of a limited area of tissue. Two populations of afferents have been distinguished by Cervero and Jänig (22). The first responds to contractions of the ureter and is also excited by low levels of distension. The second group does not respond to peristaltic contractions of the ureter, but it is excited by distension with a wide range of thresholds (22).

Activation of muscarinic and adrenergic receptors increases the amplitude of urteral contractions. The sympathetic nerves modulate contraction by α-adrenoceptors and relaxation by α-adrenoceptors. The purinergic system is important in sensory/motor functions. Important non-adrenergic non-cholinergic transmitters are ATP, nitric oxid (NO) and serotonin, as well as the prostataglandins F2, E1 and E2 (23). Understanding ureteral function and physiology is the basis for developing new drugs, for example, in renal colic (23).

Urinary bladder

Two distinct groups of afferent fibres capable of signalling noxious stimuli have been identified in the urinary bladder. Most visceral afferents from the urinary bladder are unmyelinated fibres, although a population of

myelinated A-fibres is also present (18). The majority of visceral primary afferents from the bladder, urethra and reproductive and other pelvic organs encode for both noxious and non-noxious stimuli (19-21).

Graded distension of the healthy urinary bladder in humans initially gives rise to a sensation of fullness and eventually pain as volume increases and intravesical pressure exceeds 25-35 mmHg (19-21). In the inflamed bladder, the sensations during bladder emptying become unpleasant and painful. Nearly all afferents are small, myelinated or unmyelinated, and travel with sympathetic (hypogastric) or parasympathetic (pelvic) nerves.

Male reproductive organs
The sensory innervation of the testes (dog model) shows that more than 95% of the fibres of the superior spermatic nerve are unmyelinated, with the great majority having polymodal properties (i.e., responding to mechanical, chemical and thermal stimuli) (24). Myelinated and unmyelinated afferent fibres form a homogeneous group with polymodal receptors in testes and/or epididymis. Prostaglandins do not excite but sensitise the afferents to other stimuli (25).

2.6 Pain evaluation and measurement

*2.6.1 **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 PQRST characteristics:

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?'

Pain in patients with cancer is a complex phenomenon. Not all pains will be of malignant origin, they will often have more than one pain problem, and each pain must be individually assessed and evaluated. A key principle is constantly to re-evaluate pain and the effect and side-effects of analgesic therapy.

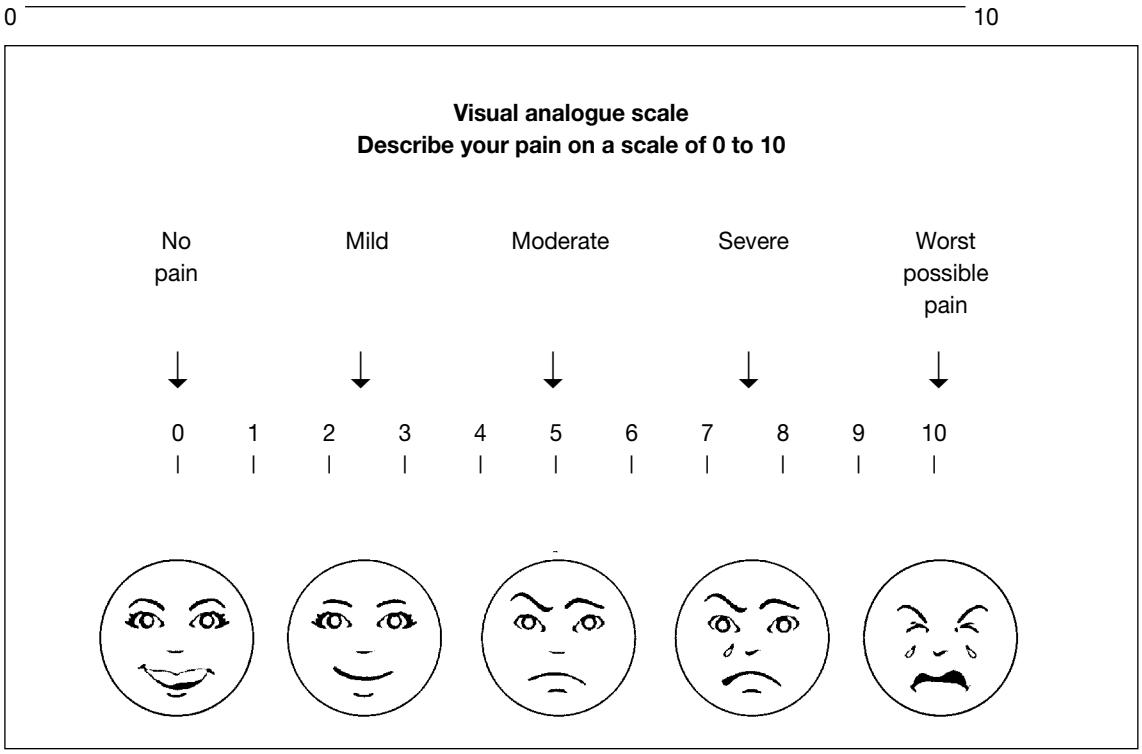
Pain in cancer patients could be caused by the cancer itself, be due to secondary muscular spasm, be secondary to cancer treatments, or have no relation to the cancer, e.g. arthritis.

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 central nervous system. 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 anti-convulsants should be used in the first instance.

*2.6.2 **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, Figure 1) 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.

Figure 1: Visual analogue scale



To study the effects of both physical and non-physical influences on patient well-being, 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) (26-30).

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3. CANCER PAIN MANAGEMENT (GENERAL)

3.1 Classification of cancer pain

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, 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 (1).

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 (2). 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 (3). Patients with severe neuropathic pain are a special challenge. Psychological changes frequently occur, and specific therapeutic intervention may be necessary (4).

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 (5).

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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, 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 are sometimes in particular need of invasive measures, not only to relieve pain in the terminal phase, but also to improve the general QoL, despite the potential for surgery to 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 (LE: 4):

- 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).
- 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 where comfort is the overriding goal can elect to be deeply sedated.

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 (1-3). 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 (4) (LE: 2b).

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3.3.2 ***Radionuclides***

3.3.2.1 Clinical background

Bone metastases are the most frequent source of pain during the evolution of cancers (1). Approximately 30% of patients with osseous metastases have pain that requires analgesia, interfering with QoL, causing anxiety, isolation, immobility, depression, and sleeplessness (1).
In single lesions, bone stability and pain reduction can be achieved by external beam radiotherapy (LE: 1b) (GR: A). About 80-90% of patients will experience durable pain relief, but many will develop further multiple painful metastases (1).

3.3.2.2 Radiopharmaceuticals: physical characteristics

- Strontium-89 chloride (^{89}Sr) emits a beta particle with a maximum energy of 1.46 MeV, a mean energy of 0.58 MeV, an average soft-tissue range of 2.4 mm and 0.01% abundant gamma emission with a 0.91 MeV photopeak. The physical half-life is 50.5 days (2,3).
- Samarium-153 lexidronam (^{153}Sm) emits a beta particle with a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV, an average soft-tissue range of 0.6 mm and 28% abundant 0.103 MeV gamma emission with a 0.103 MeV photopeak. The physical half-life is 1.9 days (4).

- Renium-186 etidronate (^{186}Re) emits a beta particle with a maximum energy of 1.07 MeV, a mean energy of 0.349 MeV, an average soft-tissue range of 1.1 mm and a 9% abundant gamma emission with a 0.137 MeV photopeak. The physical half-life is 3.7 days (5).
- Therapy in this context means the intravenous administration of ^{89}Sr or ^{153}Sm (^{153}Sm ethylenediaminetetramethylenephosphonate [EDTMP]).

The most important radiopharmaceuticals are ^{89}Sr, ^{153}Sm and, to a lesser extent, ^{186}Re. There is no clear difference in treatment response between them (2), but, because of the differences in half-life, there is a difference in onset and duration of response, and in toxicity. For ^{153}Sm and ^{186}Re, the onset of response is rapid but duration is shorter (6,7). Note that ^{186}Re is no longer used in many European countries.

3.3.2.3 Indications and contraindications

^{89}Sr and ^{153}Sm are indicated for the treatment of bone pain resulting from skeletal metastases involving more than one site and associated with an osteoblastic response on bone scan but without spinal cord compression (1,8-15) (LE: 2, GR: B).

^{89}Sr and ^{153}Sm have no place in the management of acute or chronic spinal cord compression or in treating pathological fracture (1,8,11) (LE: 2, GR: B).

Some 60-80% of patients presenting with osteoblastic metastases benefit from ^{89}Sr and/or ^{153}Sm (1) (LE: 2). The choice between the two depends solely on practical considerations. ^{89}Sr and/or ^{153}Sm should be administered by a slow (^{89}Sr) or bolus (^{153}Sm) injection using an intravenous (iv) catheter. The recommended doses are 148 MBq (^{89}Sr) (16) and 37 MBq/kg (^{153}Sm) (1,16) (LE: 2).

About 10% of patients experience a temporary increase in bone pain (pain flare) (3,6,7,17), generally 2-4 days after ^{153}Sm, and 1-2 weeks after ^{89}Sr (acute side-effect) (1,4,8,11,12,15,18). Pain flare is associated with a good clinical response (LE: 2) (3,6,7,17), 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. Analgesics should therefore be continued until bone pain improves (GR: B). Late side-effects include temporary myelosuppression (platelets, white blood cells). Recovery occurs 4-6 weeks later depending on bone marrow reserve. There is generally no significant effect on haemoglobin.

The patient can pose a radiation exposure risk for 2-4 days after ^{153}Sm, and 7-10 days after ^{89}Sr (4,8,11,13-15,18-23) (LE: 2). Information about radioprotection should be provided (GR: B).
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 (1,2,23) (LE: 2, GR: B). The response rate for second and subsequent treatments may be lower than for the first (1,8,12,23) (LE: 2).

3.3.2.4 Contraindications

Absolute contraindications:

- During or within 4 weeks of myelotoxic chemotherapy (all compounds except cisplatin), or within 12 weeks of hemibody external radiation therapy. The delay between these treatments and metabolic radiotherapy is necessary to avoid severe haematopoietic toxicity. However, treatment can be safely combined with limited local field external beam radiotherapy (LE: 3, GR: C).
- Known hypersensitivity to EDTMP or similar phosphonate compounds for ^{153}Sm (1).
- Glomerular filtration rate (GFR) < 30 mL/min (1,2).
- Pregnancy; continued breastfeeding (2).

Relative contraindications:

- Not recommended for women of child-bearing age (negative pregnancy test and contraception mandatory).
- In acute or chronic severe renal failure (GFR 30-60 mL/min), the dose administered should be adapted: if the GFR is > 60 mL/min, reduce the normal dosage by 25%; if the GFR is 30-60 mL/min, reduce the normal dosage by 50% (LE: 4). GFR should be measured if creatinine is > 20 mg/L.
- With a single painful lesion: external limited field radiotherapy should be performed (16,24) (LE: 1b).

Caution:

Caution must be used in the following circumstances.

- Risk of fracture.
- Nerve or spinal cord compression that requires other treatments in an emergency: external radiotherapy or surgery, or a combination of the two.
- Urinary incontinence: special recommendations including catheterisation before administration of the radionuclide. The catheter should remain in place for 4 days (^{89}Sr), 3 days (^{186}Re), and 24 hours (^{153}Sm), respectively (2) (GR: A).

- Compromised bone marrow reserve.
- White blood cell count of < 2500/µL (LE: 4) (preferably > 3500/µL according to European Association of Nuclear Medicine guidelines) (2).
- Platelets < 80,000/µL (LE: 4) (preferably > 100,000/µL according to the European Association of Nuclear Medicine guidelines) (2).
- Haemoglobin < 90 g/L (2).

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3.3.3 ***Radiotherapy for metastatic bone pain***

3.3.3.1 Clinical background

Radiotherapy alleviates metastatic bone pain in the majority of patients (1) (LE: 1a). Pain relief is obtained in 50-80% of patients, with complete pain relief at the treated site in up to 30% of patients (1,2) (LE: 1a). The onset of pain relief varies from a few days to 4 weeks (1) (LE: 2b). Re-irradiation should therefore not be considered sooner than 4-6 weeks after the initial radiotherapy. The median duration of pain relief reported by most studies is 3-6 months (1) (LE: 1a).

3.3.3.2 Mechanism of pain relief by radiotherapy

Tumour shrinkage and inhibition of the release of chemical pain mediators are the main mechanisms by which radiotherapy relieves pain. Tumour shrinkage is unlikely to account for early pain relief, which is hypothesised to involve early-reacting and sensitive cells, as well as the molecules that they produce. Obvious candidates are the inflammatory cells present in the bone metastasis microenvironment. Reduction of these cells by ionising radiation inhibits the release of chemical pain mediators, and is probably responsible for the rapid reaction seen in some patients. Another possible mechanism for the analgesic action of ionising irradiation includes its direct effect on osteoclast activity (3) (LE: 3).

3.3.3.3 Imaging

The detection of bone metastases is usually based on 99m technetium bone scintigraphy, which lacks diagnostic specificity (11) (LE: 3), but the addition of single photon emission computed tomography (SPECT) to planar acquisition has been reported to improve its diagnostic accuracy (12-14) (LE: 2b). Regions of increased uptake need further investigation. Plain films have a false-negative rate of 10-17% (LE: 3). At least 50% erosion must be present for a change to be seen on plain films (15) (LE: 3). The combination of bone scintigraphy and plain films results in specificity of 64% and sensitivity of 63% (16) (LE: 3).

Because of the complex anatomy of the vertebrae, computed tomography (CT) is more useful than conventional radiography for evaluating the location of lesions and analysing bone destruction and condensation (17). When combined with myelography, excellent information about the bony anatomy and an accurate view of the compressed neural elements is provided (18-19) (LE: 3). However, CT myelography is invasive and time-intensive, and so, particularly when spinal cord compression is suspected, magnetic resonance imaging (MRI) is currently the gold standard for detection and therapeutic management (20-24) (LE: 2b), with sensitivity of 93% (25) (LE: 3) and specificity of 96% (25) (LE: 3).

3.3.3.4 Radiotherapy scheme

Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (1, 4-8) (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single-fraction radiotherapy (1,9) (LE: 1a).

Single-fraction radiotherapy is the treatment of choice for alleviating bone pain because of its greater convenience for patients (LE: 1a), as well as faster patient turnover for the radiotherapy unit (10) and lower costs (5,11) (LE: 3). The recommended dose is 8 Gy (LE: 1a) (1,4-8,12,13). Pain relief can be achieved in a significant number of patients with lower doses (LE: 1b), but some studies have indicated that 4 Gy is less effective than 8 Gy (1) (LE: 1b). A dose of 6 Gy gives similar results to 8 Gy but has been insufficiently studied (1) (LE: 1b). A dose of 8 Gy in combination with zoledronic acid is associated with a longer period without skeletal events, compared to 6 Gy with zoledronic acid (14).These lower doses should be borne in mind if a third retreatment is necessary, or if there is concern about radiation tolerance (1) (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).

3.3.3.5 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%. The level of neurological function at the start of treatment determines the functional outcome (15). A delay in treatment, surgery or external radiotherapy is the most common cause of an unfavourable outcome. Magnetic resonance imaging is the best tool for diagnosing MSCC (16).

Corticosteroids reduce oedema and might have an oncolytic effect on certain tumours, such as lymphoma, breast cancer and leukaemia. However, the extent of the benefit obtained from corticosteroids and the optimal dosage are unclear. High-dose corticosteroids carry a significant risk of adverse affects. One randomised controlled trial of patients with carcinomatous MSCC has compared radiotherapy with or without dexamethasone, and showed significantly better functional outcome when dexamethasone was added (17) (LE: 1b).

Radiotherapy is generally the treatment of choice. Surgery is reserved for a selected group of patients who meet the criteria listed below.

To date, there is no standard radiotherapy regimen for MSCC. In general, 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 (e.g., 1 × 8 Gy (18) or 2 × 8 Gy (19) (LE: 1b). A small randomised trial, including patients with MSCC and a short life-expectancy (≤ 6 months), has compared a short-course (2 × 8 Gy) with a split-course (5 × 3 Gy followed by 3 × 5 Gy) radiotherapy regimen, and has concluded that there were no significant differences in functional outcome or toxicity (19).

Several uncontrolled surgical trials (20-22) and one meta-analysis (23) 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

Absolute criteria	**Surgery**	**Radiotherapy**
Operability	Medically operable	Medically inoperable
Duration of paraplegia	< 48 h	≥ 48 h
Life expectancy	> 3 months	< 3 months
Radiosensitivity		Highly sensitive
Relative criteria		
Diagnosis of primary tumour	Unknown	Known
Bone fragments with compression	Present	Absent
Number of foci of compression	1 focus	> 1 foci

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 (24) (LE: 1b).

3.3.3.6 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 (25).

3.3.3.7 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 (9).

The side effects are mostly transient, lasting a few days and include:

1) pain flare (within 24 h and due to oedema). Pain flare is common after palliative radiotherapy for bone metastases, and patients should be counselled accordingly and given breakthrough opioids. Patients receiving single-fraction radiotherapy may be at higher risk than those receiving multifraction radiotherapy (26). 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 (LE: 3) (27).
2) symptoms depend on the treatment field and location and can include:
   - nausea (especially with larger fields)
   - diarrhoea
   - irritation of the throat and oesophagus.

3.3.3.8 References

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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 (1,2). There is evidence that highly emotional cancer patients, as detected through their own narratives, experience less pain than their less emotional counterparts (3).

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 take advantage of this type of treatment (4). In this setting, structured psychotherapy seems to be more effective than antidepressant medication (5). Interestingly, effective psychological management results in a reduction in depressive complaints, inflammatory markers, pain, and fatigue in cancer patients (6).

Cognitive behavioural therapy (CBT), such as relaxation and distraction, can provide pain relief (7-9). 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 (10-12). Virtual consultation and automated symptom monitoring for cancer patients with depression can exceed all expectations (13). It has also been suggested that CBT is particularly helpful for younger cancer patients (14).

Families can be exposed to poor functioning 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 (15). Other psychological interventions targeted to minimise caregiver emotional distress have not been effective (16).

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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 (1-3). Nevertheless, certain manipulations (e.g., sciatic nerve press) seem to be effective for immediate pain relief in many oncological conditions (4). The notion that acupuncture may be effective for cancer patients is not methodologically supported by the currently available data (5). However, modest although significant improvements in depression and pain scales have been confirmed by well-conducted studies on acupuncture (6). Evidence from robust studies is still lacking on the effect of traditional Chinese medicine and complementary alternative medicine (7,8). Physical exercise (short walks) can positively affect the pain experience of prostate cancer patients (9). Similarly, moderate exercise positively affects cancer-related sleep disturbance (10).

Transcutaneous electrical nerve stimulation might mitigate hyperalgesia in cancer patients. Unfortunately, reliable studies in this field are lacking (11).

Listening to music - an otherwise harmless activity - slightly reduces distress, pain intensity and opioid requirements in cancer patients (12,13).

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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 ***Antibiotics***

Antibiotics may be analgesic when the source of the pain involves infection (e.g. pyonephrosis, abscess, osteitis pubis). In some cases, infection may be occult and confirmed only by the symptomatic relief provided by empirical treatment with these drugs (1) (LE: 2b).

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3.4.2 ***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 value even in the absence of significant tumour shrinkage (1) (LE: 1a).

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3.4.3 ***Bisphosphonates***

Bisphosphonates are pyrophosphate analogues.

3.4.3.1 Mechanisms of action

- Inhibition of bone resorption: beginning 24-48 hours after administration, the 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.

3.4.3.2 Effects and side-effects

The main effects are:

- decrease of the risk of skeleton-related events, e.g. hormone-refractory prostate cancer with bone metastasis (1) (LE: 1b, GR: A);
- pain response in 60-85% of patients (1-3) (LE: 1b, GR: A).

The main side-effects are:

- flu-like symptoms (20-40%), bone pain, fever, fatigue, arthralgia and myalgia (all < 10%);
- hypocalcaemia (caution: rapid infusion - 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%).

Some remarks (all grade B recommendations):

- Recognise and treat dehydration before administration of bisphosphonates.
- Reduce the dose in the event of impaired renal function when using zoledronate (4) (LE: 2).
- Avoid simultaneous administration of aminoglycosides (5).
- Perform clinical examination of the patient's mouth and jaws; avoid oral/dental surgery during administration of iv bisphosphonates (6-10) (LE: 2).

3.4.3.3 Denosumab

Histological findings and analysis of bone turnover markers support the view that bone metatases from prostate cancer 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 hypercalcemia. To maintain skeletal integrity and prevent skeletal complications treatment with bisphosphonates are often initiated.

The receptor activator of NF-kB ligand (RANKL), mediates the formation, function, and survival of osteoclasts.

It is hypothesised that through RANKL, tumor cells induce osteoclast activation, which then mediates bone resorption and releases growth factors, resulting in a cycle of bone destruction and tumor proliferation. Denosumab is a fully human monoclonal antibody that specifically binds and neutralises RANKL, inhibiting osteoclastogenesis and decreasing osteoclastmediated bone destruction (11). Improvement in bone metastases free survival (4.2 months) and increased time to first bone metastasis (3.7 months) has been reported with denosumab in a phase III randomised placebo controled trial (12).

Another recently published phase 3 study, randomised men with castration-resistant prostate cancer 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 cutoff date. Denosumab significantly delayed the time to first onstudy skeletal-related event by 18% compared with zoledronic acid, with a between-group difference of 3-6 months (13). 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 castration-resistant prostate cancer (13). However, data on QoL are lacking.

A small randomised phase II trial evaluated the effect of denosumab after iv bispfhosphonates (14). However, actually there are insufficient data to support a routine switch from iv bisphosphonates to denosumab.

3.4.3.3 References

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*3.4.4 **Systemic analgesic pharmacotherapy - the analgesic ladder***

Analgesic pharmacotherapy is the mainstay of cancer pain management (1-3). 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
- adjuvant analgesics.

Emphasising that pain intensity should be the prime consideration (LE: 1a), the WHO has proposed a three-step approach to analgesic selection for cancer pain (1,3). Known as the analgesic ladder, when combined with appropriate dosing guidelines it can provide adequate relief in 70-90% of patients (4,5).

- **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 aspirin, paracetamol 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 (6).
- Potential adverse effects (7): 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.
- 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.
- Rarely, paracetamol produces gastrointestinal toxicity, but 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 (8).

3.4.4.2 Opioid analgesics

Cancer pain of moderate or severe intensity should generally be treated with a systemically administered opioid analgesic (9). 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 of parenteral morphine. Equi-analgesic dose information provides guidelines for dose selection when the drug or route of administration is changed (10).

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain (10-13). 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 (14).
- **Transdermal** routes: fentanyl and buprenorphine have been demonstrated to be effective in postoperative and cancer pain (15). The fentanyl transdermal therapeutic system dosing interval is usually 72 h, but some patients require a 48 h schedule. 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 (16). The efficacy of transdermal fentanyl

is equal to morphine. The incidence of side-effects such as sedation and constipation are lower than for morphine (17,18) (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 (19). Its analgesic effect is comparable with that of other opioids, and it shows no relevant analgesic ceiling effect throughout the therapeutic dose range (20). 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 (21).

- **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 (22). 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 (23,24). Fentanyl delivered by this means is more effective than oral morphine at relieving pain (LE: 2).

Recommendation	GR
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.	B

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 (25).

- **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 minutes for methadone, to 10-15 minutes for morphine (26). 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 (27). 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% (28), 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 (29). Methadone appears to be relatively irritating and is not preferred (30). To maintain the comfort of an infusion site, the sc infusion rate should not exceed 5 cc/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.

Changing the route of administration

Switching between oral and parenteral routes should be guided by a 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

- **Around-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 (31,32).
- **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 of im morphine per 24 hours) (33). 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 (34). 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 discourage activities 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 co-morbidity 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 (35). 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 (36). 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 (37-39), and laxative medication should be prescribed prophylactically. There are no controlled comparisons of the performance of the various laxatives in opioid-induced constipation. Combination therapy is frequently used, particularly co-administration of a softening agent (e.g. docusate) 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 (40), 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 (41). 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 (42). 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.

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 (43,44), this group has been demonstrated to have analgesic effects, to improve QoL significantly (45), and to have beneficial effects on appetite, nausea, mood and malaise in patients with cancer (46). 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 (47), 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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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 (1,2). However, the potential complications of opioids mean that they are not always a satisfactory option (3). Beside 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 (4,5).

3.4.5.1 Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain (5), which work primarily via interaction with pathways running through the spinal cord from serotoninergic 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 (6,7) (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 (7) (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).

Recommendations	GR
Amitriptyline and nortriptyline are the first line treatment for neuropathic pain; nortriptyline has fewer side-effects.	A
TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention.	
Duloxetine is the first-line treatment for neuropathic pain due to diabetic polyneuropathy.	A
Duloxetine may be tried as an analgesic in other neuropathic pain syndromes.	GCP

GCP = good clinical practice.

3.4.5.2 Anticonvulsant medication

The rationale for the use of anti-epileptic drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain (8). 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) (9,10). 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 (11) (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 (12).

Gabapentin and pregabalin are first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy (13-15) (LE: 1a). The combination of gabapentin with opioids seems to display synergistic effects in relieving neuropathic pain (16,17). 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 (18). Recent studies confirm the effectiveness of pregabalin in peripheral (including post-herpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain (19).

Recommendation	GR
Gabapentin and pregabalin are first line treatments for neuropathic pain, especially if tricyclic antidepressants are contraindicated.	A

3.4.5.3 Topical 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.

Topical 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 (20,21) (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 (22) (LE: 3).

Recommendations	GR
Topical lidocaine 5% should be used as an adjuvant in patients suffering from post-herpetic neuralgia.	A
Transdermal capsaicin may be used as an adjuvant in patients with neuropathic pain.	C

3.4.5.4 NMDA receptor antagonists

Within the dorsal horn, ionotropic glutamate receptors (NMDA, ⟨-amino-3-hydroxyl-5-methyl-4-

isoxazolepropionate [AMPA], kainate) and metabotropic glutamate receptors are all involved in neuropathic pain (23). 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 allodynia, and primary and secondary hyperalgesia.

Subanaesthetic doses of ketamine, and its active enantiomer S(+)-ketamine, given parenterally, neuraxially, nasally, transdermally or orally, alleviate pain post-operatively and in a variety of neuropathic pain syndromes, including central pain (24) (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 (25). It must therefore be reserved as a third-line option for when other standard analgesic treatments are exhausted (26,27).

Low dose systemic ketamine's primary role (bolus 0,25 mg/kg followed by a continuous administration between 0.1 - 0.4 mg/kg/h) is as an anti-hyperalgesic, anti-allodynic, or tolerance-protective compound in patients with severe acute pain, chronic or neuropathic pain, opioid tolerance, or those at risk for developing chronic post surgical pain (following laparotomy, thoractomy, breast surgery, and nephrectomy) (28,29).

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 (30).

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 (31,32).

Recommendation	**GR**
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).	B

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 (33). 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 trigeminus 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 topically, 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 (34) (LE: 2b).

Summary: treatment of neuropathic pain

- **First-line agent:**
  - nortirptylinepregabalin, 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 (35,36). 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 (37,38).

Recommendation	GR
Reversible regional anaesthetic techniques must be considered for the management of neuropathic pain.	GCP

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 (39,40). 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) (41) (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 (LE: 3) (42-44).

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 (45,46). Contraindications include bleeding diathesis, profound leucopenia 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 (47,48). The potential morbidity of these procedures requires well-trained clinicians and long-term monitoring (LE: 2).

Recommendation	GR
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.	B

Chemical rhizotomy

Chemical rhizotomy, produced by the instillation of a neurolytic solution into the epidural or intrathecal space, can be an effective method of pain control for patients with otherwise refractory localised pain syndromes (49,50). The technique is most commonly used in chest-wall pain due to tumour invasion of somatic and neural structures. Other indications include refractory upper limb, lower limb, pelvic or perineal pain (lower end block).

Because of the significant risk of increased disability through weakness, sphincter incompetence and loss of positional sense, chemical rhizotomy of lumbosacral nerve roots is best reserved for patients with limited function and pre-existing urinary diversion. Adverse effects can be related to the injection technique (spinal headache, mechanical neural damage, infection and arachnoiditis) or to the destruction of nonnociceptive nerve fibres (51) (LE: 4).

Recommendation	GR
Lower end block may be considered in patients with intractable perineal pain (bladder, rectum) that has responded insufficiently to more conservative therapy. This technique may only be performed in patients with loss of sphincter function (rectum and/or bladder).	C

Cordotomy

During cordotomy, the anterolateral spinothalamic tract is sectioned to produce contralateral loss of pain and temperature sensitivity. The patient with severe unilateral pain arising in the torso or lower extremity is most likely to benefit from this procedure. The percutaneous technique is generally preferred. Significant pain relief is achieved in more than 90% of patients during the period immediately following cordotomy (52). Of surviving patients, 50% have recurrent pain after 1 year. Repeated cordotomy can sometimes be effective. The neurological complications of cordotomy include paresis, ataxia and bladder dysfunction (53) (LE: 3).

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3.5 Quality of life

It seems beyond question that systematic assessment and objective pain evaluation can be of help for pain control in cancer patients (1-3). There is also proof of the strong relationship between pain, anxiety and depression, and health-related QoL in cancer patients (4,5). Anxiety is a common symptom in patients near the end of life. There is currently insufficient evidence on the role of drugs for treatment of anxiety associated with terminal illness, and it is therefore not possible to draw any conclusions about the effectiveness of

pharmacotherapy in this setting (6).

Cancer-related fatigue (CRF) is a significant problem. It can occur because of the side effects of treatment or the disease itself, and can have a significant impact on a person's ability to function. The causes of fatigue are not fully understood and so it is difficult to treat it appropriately. Trials of erythropoietin and darbopoetin (for anaemic patients on chemotherapy) and psychostimulants (amphetamines) provide evidence for improvement in CRF at a clinically meaningful level. There are no data to support the use of paroxetine or progestational steroids for the treatment of CRF. Methylphenidate is an obvious candidate for a large CRF study (7).

The proportion of people surviving and living with cancer is growing, which has led to increased awareness of the importance of QoL, including sexual function, to people with cancer. Sexual dysfunction is a potential long-term complication of cancer treatment. Following treatment for prostate cancer, there is evidence that transurethral alprostadil and vacuum constriction devices reduce sexual dysfunction, although negative effects are common. Vaginal lubricating creams are also effective, as are PDE5 inhibitors for sexual dysfunction secondary to prostate cancer treatment (8). Psychological **interventions** focused on **sexual dysfunction following cancer** can be considered as moderately effective (9).

Chronic constipation can be a serious problem for cancer patients taking opioids. In this setting, lactulose seems more effective than polyethylene glycol (10).

Palliative care / physical-psychological support / quality of life
Palliative care includes pain management as well as functional, psychosocial and spiritual support. Medical, psychological, physical, social, hospicial, and pastoral interdisciplinary services could be helpful at the end of life (11). Patients facing advance stages of prostate cancer frequently experience 'total pain', a mix of physical, psychological, spiritual and social suffering (12). Information about the illness and the process of care has been proved to reduce distress (13,14). Treatment should include both psychological and somatic symptoms (12). Moderate exercise seems to provide a certain benefit in the treatment of fatigue (15,16). Family caregivers and support groups are crucial components of the patient support system (11). Members of prostate cancer self-help groups provide each other with various types of help, usually nonprofessional and nonmaterial, for a particular shared, usually burdensome, characteristic (14). The help may take the form of providing and evaluating relevant information, relating personal experiences, listening to and accepting others' experiences, providing sympathetic understanding and establishing social networks. A supporting self-help group may also work to inform the public or engage in advocacy. All efforts aimed the improvement of the QoL (14).

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.

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4. PAIN MANAGEMENT IN UROLOGICAL CANCERS

4.1 Pain management in prostate cancer patients

*4.1.1 **Clinical presentation***

Pain in both early and advanced prostate cancer (PCa) can be caused directly by the cancer (77%), be related to the treatment (19%), or be unrelated to either (3%) (1). 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% (2). 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 (3). If the outlet obstruction persists

transurethral palliative resection (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 (4-7). 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.

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 (8,9) as a result of:
  - endosteal or periosteal nociceptor activation (mechanical distortion or release of chemical mediators)
  - tumour growth into adjacent soft tissues or nerves and
  - other complex mechanisms (9).
- 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 (10).
- 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 options are:

- hormone therapy;
- radiotherapy;
- orthopaedic surgery;
- radioisotopes;
- bisphosphonates;
- calcitonin;
- chemotherapy;
- systemic analgesic pharmacotherapy (the analgesic ladder).

Other pain management tools such as nerve blocks are rarely used.

Hormone therapy

Huggins and Hodges (11) first noted the effect of exogenous oestrogen administration on prostatic carcinoma. Hormone changes may cause complex endocrine effects, such as pituitary inhibition of luteinising hormone (LH), follicle-stimulating hormone (FSH) and prolactin, as well as changes in endogenous corticosteroid hormone production (12). 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 that due to bone deposits.

Side-effects

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 (13). The side-effects are:

- GnRH analogues and orchidectomy:
  - loss of body hair
  - testicular atrophy
  - gynaecomastia
  - loss of libido
  - impotence
  - increased cardiovascular mortality rate in long term administration
  - psychological morbidity.
- anti-androgens:
  - gynaecomastia (more often if used alone than when used in combination with GnRH analogues)
  - hepatic impairment
  - less sexual dysfunction than with GnRH analogues.
- cyproterone acetate:
  - fewer side-effects than oestrogens
  - lower incidence of cardiovascular complications than with oestrogens.
- oestrogens:
  - loss of body hair
  - testicular atrophy
  - gynaecomastia
  - loss of libido
  - impotence.
- Long-term administration results in higher mortality from cardiac and cerebrovascular disease as compared to GnRH analogues.
- adrenalectomy:
  - major operative procedure.
- hypophysectomy:
  - small but significant mortality rate
  - hormone replacement is subsequently required for life.

Efficacy

In a collected series of protocols, pain relief has been estimated at between 35% (14) and 70% (15). The differences may be due to the selection of patients and problems in 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.

Problems

To date, most patients with adenocarcinoma of the prostate present in early tumour stages and undergo radical surgery or radiotherapy. In cases of disease progression and symptoms, hormone therapy can be indicated with patients remaining asymptomatic for years. Pain is associated with a hormone-resistant tumour in progression, which necessitates alternative therapeutical options.

Radiotherapy

- The role of radiotherapy in the management of pain due to bone metastases is unquestionable.
- Radiotherapy techniques vary widely, from a large dose given as a single treatment to as many as 20 smaller treatments given over 4 weeks.
- Dose-time factors: 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.
- Bear in mind 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

(16). This effect does not appear to be significantly influenced by dose-time relationships or histology. The proportion of patients achieving complete pain relief approaches 80% (17) (see also Section 3.3.3).

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 (18,19). 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 (20).

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 strontium-89 chloride (^{89}Sr) and samarium-153-ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP). The addition of ^{89}Sr 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 (16), 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 leucocytopenia and thrombocytopenia, have been experienced (21).

Bisphosphonates
Bisphosphonates are routine supportive care for patients with bone metastases, and in a meta-analysis of 8 randomised studies some improvement in pain control due to bone metastases could be demonstrated (22). Bisphosphonates act by inhibiting osteoclast activities. Recent studies showed no statistically significant difference between the bisphosphonate and control groups in terms of PCa death, disease progression, and radiological and PSA response, but they should be considered for treating refractory bone pain and preventing skeletal events in those with metastatic PCa (22).

Zoledronic acid is effective for treating the complications of bone metastasis. Its efficacy and safety have been established in three pivotal trials involving more than 3000 patients (23). Although they appear osteoblastic on radiographic imaging, most bone metastases are characterised by excess osteoclast volume and activity. Pathological osteoclast activation is associated with increased risk of skeletal complications. Zoledronic acid, a potent inhibitor of osteoclast activity, differentiation and survival, decreases the risk of skeletal complications in men with androgen-independent PCa and bone metastases. Other bisphosphonates, including pamidronate and clodronate, seem to be less effective (24).

Zoledronic acid administration for one year to patients with hormone-sensitive PCa and bone metastases who were on androgen-deprivation therapy was safe and prevented bone loss, as shown by significant increases in bone mineral density and sustained suppression of biochemical markers of bone turnover (25). Zoledronic acid (4 mg intravenously over 15 minutes every 3-4 weeks) decreased the frequency of skeleton-related events, delayed the time to the first occurance, and reduced pain (23). Visual analogue scale improvement is positively correlated with a decrease of C-telopeptide and bone phosphatase alkaline ($p < 0.05$) serum levels (26). Studies are needed to determine the optimal timing, schedule and duration of treatment in men with bone metastases, as well as other potential roles for bisphosphonates, e.g. prevention of bone metastases (see Section 3.4.3).

Calcitonin
Current evidence does not support the use of calcitonin to control pain arising from bone metastases (27).

Chemotherapy
In about 80% of men with metastatic PCa, primary androgen ablation leads to symptomatic improvement and a reduction in the serum levels of PSA. The disease eventually becomes refractory to hormone treatment, and 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 (28), particularly with docetaxel.

Trials using single-agent chemotherapy in advanced disease have shown poor results, but newer studies suggest multiagent chemotherapies may be more effective. A randomised trial showed that mitoxantrone plus low-dose prednisone relieved pain and improved QoL more frequently than did prednisolone alone.
Other studies have confirmed the symptomatic effect of this regimen, 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 can be traced to the burden of bone metastases (29). 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 mCRPC targeting different mechanisms of progression have been applied successfully: docetaxel, cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate (30). Docetaxel is the standard first-line chemotherapeutic agent (31). Despite a survival benefit the prognosis remains limited. 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 (31,32). In 2010 two further randomized trials were published which demonstrate a survival benefit in the second-line setting: sipuleucel-T (immunotherapy) and abiraterone acetate versus placebo (20). The identification of intracellular androgen synthesis by prostate cancer cells has led to the development of third generation drugs for the therapy of mCRPC. Inhibitors of androgen synthesis and more potent androgen receptor antagonists will relief pain and improve palliation. 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) (32) (LE: 1b, GR: A).

Table 4: PSA-response rates to selected combined chemotherapy regimens

Chemotherapy agent	Plus	Response rate (%)
Ketoconazole	+ doxorubicin	55
Vinblastine	+ estramustine	54-61
Estramustine	+ etoposide	39-58
Mitoxantrone	+ prednisone	33
Paclitaxel	+ estramustine	53

In 2005, two studies demonstrated that docetaxel-based regimens have a very good symptomatic effect that is significantly better than that of the mitoxantrone-based approach (Table 5) (25,26). Additionally, for the first time, a significant survival benefit was shown for the docetaxel group (18.9 versus 16.5 months).

Table 5: Docetaxel-based chemotherapy versus mitoxantrone-based regimens

Chemotherapy	Plus	Frequency	Response rate (29)	
agent			Pain (%)	Quality of life (%)
Docetaxel	+ prednisone	Every 3 weeks	35	22
Docetaxel	+ prednisone	Weekly	31	23
Mitoxantrone	+ prednisone	Every 3 weeks	22	13

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 (33). The docetaxel-based regimens are now the standard of care for patients with advanced hormone-refractory PCa. Soft-tissue lesions could be influenced to a greater extent than bony metastases. 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.

4.1.4 Systemic analgesic pharmacotherapy (the analgesic ladder)

If the treatments described above provide insufficient pain relief, systemic analgesic pharmacotherapy should be administered (see Section 3.4.4). In most cases, the drug selection scheme proposed by the World Health Organization (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 versus either medication alone (34).

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 the tramadol giving slightly better pain management and fewer side-effects, particularly constipation (35). The treatment of constipation in palliative care is based on experimental evidence, and uncertainty persists about its optimum management in this group of patients (36).

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 now available, but no clinically significant difference has been shown compared to and other strong opioids such as morphine (37). 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 (38).

Breakthrough pain is a common and debilitating problem for patients with cancer. Evidence suggests that oral transmucosal fentanyl citrate is effective for breakthrough pain (39), giving more rapid relief than morphine (40).

4.1.5 ***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% (42). Thoracic cord compression is the most common area (70%), and the incidence of multiple extradural sites can be as high as 18% (43). 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 hours' duration, nonradiosensitive tumours and predicted survival of > 3 months. There is a significant risk of serious adverse effects from high-dose corticosteroids (44).

4.1.6 ***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 (45). Doses should not exceed 30 Gy in 15 daily fractions or its equivalent if radiation hepatitis is to be avoided.

4.1.7 ***Pain due to cancer treatment***

4.1.7.1 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 (46,47), presumably caused by an initial stimulation of LH release before suppression is achieved (47,48). The syndrome typically presents as an exacerbation of bone pain or urinary retention. Spinal cord compression and sudden death have also been reported (46). 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 (49).

4.1.7.2 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 (50), it is less common with flutamide and cyproterone (51-53), and uncommon in patients receiving LHRH agonist therapy (54). In elderly patients, it must be distinguished from primary breast cancer or secondary cancer in the breast (54).

4.1.8 ***Conclusions***

Radio-, chemo- and hormone therapy are all valuable options for relieving cancer pain. The side-effects of

inappropriate anticancer treatments can be very distressing, and so the disadvantages of treatments must be balanced against the palliative benefits. In many patients, the best approach to pain relief is through interdisciplinary co-operation.

Surgery, radio-, chemo- and hormone therapy are mainly used as antitumour treatment in the relief of pain. The rational use of any of these treatments demands knowledge not only of tumour biology, but also of the mechanisms of action of these specific oncological techniques. The therapeutic aim should be clearly understood prior to starting treatment.

Radical treatment should be given if the disease is potentially curable, but the intent should be symptomatic or palliative if the tumour is advanced or widely disseminated (55). The importance of early intervention needs to be emphasised, and education is crucial: patients must be aware of the early signs and symptoms of metastatic disease, which does not necessarily involve pain.

*4.1.9 **Recommendations at a glance (stage M1) (56-61)***

ANTICANCER TREATMENT		
Recommendation	**LE**	**GR**
Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)	1a	A
Total androgen blockade: flare prevention, second-line	2b	B
Intermittent androgen suppression experimental	3	B
Monotherapy with anti-androgen is an option	2	B
First-line treatment controls disease for 12-18 months, second-line individualised	1b	A
Supportive care		
Low-dose glucocorticoids	1b	A
Chemotherapy		
Mitoxantrone plus prednisolone	1b	B
Estramustine + vinblastine or etoposide or paclitaxel	2b	B
Docetaxel	1b	A
PAIN MANAGEMENT		
Recommendation	**LE**	**GR**
Pain assessment (localisation, type, severity, overall distress)		B
Pain due to painful or unstable bony metastases (single lesions)		
External beam irradiation	1b	A
Pain due to painful bony metastases (widespread)		
Radioisotopes (^{89}Sr or ^{153}Sm-EDTMP)	2	B
Pain due to painful metastases (many spots)		
Bisphosphonates	1b	A
Systemic pain management		
WHO analgesic ladder step 1: NSAID or paracetamol	1a	A
Opioid administration		
Dose titration	2	B
Access to breakthrough analgesia	1b	A
Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain	1a	A

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4.2 Pain management in transitional cell carcinoma patients

*4.2.1 **Clinical presentation***

In more developed countries, urothelial cancer is the 5th most common cancer in men and the 13th in women (1). Transitional cell carcinoma (TCC) is the most frequent cancer of the bladder and upper urinary tract. It arises much more frequently in the bladder than in the collecting system (calices, renal pelvis and ureter).

From the perspective of pain, there are no differences between 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.

TCC of the renal collecting system represents 5-10% of all kidney tumours and 5% of all TCC of the urinary tract (2). TCC of the ureter accounts for only 3% of all TCC (3). In upper urinary tract TCC, pain is an initial symptom in 18-30% of cases (4,5).

*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 prostate cancer (6).

In locally advanced disease, symptoms are comparable with those caused by T4 prostate cancer. 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 irradiating 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) (6).

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 (see 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 (7). In a small retrospective study of patients with tumour infiltration of the rectum by locally recurrent prostate cancer, total exenteration resulted in significant pain reduction in all patients, and 79% were completely pain free (8). 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% (9).

First-line chemotherapy strategies that are mainly based on platinum-containing regimens have some effect in 12-75% of patients with advanced disease (see EAU Guidelines on Muscle Invasive Bladder Cancer Guidelines, Chapter 12). It probably relieves pain by decreasing the neoplastic mass in respondent patients (10-14) (LE: 1a), but pain control was one of the study end points in only one small study (15).

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 (16).

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 3 fractions) were compared for symptomatic improvement of bladder-related symptoms. 68% 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 2 study arms (17) (LE 1a). Some smaller studies have shown comparable results with respect to improvement of QoL by local radiotherapy (18).
The effect of radiotherapy in controlling local symptoms of advanced bladder cancer needs to be balanced against the risk of inducing proctitis.

4.2.3.2 Upper urinary tract TCC

Transitional cell carcinoma (TCC) 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 (see 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 with patients with incidentally detected upper urinary tract TCC (19). 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 provide moderately prolonged survival are MVAC (methotrexate, vinblastin, adriamycin, cisplatin) and gemcitabine/cisplatin as first-line drugs, as in bladder cancer (20). 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 (21)

*4.2.4 **Pain due to metastases***

Haematogenous metastases to the bone are often found in advanced bladder or upper urinary tract TCC. No data are available in the literature concerning the specific effect of chemotherapy on bone metastases alone.

Radiotherapy has a palliative analgesic role in bone metastases (see Chapter 3.3.3) and pain reduction > 50% can be achieved in 50% of patients (22) (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 (23,24) (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single-fraction radiotherapy (23,24) (LE: 1a).

Radioisotope treatment (see Chapter 3.3.2) or hemi-body irradiation can be used in patients with multiple bone metastases (22). There are no specific studies of radioisotope therapy for bone metastasis in TCC.

Orthopaedic surgery can stabilise pathological fractures, as for those from prostate cancer (see Chapter 3.3.3.6).

*4.2.5 **Conclusion for symptomatic locally advanced or metastatic urothelial cancer***

- In locally advanced bladder cancer, palliative cystectomy or exenteration might be an option for symptom relief (LE 3; GR B)
- Chemotherapy in urothelial cell carcinoma is effective in terms of disease control (LE 1b, GR A)
- The effect on pain control and quality of life seems to be analogue (LE 2a)
- Radiotherapy reduces pain and symptoms of locally advanced bladder cancer (LE 1a, GR B), but this needs to be balanced against the risk of inducing proctitis
- Radiotherapy is effective in reducing pain due to bone metastases (LE 1b; GR A)

*4.2.6 **References***

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4.3. Pain management in renal cell carcinoma patients

*4.3.1 **Clinical presentation***

Renal cell carcinoma (RCC) is mainly diagnosed incidentally. There is no pain unless 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. RCC 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 post-operative radiotherapy offers no survival benefit, and its role in delaying local progression is questionable (1). Radiotherapy of soft tissue has no proven benefit for pain and tumour control.

In metastatic disease, the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group study 30947 demonstrated a significant increase in survival with palliative nephrectomy plus immunotherapy compared with immunotherapy (interferon-alpha) alone (median survival of 17 compared with 7 months) (2) (LE: 2b). There is no special effect on pain relief from immunotherapy.

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 (GCP). 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 (GCP).

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) (3).

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 (4-6) (LE: 2b/3). Additionally, surgery prevents pathological fractures and spinal compression, and there is a significant impact on survival.

Pre-operative embolisation of bone metastases or embolisation alone achieves good pain relief in hypervascular bone metastases (7,8) (LE: 3).

High dose radiation therapy for palliation of painful bony metastases has been shown to be effective in 50-75% of all renal cancer patients (9-11) (LE: 3), and in 67% with general bone metastases (12) (LE: 2b). There is no impact on survival. Small studies of radionuclide therapy (e.g. with 89Sr) have shown good pain relief in bony metastases from RCC (13) (LE: 3).

Standard pre-operative (30 Gy) or post-operative radiotherapy offers no survival benefit; its role in delaying local progression is questionable (1); there is no proven benefit for pain and tumour control for soft tissue metastases.

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 (14). Immunotherapy in combination with chemotherapy (interleukin-2 + interferon-alpha + 5-fluorouracil) is the most effective therapy, achieving partial tumour response in up to 46% of patients and complete response in a maximal 15%, although these rates are mainly for lung/lymph node metastases (15).

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.

First-line chemotherapy (docetaxel), second line chemotherapy (microtubule inhibitor cabazitaxel), and third generation anti-androgen therapy (abiraterone acetate)

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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 (1).

*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 (2). When correctly diagnosed and treated, the disease is curable, unless there are metastases.

Computed tomography (CT) and magnetic resonance imaging (MRI) have the highest sensitivity in detecting the tumour, achieving 94-100%. A 131J-metaiodobenzylguanidine (131J-MIBG) scan is positive in approximately 87% of cases (3).

Chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect on metastases (4) (LE: 2b), but therapeutic doses of 131J-MIBG (33 GBq = 900 mCi) may produce some results (5, 6) (LE: 2b). The hormone response rate is 50%. There are no data on pain relief with 131J-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 (7) (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 131J-MIBG, if the phaeochromocytoma takes up this radionuclide (8) (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 (9). An autopsy study showed metastasis to lung (60%), liver (50%), lymph nodes (48%), bone (24%) and pleura/heart (10%) (10). 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% (9,11) (LE: 2a). It remains to be proven whether chemotherapy prolongs survival. Radiation therapy has not been useful except for palliation and pain management (12) (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 (8,12). 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.

4.4.3 ***References***

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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 (1). 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 (2). 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 them will be found to have metastatic disease (3). 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 (4). 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***

4.5.2.1 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 inguinal 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 (6). The chemotherapy regimen that is so far most effective and well tolerated is paclitaxel, ifosfamide and cisplatin (TIP), although large randomised trials are lacking (5). 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 (7). 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 (8,9).

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 tumor erosion of the large groin vessels.

4.5.6 ***References***

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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 (1). 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 (LE: 2b) (see EAU Guidelines on Testicular Cancer). 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 (2,3). Treatment with chemotherapy or second-line chemotherapy may be possible (see EAU Guidelines on Testicular Cancer). 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 (4) (LE: 3).

*4.6.4 **References***

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4.7 Recommendations at a glance

Table 6: Efficacy of the therapeutic options in pain relief (expert opinion)

Origin of pain/therapeutic options	RCC	TCC	PCa	Penile cancer	Adrenergic cancer	Testicular cancer
Bone metastases						
Surgery	+++	?	+	?	?	+
Radiation	++	++	+++	?	+	?
Radionuclide	+	?	+++	?	++	-
Chemotherapy	-	?	+	?	-	
Immunotherapy	-	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++
Soft tissue infiltration						
Surgery	+++	+++	-	?	?	+
Radiation	-	+	++	?	+	?
Chemotherapy	+	++	+	?	++	+++
Immunotherapy	+	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++
Nerve compression/nerve infiltration						
Surgery	+++	+++	++	?	?	++
Radiation	+	+	++	?	+	?
Chemotherapy	+	++	+	?	?	+++
Immunotherapy	+	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++

RCC = renal cell carcinoma; TCC = transitional cell carcinoma; PCa = prostate cancer;
? = no conclusive data on pain control; - = no pain control; + = low pain control;
++ = moderate pain control; +++ = good pain control.

5. POSTOPERATIVE PAIN MANAGEMENT

Key Words: Postoperative analgesia, postoperative pain, opioids, NSAIDs, coxibs, paracetamol, urological procedures, epidural, PCA, PCEA, ketamine, clonidine, local anaesthetics

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 (1,3), leading to increased morbidity and mortality, mostly due to respiratory and thromboembolic complications, increased hospital stay, impaired QoL, and development of chronic pain (1,3,5-7) (LE: 1a).

5.2 Importance of effective postoperative pain management

The physiological consequences of postoperative pain are shown in Table 7. All of these can delay or impair postoperative recovery and increase the economic cost of surgery (longer hospitalisation) (13,14) (LE: 3). Inadequate postoperative pain control may also lead to development of chronic pain (15,16) (LE: 2b).

Table 7: Physiological consequences of postoperative pain

Condition	Consequences	Ref.	LE
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	8	2a
Respiratory complications	Shallow breathing Cough suppression Lobular collapse Retention of pulmonary secretions Infections	9	2b
Cardiovascular complications	Hypertension Tachycardia Increased myocardial work, - myocardial ischaemia - angina - infarction	10	2b
Thromboembolic complications	Reduced mobility due to inadequate pain management can lead to thromboembolic episodes	11	2a
Gastrointestinal complications	Gastric stasis Paralytic ileus mostly after open urological operations	12	2b
Musculoskeletal complications	Prolonged confinement to bed: - reduced mobility - muscle atrophy	13	3
Psychological complications	Perioperative pain may provoke fear and anxiety, which can lead to: - anger - resentment - hostility to medical and nursing personnel - insomnia	13, 14	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 (1-3) (LE: 1a).

Recommendation	GR
Postoperative pain should be treated adequately, to avoid complications and development of chronic pain.	B

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 post-opeative analgesic requirements and result in better pain management (1) (LE: 1a).

Recommendation	GR
Preoperative assessment and preparation of patients allow more effective pain management.	A

*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 (1,4) (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 (17,18).

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 (18).

Recommendation	GR
Adequate postoperative pain assessment can lead to more effective pain control and fewer complications.	B

*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 (19). The results of clinical trials on its efficacy are controversial (19,20) (LE: 2b).

*5.3.4 **Systemic analgesic techniques***

5.3.4.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

These drugs 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 (21). However, their analgesic effect is not strong enough for the management of severe postoperative pain (22). For NSAID dosage and administration, see Table 12.

Intravenous (iv) 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 (23).

Their main adverse effects are (22):

- 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 (24). However, COX-2 inhibitors are contraindicated for long-term use in patients with cardiovascular problems (25). The use of COX-2 inhibitors is approved only for short-term postoperative pain therapy.

Recommendations	GR
NSAIDs are often effective after minor or moderate surgery.	B
NSAIDs often decrease the need for opioids.	B
Avoid long-term use of COX inhibitors in patients with atherosclerotic cardiovascular disease.	B

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 (26) (LE: 2). Its exact mode of action is unclear, although it may act by centrally inhibiting COX production (27).

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 13.

Recommendations	GR
Paracetamol can be very useful for postoperative pain management because it reduces consumption of opioids.	B
Paracetamol can alleviate mild postoperative pain as a single therapy without major adverse effects.	B

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 (28,29) (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 (30). Opioid dosage and administration can be found in Table 14 and 15.

5.3.4.5 Patient-controlled analgesia (PCA)

Systemic administration of opioids may follow the “as needed” schedule or “around-the-clock” dosing. The most effective mode is PCA (31,32) (LE: 1a) (Table 8).

Table 8: Typical PCA dosing schedule

Drug (concentration)	Bolus size	Lockout interval (min)	Continuous infusion
Morphine (1 mg/mL)	0.5-2.5 mg	5-10	0.01-0.03 mg/kg/h
Fentanyl (0.01 mg/mL)	10-20 µg	5-10	0.5-0.1 µg/kg/h
Pethidine (10 mg/mL)	5-25 mg	5-10	-

Recommendation	GR
Intravenous patient controlled analgesia provides superior postoperative analgesia, improving patient satisfaction and decreasing risk of respiratory complications.	A

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, dexmedetomidine) 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 (33,34) (LE:1a, GR: A).

Low-dose ketamine is defined as a bolus dose < 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via the intravenous or epidural route. For continuous i.v. administration, low-dose ketamine is defined as a rate of ≤ 20 g/kg/min (35). 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 (36) (LE:2b).

Clonidine when given preoperatively, or epidurally postoperatively (1mcg/kg) can reduce opioid requirements (37) (LE:1a, GR: A).

More clinical evidence on dexmedetomidine is necessary to confirm its definite role in acute postoperative pain control (38).

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 before and after surgery, decreases pain severity and the need for analgesic supplementation (39) (LE:1a, GR:A).

Perioperative pregabalin (300 mg/day) reduces opioid consumption and opioid-related adverse effects after surgery, however postoperative pain intensity is not reduced by pregabalin (40).

Single-injection caudal blocks with clonidine or ketamine are beneficial in paediatric patients (41).

5.3.5 ***Regional analgesic techniques***

5.3.5.1 Local anaesthetic agents

The most commonly used local anaesthetics are:

- bupivacaine
- l-bupivacaine
- ropivacaine.

Bupivacaine is considered to be cardiotoxic in high doses. l-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 9).

Table 9: Typical epidural dosing schemes*

Drug	Single dose	Continuous infusion
Morphine	1-5 mg	0.1-1 mg/h
Fentanyl	50-100 µg	25-100 µg/h
Sufentanil	10-50 µg	10-20 µg/h
Pethidine	10-30 mg	10-60 mg/h

Bupivacaine 0.125% or ropivacaine 0.2% + fentanyl 2 µg/mL	10-15 mL	2-6 mL/h

**l-bupivacaine doses are equivalent to those of bupivacaine.*

5.3.5.3 Patient-controlled epidural analgesia (PCEA)

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 (42,43) (LE: 1a) (Table 10).

Table 10: Typical PCEA dosing schemes

Drug	Demand dose	Lockout interval (min)	Continuous rate
Morphine	100-200 µg	10-15	300-600 µg/h
Fentanyl	10-15 µg	6	80-120 µg/h
Pethidine	30 mg	30	-
Bupivacaine 0.125% + fentanyl 4 µg/mL	2 mL	10	4 mL/h
Ropivacaine 0.2% + fentanyl 5 µg/mL	2 mL	20	5 mL/h

Recommendation	GR
Epidural analgesia, especially PCEA, provides superior post-operative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques (2).	A

5.3.5.4 Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement postoperative analgesia (44) (LE: 2a) (Table 11).

Table 11: Examples of neural blocks

Procedure	Drug/dosage
Iliohypogastric or ilioinguinal nerve infiltration after hernia repair	10-20 mL bupivacaine or ropivacaine 0.25-0.5%
Intercostal nerve infiltration	5-10 mL bupivacaine or ropivacaine 0.25-0.5%
Continuous intrapleural infusion	10 mL/h bupivacaine or ropivacaine 0.1-0.2%

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 (45) (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 (46-48) (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 (49) (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).

Recommendations	GR
Multimodal pain management should be used whenever possible because it helps to increase efficacy while minimising adverse effects.	B

*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 (50,51, LE: 2a; 52, LE: 2b).

Recommendations	GR
For postoperative pain control in outpatients, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	B
If possible, avoid opioids.	B

5.3.7.2 Geriatric patients

Pain perception appears to be reduced in geriatric patients, and requirement for analgesia generally decreases with increasing age (53,54). Geriatric patients can also suffer from emotional and cognitive impairment such as depression and dementia, which could affect adequate pain management (55). Postoperative delirium in elderly patients is a common complication and is often multifactorial. It may be associated with administration of pethidine (56). 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 (57) (LE: 2b). Epidural analgesia might diminish the risk of postoperative delirium and respiratory complications in elderly patients (58) (LE: 2b).

Recommendations	GR
Multimodal and epidural analgesia are preferable for postoperative pain management in elderly patients because these techniques are associated with fewer complications.	B

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 (59,60). 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 (61,62) (LE: 2b).

If absolutely necessary, opioids should be used with caution under careful titration to avoid depression of the respiratory drive (62). Oxygen therapy should also be applied postoperatively to increase oxygen saturation (63).

Recommendations	GR
Postoperative use of opioids should be avoided in obese patients unless absolutely necessary.	B
An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable.	B

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 (64) (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).

Recommendations	GR
There are no sufficient data to support a specific postoperative pain management plan for critically ill or cognitively impaired patients.	B

*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 (65-67) (LE: 2b). Improved pain control can lead to shorter hospitalisation and fewer unscheduled readmissions after day surgery (68) (LE: 3).

5.4 Specific pain treatment after different urological operations

*5.4.1 **Extracorporeal shock wave lithotripsy (ESWL)***

ESWL is a minimally invasive treatment, during and after which 33-59% of patients do not need any analgesia (69-71) (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 ESWL.

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 (72). 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% (73). After premedication with midazolam (2 mg iv, 5 min before treatment), diclofenac or tramadol was safe and effective, with fewer side effects than fentanyl (74) (LE: 1b). Other effective regimes for intraoperative pain treatment are fentanyl (1 µg/kg iv [75]), 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 (76,77) (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.

Recommendations	GR
Analgesics should be given on demand during and after ESWL because not all patients need pain relief.	B
Premedication with NSAIDs or midazolam often decreases the need for opioids during the procedure.	B
iv opioids and sedation can be used in combination during ESWL; dosage is limited by respiratory depression.	C

Post-ESWL, analgesics with a spasmolytic effect are preferable (C).

*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 (78) (LE: 1b).

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- 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 (78) (LE: 1b).

Recommendations	GR
Postoperative analgesics with spasmolytic effect or mild opioids are preferable.	C
Antimuscarinic drugs could be helpful in reducing discomfort resulting from the indwelling catheter.	B
Antimuscarinic drugs may reduce the need for opioids.	B

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 (79-81) (LE: 1b). The same could apply for some transabdominal urological laparoscopic interventions.

Analgesic plan

Preoperative assessment: see Section 5.3.2.

Intraoperative: iv opioids ± NSAIDs, paracetamol or metamizole administered by an anaesthesiologist. The infiltration of local anaesthetic into the port incisions reduces pain after laparoscopy (82).

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 (82,83).

Recommendations	GR
Low intra-abdominal pressure and good desufflation at the end of the procedure reduces postoperative pain.	A
NSAIDS are often sufficient for postoperative pain control.	B
NSAIDs decrease the need for opioids.	B

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	GR
For postoperative pain control, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	B
If possible, avoid opioids for outpatients.	C

5.4.3.2 Transvaginal surgery

General, local or regional anaesthesia can be used for these operations.

Recommendations	GR
NSAIDS are often sufficiently effective after minor or moderate surgery.	B
NSAIDs decrease the need for opioids.	B

5.4.3.3 Perineal open surgery

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- 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 5.3.2.
- 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 (84).

Recommendations	**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.	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).	A

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 5.3.2.
- 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 5.3.2.
- 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 (85,86) . 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.

Recommendations	**GR**
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.	A

5.5 Dosage and method of delivery of some important analgesics

5.5.1 ***NSAIDs***

Table 12: Dosage and delivery of NSAIDs

Drug	Daily dose	Route of administration
Conventional NSAIDs (non-selective COX inhibitors)		
Ketorolac	10-30 mg four times daily	Orally or iv
Ibuprofen	400 mg three times daily	Orally
Ketoprofen	50 mg four times daily	Orally or iv
Diclofenac	75 mg twice daily	Orally or iv
	50 mg three times daily	Orally or iv
	100 mg twice daily	Rectally
COX-2 selective inhibitors		
Meloxicam	15 mg once per day	Orally
Lornoxicam	4-8 mg twice daily	Orally or iv
Celecoxib	200 mg once per day	Orally
Parecoxib	40 mg once or twice daily	iv form only
Etoricoxib	90-120 mg once daily	Orally

Table 13: Dosage and delivery of paracetamol, metamizole and its combinations with opioids

Drug	Method of administration	Single dose (mg)	Maximal dose (mg/day)
Paracetamol	Orally	500-1000	4000 (50 mg/kg)
Paracetamol	iv	1000	4000 (50 mg/kg)
Metamizole	Orally	500-1000	4000
Metamizole	iv	1000-2500	5000

Paracetamol	Opioid	Times per day	Route of administration
Paracetamol 1 g	Codeine 60 mg	Four	Orally or rectally
Paracetamol 600-650 mg	Codeine 60 mg	Four	Orally or rectally
Paracetamol 500 mg	Codeine 30 mg	Four	Orally or rectally
Paracetamol 300 mg	Codeine 30 mg	Four	
Orally or rectally			
Paracetamol 650 mg	Dextropropoxyphene 65 mg	Four	Orally
Paracetamol 600-650 mg	Tramadol 75-100 mg	Four	Orally
Paracetamol 325 mg	Oxycodone 5 mg	Four	Orally

5.5.2 ***Opioids***

Table 14: Dose and delivery of opioids

Drug	Method of administration	Common single dose (mg)	Maximal dose (mg)
Tramadol	Orally	50	400-600
Tramadol	iv	50-100	400-600
Dihydrocodeine	Orally	60-120	240
Piritramid	sc/im	15-30	120

Pethidine	Orally	25-150	500
Pethidine	Rectally	100	500
Pethidine	sc/im	25-150	500
Pethidine	iv	25-100	500
Morphine*	Orally	Starting with 10	No maximal dose
Morphine*	Rectally	Starting with 10	No maximal dose
Morphine*	sc/im	Starting with 5	No maximal dose
Morphine*	iv	Starting with 2	No maximal dose
Morphine*	iv (PCA)	0.5-2.5 mg bolus 10-15 min lockout	No maximal dose

**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 (see 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 15: Common equi-analgesic doses for parenteral and oral administration of opioids*

Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30
Fentanyl	0.1	-
Pethidine	75	300
Oxycodone	15	20-30
Dextropropoxyphene	-	50
Tramadol	37.5	150
Codeine	130	200

**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 (87) (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 (88) (LE: 1a). Atropine, 0.01-0.02 mg/kg iv, im, orally or rectally, prevents bradycardia during anaesthesia induction.

Table 16: Premedication drugs in children

Drug	Dosing	Route of administration	Category
Ketamine	6 mg/kg	Oral, intranasal, im	NMDA antagonist
Midazolam	0.5 mg/kg	Oral, intranasal, rectally	Benzodiazepine
Dexmedetomidine	4 µg/kg	Oral, intranasal	α2-receptor agonist
Clonidine	4 µg/kg	Oral	α2-receptor agonist
Pentobarbital	4-6 mg/kg	im	Barbiturate
Chloral hydrate	50-100 mg/kg	Oral	Barbiturate
Methohexital	25-30 mg/kg	Rectally	Barbiturate

Recommendations	GR
EMLA local application alleviates significantly venipuncture pain in children.	A

*5.6.2 **Postoperative analgesia***

Postoperatively, paracetamol, NSAIDs, opioids and their combinations are used according to the severity of the surgical procedure (Table 17).

Table 17: Dosage of analgesics in children for postoperative analgesia

Drug	Dose	Route of administration	Severity of surgical procedure
Paracetamol	10-15 mg/kg every 4 h 20-30 mg/kg every 6 h	Oral Rectally	Minor Minor
Ibuprofen	10-15 mg/kg every 6 h	Oral, iv, rectally	Minor, medium
Naproxen	6-8 mg/kg every 8-12 h	Oral, iv, rectally	Minor, medium
Codeine	0.5-1 mg/kg every 3-4 h	Oral	Minor, medium
Morphine	0.1 mg/kg every 2-4 h Infusion: 0.03 mg/kg/h 0.3 mg/kg every 3-4 h	iv, sc Oral	Medium, major
Oxycodone	0.1-0.2 mg/kg every 3-4 h	Oral	Medium
Hydromorphone	0.04-0.08 mg/kg every 3-4 h	Oral	Medium
Tramadol	1 mg/kg every 4-6 h	iv	Medium, major
Pethidine	2-3 mg/kg every 3-4 h	iv	Medium, major

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 (89).

Locoregional techniques such as wound infiltration, nerve blocks, and caudal and epidural analgesia are also successful (90,91). The most commonly drugs used are bupivacaine and ropivacaine (Table 18). Higher volumes of lower drug concentrations appear to be more effective than lower volumes of higher concentrations (92) (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 (93-95) (LE: 1a).

Table 18: Epidural dose of local anaesthesia

Drug	Bolus 0-12 months	Bolus > 1 year	Infusion for 0-12 months	Infusion > 1year
Bupivacaine	2 mg/kg	2.5 mg/kg	0.2 mg/kg/h	0.4 mg/kg/h
Ropivacaine	2.5 mg/kg	3.5 mg/kg	0.3 mg/kg/h	0.6 mg/kg/h

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6. NON-TRAUMATIC ACUTE FLANK PAIN

6.1 Background

Acute flank pain is a frequently occuring 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 32).

Table 32: Main urological and non-urological causes of flank pain

Urological causes	Non-urological causes
Renal or ureteral stones	Aortic aneurysm
Urinary tract infection (pyelonephritis, pyonephrosis, renal abscess)	Gallbladder disorder
Uretero-pelvic junction obstruction	Gastrointestinal disorders
Renal vascular disorders (renal infarction, renal vein thrombosis)	Pancreatic disease
Papillary necrosis	Gynaecological disorders
Intra- or peri-renal bleeding	Musculoskeletal disease
Testicular cord torsion.	

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 hours), 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 (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 UPJ** 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	GR
Febrile patients (> 38°C) with acute flank pain and/or with a solitary kidney need urgent imaging.	B

*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/mm^3.

*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 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 (IVU)

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 58-96% in untrained staff in emergency rooms (15), 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 (15) (LE: 2b). US is the diagnostic imaging modality of choice during pregnancy.

6.2.3.3 Unenhanced helical CT (UHCT)

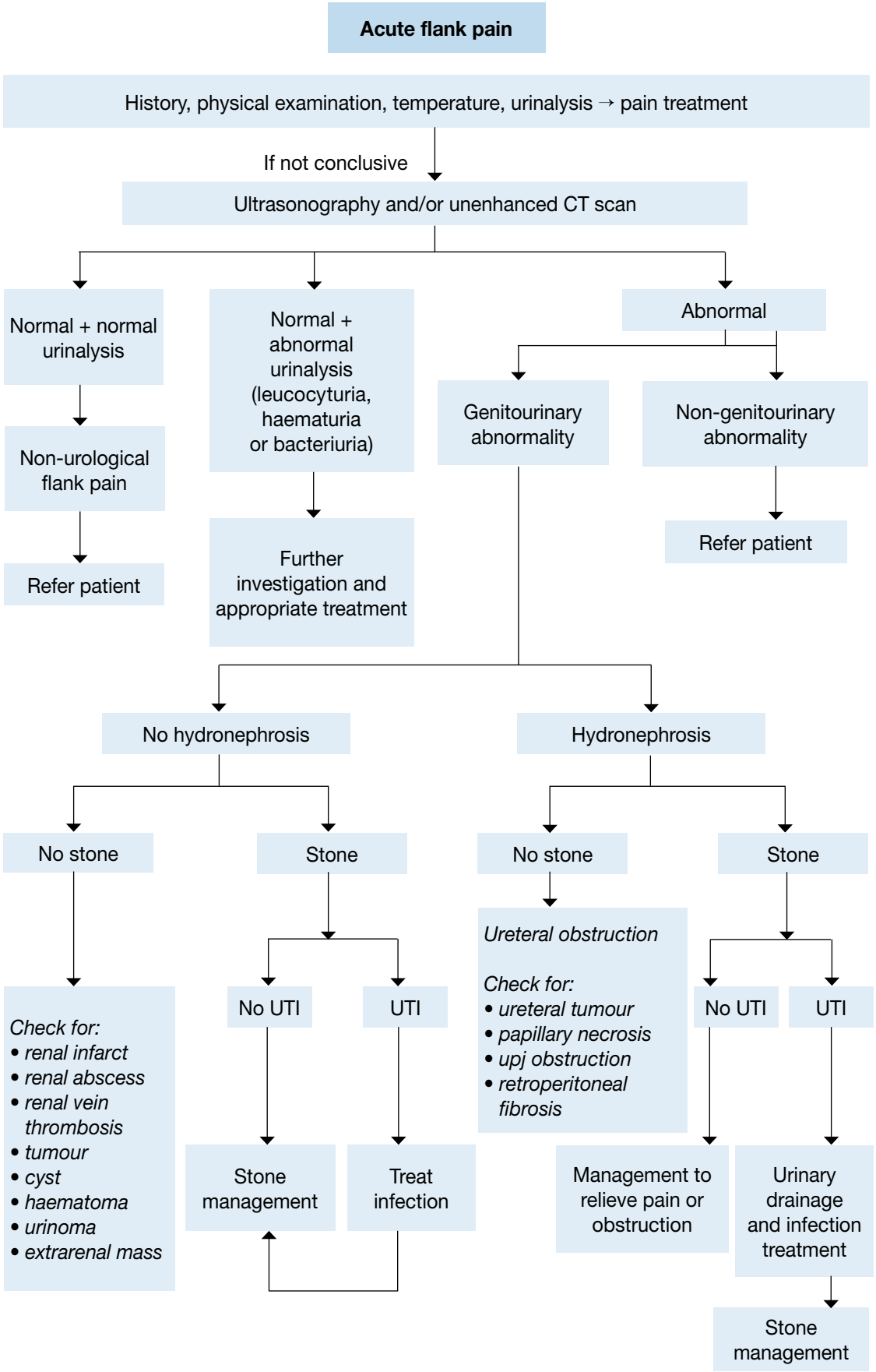
IVU reliably provides information on the anatomy of the urinary collecting system (ureteral and renal pelvic dilatation) in 80-90% of cases and can indentify ureteral calculi in 40-60% of cases.

Direct identification of ureteral calculi can be achieved in 40-60% of cases, whereas indirect signs (e.g. ureteral and renal pelvic dilatation) allows 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.

UHCT 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 33 shows comparative results of UHCT US and IVU in assessing acute flank pain and suspicion of ureterolithiasis (17-19). Figure 2 summarises the diagnostic approach to non-traumatic acute flank pain.

Figure 2: Diagnostic approach to non-traumatic acute flank pain



CT = computed tomography; UTI = urinary tract infection.

Recommendations	GR
Unenhanced helical computed tomography is the diagnostic imaging modality with the highest sensitivity and specificity for evaluation of non-traumatic acute flank pain.	A
Ultrasound can be an alternative to unenhanced helical computed tomography in the initial approach to non-traumatic acute flank pain.	A

Table 33: Comparative results of UHCT, US and IVU in assessment of acute flank pain and suspected ureterolithiasis (12)

Imaging modality	Performance	Ref. no.
UHCT	Sensitivity 100%, specificity 96%, accuracy 98%	17
Abdominal radiograph + US versus UHCT	UHCT: sensitivity and specificity of 100% US: sensitivity 100%, specificity 90%	18
Low-dose UHCT versus IVU	UHCT: sensitivity 97%, specificity 96% Low-dose UHCT is superior to IVU	19

6.3 Initial emergency treatment

*6.3.1 **Systemic analgesia***

Pain relief is usually the first, most urgent, therapeutic step (20,21):

- Intravenous (iv) non-steroidal anti-inflammatory drugs (nsaids) are very effective in most cases, e.g. a bolus of diclofenac sodium, 75 mg (le: 1a) (21); a slow iv injection of ketorolac, 30 mg, 4 times daily, is equivalent to diclofenac in the treatment of renal colic (22).
- Tests have shown a single dose of dipyrone to be less effective than diclofenac, 75 mg (23) (le: 1a), but a slow iv infusion of dipyrone, 1 g or 2 g, is just as effective as diclofenac (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) (21).
- 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.

Recommendation	GR
In patiens presenting with acute flank pain NSAIDs such as diclofenac (75 mg bolus) and dipyrone (1-2 g slow iv injection) are the drugs of first choice.	A

*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 (28); 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.

6.4 Aetiological treatment

*6.4.1 **Urolithiasis***

General concepts for treating urolithiasis have been defined in the EAU Guidelines on Urolithiasis (32).

*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 (33).

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 Uretero-pelvic junction obstruction

Uretero-pelvic junction obstruction 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 (34).

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 (35).

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 (36).

6.4.3.4 RVT

RVT 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 (37) is standard, but the successful use of fibrinolytic agents in selected patients without clinical contraindications has been reported (38). Thrombectomy or nephrectomy is reserved for cases refractory to medical therapy.

6.4.3.5 Intra- or peri-renal bleeding

Acute spontaneous intra- or peri-renal 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 (39,40).

6.4.3.6 Testicular cord torsion

Testicular cord torsion can produce lower abdomen and flank pain; it should be treated surgically at once.

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7. 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
CNS	central nervous system
COX	cyclo-oxygenase
CT	computed tomography
EDTMP	ethylenediaminetetramethylenephosphonate
EORTC	European Organisation for Research and Treatment of Cancer
ESWL	extracorporeal shock wave lithotripsy
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
^{131}J-MIBG	131J-metaiodobenzylguanidine
MRI	magnetic resonance imaging
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
RCC	renal cell carcinoma
RLND	retroperitoneal lymph node dissection
sc	subcutaneous
^{153}Sm	samarium-153
^{89}Sr	strontium-89
SRI	selective serotonin reuptake inhibitors
SPECT	single photon emission computed tomography
TCA	tricyclic antidepressants
TCC	transitional cell carcinoma
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 Management Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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
Chronic Pelvic Pain

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European
Association
of Urology

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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 this 2012 update the panel focused 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.

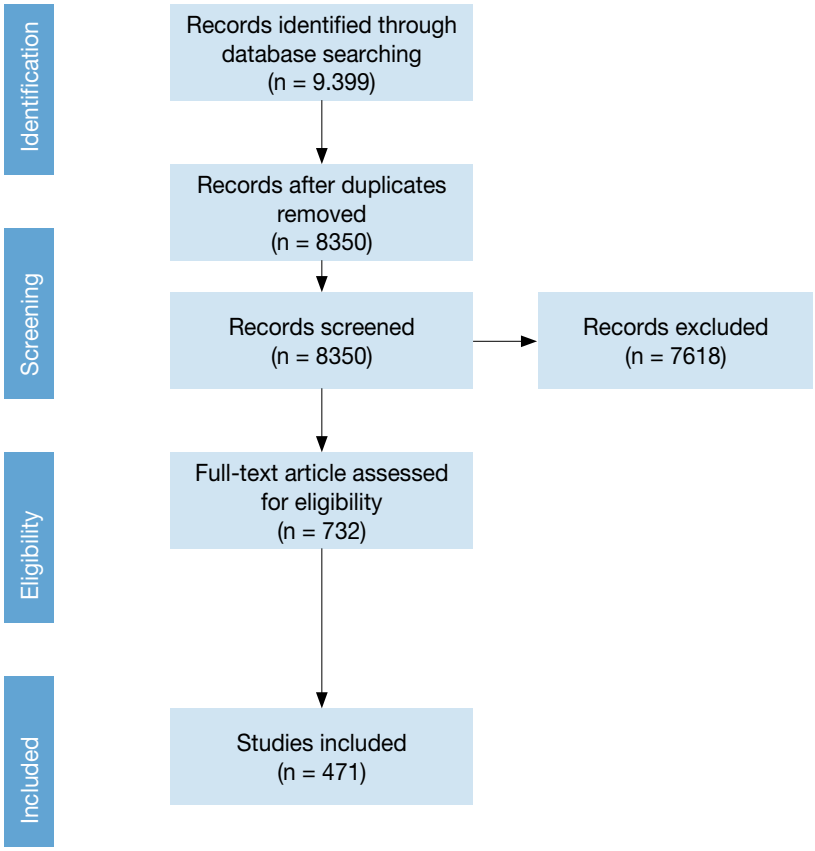
As a result, two new chapters have been added; Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain.

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 (LE1), according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (Table 1) [5]. Where no LE1 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.

Flowdiagram update procedure



*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)*

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

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)*

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

**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.

Prof. Jan Borovicka, gastro-enterologist at the Kantonsspital St. Gallen, Switzerland, authored Chapter 5 'Gastrointestinal aspects of chronic pelvic pain' of this document.

Dr. Yacov Reisman, urologist at the Amstelland Hospital in Amstelveen and sexologist at the Academic Medical Center in Amsterdam, the Netherlands, authored Chapter 7 'Sexological aspects of chronic pelvic pain'.

The CPP panel are most grateful for their assistance and willingness to lend their expertise to the EAU and their Guidelines Office. Their input greatly enhance these guidelines.

The support provided by research scientist Drs. J. Krabshuis has proved to be highly valuable in enhancing the methodological quality of this publication.

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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 will be covered in chapter 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

	Visceral pain	**Somatic pain**
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised but well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A∂ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on. These fibres are very important in the central sensitisation process.	Silent afferents present, but form a lower percentage.

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 effect nociceptor response to a nociceptive stimulus

Nerve growth factor (NGF)	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.
Adenosinetriphosphate (ATP)	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.
Substance P and other neurokinins (17)	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.

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 inpost-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-facilitary 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 facilitary modulation are even less well understood, but the mechanisms are well accepted.

*2.2.6 **Neuromodulation 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 for 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 bilary 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 (enthesitis) 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).

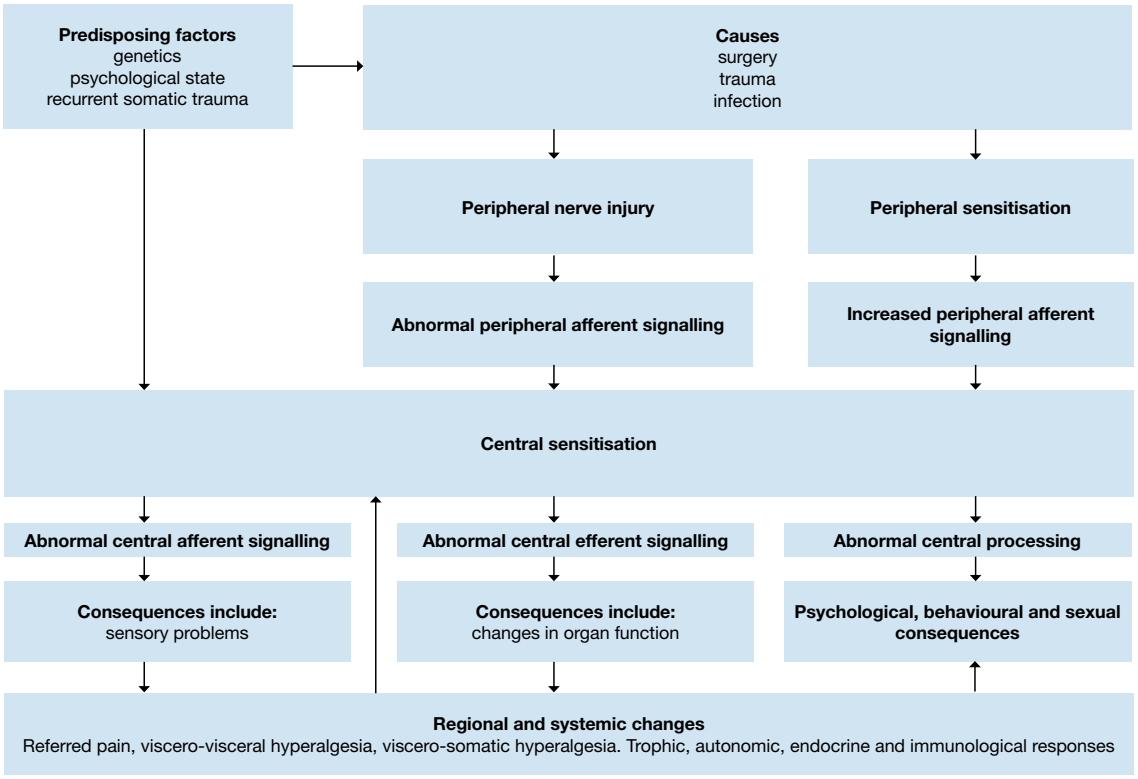
2.3.4 ***Visceral hyperalgesia***

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



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-ocurrence 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

Axis I Region		Axis II System	Axis III End organ as pain sundrome as identified from Hx, Ex and Ix		Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Specific disease associated pelvic pain OR Pelvic pain syndrome	Urological	Prostate		Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urge Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urge Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalegesie SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrofic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
				Bladder					
				Scrotal Testicular Epididymal					
				Penile Urethral					
				Post-vasectomy					
		Gynaecological	Vulvar Vestibular Clitoral						
			Endometriosis associated						
			CPPS with cyclical exacerbations						
			Dysmenorrhoea						
		Gastrointestinal	Irritable blowel						
			Chronic anal						
			Intermittent chronic anal						
		Peripheral nervers	Pudendal pain syndrome						
		Sexological	Dyspareunia						
			Pelvic pain with sexual dysfunction						
		Psychological	Any pelvic organ						
		Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal						
			Coccyx						

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 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, behavioral, 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 (CPPS)

Chronic pelvic pain syndrome 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 subdivide 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: Urologicalpain syndromes

Urological Pain Syndromes - Chapter 3	
Prostate pain syndrome	PPS is the occurrence of persistent or recurrent episodic pain (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, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The term “chronic prostatitis” continues to be equated with that of PPS. In the author’s and others’ opinion, this is an inappropriate term, although it is recognised that it has a long history of use. The National Institutes of Health (NIH) consensus (34) includes infection (types I and II), which the authors feel should not be considered under PPS, but as specific disease-associated pelvic pain. The term prostadynia has also been used in the past but is no longer recommended by the expert panel. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPS of the male is used instead of PPS, which has been agreed by the majority.
Bladder pain syndrome	BPS is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. BPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. BPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of subclassifications (11) to acknowledge differences and make it easier to compare various studies. Other terms that have been used include “interstitial cystitis”, “painful bladder syndrome”, and “PBS/IC” or “BPS/IC”; these terms are no longer recommended.
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.
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 orchiodynia. These terms are no longer recommended.
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.

Penile pain syndrome	Penile pain syndrome is the occurrence of pain within the penis that is not primarily in the urethra, in the absence of proven infection or other obvious local pathology. Penile 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.
Urethral pain syndrome	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.
Postvasectomy scrotal 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.
Gynaecological Pain Syndromes: external genitalia - Chapter 4	
Vulvar pain syndrome	Vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain. There is no proven infection or other local obvious pathology. 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. Although pain perceived in the vulva was subsumed under sexual disorders in the DSM-IV-R manual for classifying psychiatric disorders, there is no scientific basis for this classification, and pain perceived in the vulva is best understood as a pain problem that usually has psychological consequences. There is no evidence for its classification as a psychiatric disorder. The International Society for the Study of Vulvovaginal Disease (ISSVD) has used the term vulvodynia, where we use the term vulvar pain syndrome. According to the ISSVD, vulvodynia is vulvar pain that is not accounted for by any physical findings. The ISSVD has defined vulvodynia as “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder”. If physical findings are present, the patient is said to have vulvar pain due to a specified cause. The ISSVD has subdivided vulvodynia based on pain location and temporal characteristics of the pain (e.g., provoked or unprovoked). The following definitions are based on that approach.
Generalised vulvar pain syndrome	Generalised vulvar pain syndrome refers to a vulvar pain syndrome in which the pain/burning cannot be consistently and precisely localised by point-pressure mapping via probing with a cotton-tipped applicator or similar instrument. Rather, the pain is diffuse and affects all parts of the vulva. The vulvar vestibule (the part that lies between the labia minora into which the urethral meatus and vaginal introitus open) may be involved but the discomfort is not limited to the vestibule. This pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included “dysesthetic vulvodynia” and “essential vulvodynia”, but are no longer recommended.
Localised vulvar pain syndrome	Localised vulvar pain syndrome refers to pain that can be consistently and precisely localised by point-pressure mapping to one or more portions of the vulva. Clinically, the pain usually occurs as a result of provocation (touch, pressure or friction). Localised vulvar pain syndrome can be subdivided into vestibular pain syndrome and clitoral pain syndrome.
Vestibular pain syndrome	Refers to pain that can be localised by point-pressure mapping to the vestibule or is well perceived in the area of the vestibule.
Clitoral pain syndrome	Refers to pain that can be localised by point-pressure mapping to the clitoris or is well perceived in the area of the clitoris. Gynaecological system: internal pelvic pain syndromes - Chapter 4

Endometriosis-associated pain syndrome	Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain in patients with laparoscopically confirmed endometriosis, and the term is used when the symptoms persist despite adequate endometriosis treatment. 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. Many patients have pain above and beyond the endometriotic lesions; this term is used to cover that group of patients. Endometriosis may be an incidental finding, is not always painful, and the degree of disease seen laparoscopically does not correlate with severity of symptoms. As with other patients, they often have more than one end organ involved. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
CPPS with cyclical exacerbations	CPPS with cyclical exacerbations covers the non-gynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or BPS) as well as pain similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation.
Dysmenorrhoea	Dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.
Musculoskeletal System - Chapter 9	
Pelvic floor muscle pain syndrome	Pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. 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. This syndrome may be associated with overactivity of or trigger points within the pelvic floor muscles. Trigger points may also be found in several muscles, such as the abdominal, thigh and paraspinal muscles and even those not directly related to the pelvis.
Coccyx pain syndrome	Coccyx pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the region of the coccyx, in the absence of proven infection or other obvious local pathology. Coccyx 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. The term “coccydynia” was used but is no longer recommended.
Gastrointestinal Pelvic Pain Syndromes - Chapter 5	
Irritable bowel syndrome	IBS is the occurrence of chronic or recurrent episodic pain perceived in the bowel, in the absence of proven infection or other obvious local pathology. Bowel dysfunction is frequent. IBS is often associated with worry and preoccupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract or gynaecological dysfunction. The above classification is based upon the Rome III Criteria (35): 3 months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> 3 bowel movements per day or < 3 per week); noticeable difference in stool form (hard, loose, watery or poorly formed stools); passage of mucus in stools; bloating or feeling of abdominal distension; or altered stool passage (e.g., sensation of incomplete evacuation, straining, or urgency). Extra- intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.

Chronic anal pain syndrome	Chronic anal pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the anus, in the absence of proven infection or other obvious local pathology. Chronic anal 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.
Intermittent chronic anal pain syndrome	Intermittent chronic anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a subgroup of the chronic anal pain syndromes. It was previously known as "proctalgia fugax"; this term is no longer recommended.

2.6 Conclusions and recommendations: CPP and mechanisms

Conclusions	**LE**
CPPS mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1
End organ function can also be altered by the mechanisms of neuroplasticity and neuropathic pain, so that symptoms of function can also occur.	1
CPP is associated with a high impact on QoL.	1
The diagnosis of a CPPS as a pain syndrome is essential as it encourages a holistic approach to management with multispecialty and multidisciplinary care.	2

Recommendations	**GR**
All of those involved in the management of CPP should have an understanding and training in CPPS pain mechanisms.	A
The early assessment of patients should involve not only investigations aimed at specific disease-associated pelvic pain but also to assess functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation.*	A
CPPS patients should be managed in a multispecialty and multidisciplinary environment with consideration of all their symptoms.	A
Future classification should involve consideration of all three recommendations above.	A

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 diagnosis of a patient 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 we 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

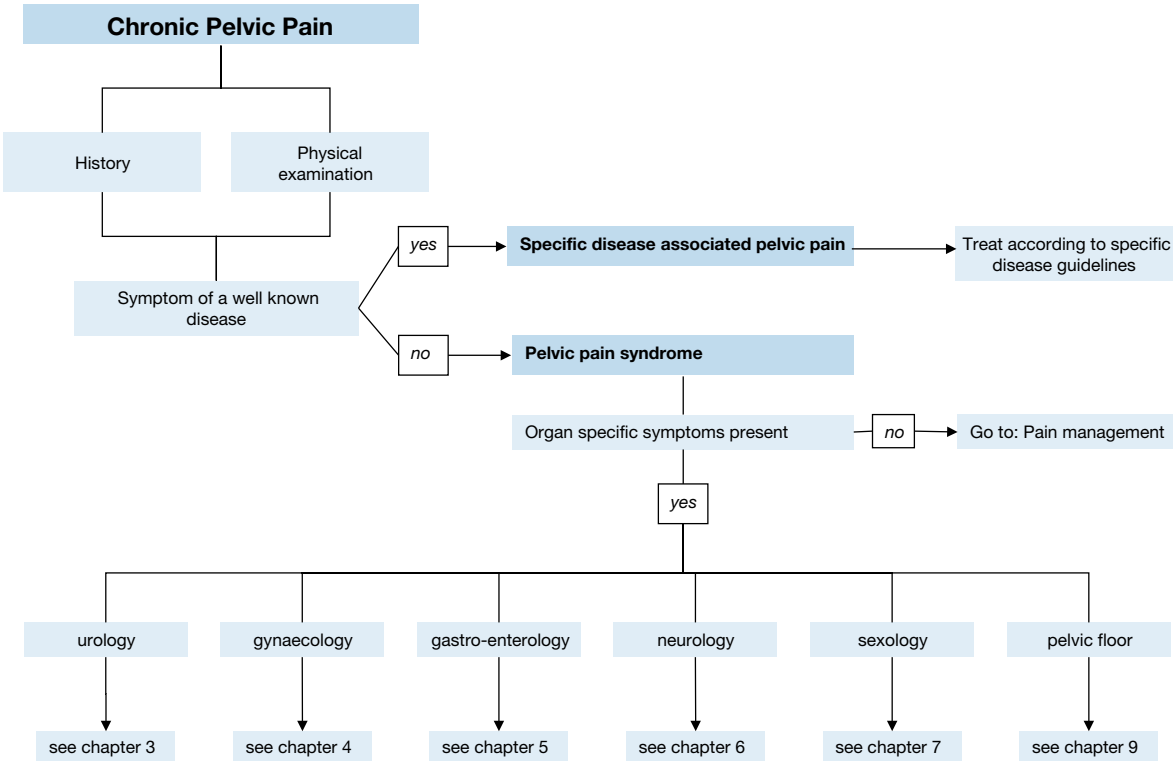


Figure 3: an algorithm for pain management

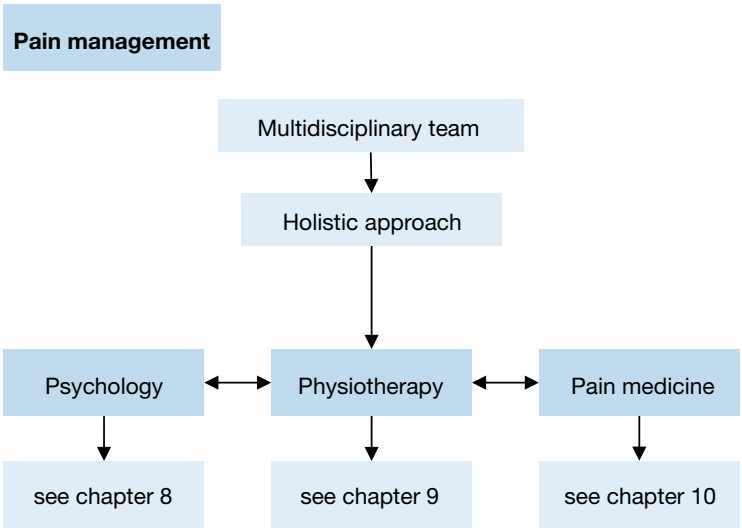


Figure 4: phenotyping and assessment algorithm for CPP

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry
Psychology	History of negative experiences, important loss, coping mechanism, depression
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints Gynaecological examination, rectal examination
Infection	Semen culture and urine culture, vaginal swab, stool culture
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles

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3. UROLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

3.1 Prostate pain syndrome (PPS)

*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 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. QoL 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*

Conclusions	LE
PPS is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.	2b
PPS has no known single aetiology.	3
Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
PPS has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPS-like symptoms is high in population-based studies (> 2%).	2b
There is significant overlap of symptoms with other conditions.	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	GR
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.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with prostate pain syndrome.	A
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.	B
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.	B

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 does 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

After 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 (47). 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 (BTX-A)

Botulinum toxin A (BTX-A) may have pain-alleviating effects through non-neuromuscular action on afferent nociceptive pathways. Local treatment with periurethral 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.

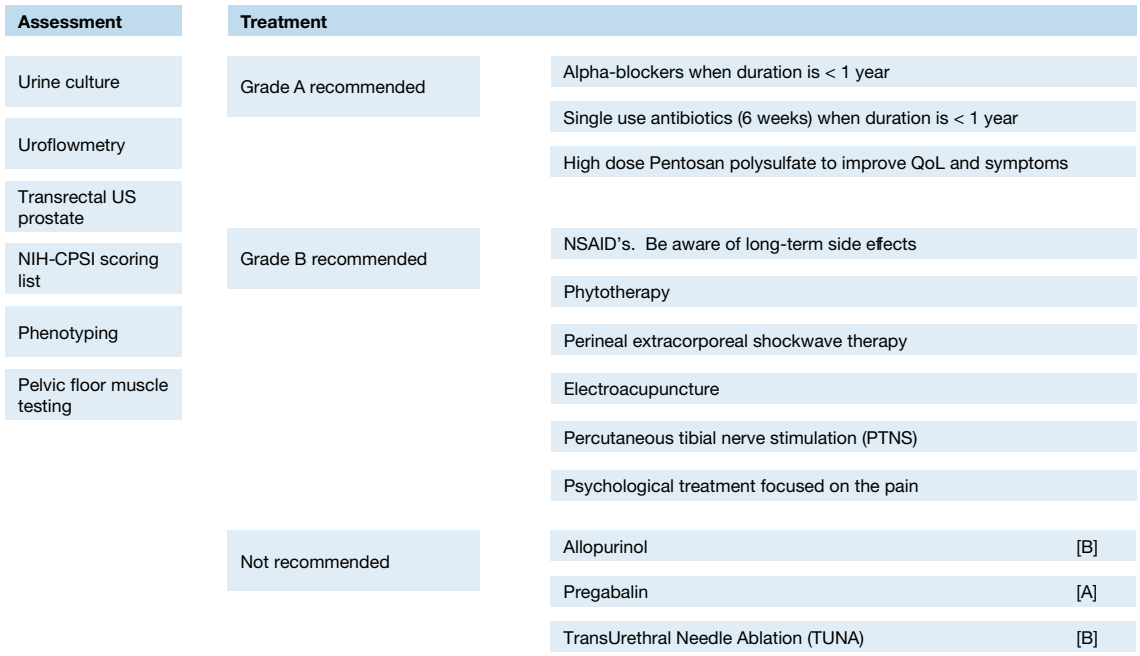
*3.1.8 **Conclusions and recommendations: treatment of PPS***

Conclusions	**LE**
Monotherapeutic treatment regimens in PPS may fail.	3
Phenotypically directed treatment may improve treatment success.	3
Alpha-blockers have moderate treatment effect regarding total, pain, voiding, and QoL scores in PPS.	1a
Antimicrobial therapy has a moderate effect on total, pain, voiding, and QoL scores in PPS.	1a
NSAIDs have moderate overall treatment effects on PPS.	1a
There are insufficient data on the effectiveness of steroids in PPS.	2b
There are insufficient data on the effectiveness of opioids in PPS.	4
There are insufficient data on the effectiveness of 5-alpha-reductase inhibitors in PPS.	2b
There are insufficient data on the effectiveness of allopurinol in PPS.	2b
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPS.	1a
Pentosan polysulphate improves global assessment and QoL score in PPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPS.	2b
Pregabalin is not effective for the treatment of PPS.	1b
BTX-A injection into the pelvic floor may have a modest effect in PPS.	2b
There are only limited data on the effectiveness of electromagnetic therapy in PPS.	2b
There are only limited data on the effectiveness of microwave thermotherapy in PPS.	3
Perineal extracorporeal shock wave therapy probably is effective for the treatment of PPS.	1b
There are limited data on the effectiveness of electroacupuncture for the treatment of PPS.	2b
Posterior tibial nerve stimulation is probably effective for the treatment of PPS.	1b
There are insufficient data on the effectiveness of myofascial physical therapy for the treatment of PPS.	2b
There are limited data on lack of effectiveness of TUNA of the prostate for PPS.	2b
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.	3
Cognitive behavioural therapy designed for PPS may improve pain, and quality of life.	3

Recommendations	GR
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



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3.2 Bladder pain syndrome (BPS)

*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 refered 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 (Table7) (8).

Table 7: ESSIC classification of types of BPS according to the results of cystoscopy with hydrodistension and biopsies (8)

		Cystoscopy with hydrodistension		
	Not done	**Normal**	**Glomerulations[a]**	**Hunner's lesion[b]**
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

[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 (43). Urinary NO is significantly increased in ulcer patients and decreases with treatment, but not in non-ulcer BPS patients (44). 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-Horsefall 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 agression mode, induced on urethelial 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 oestradiol 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 (55,59,60).

Some of the clinical and histopathological characteristics are similar to autoimmune phenomena. However, only some BPS patients demonstrate autoantibodies, immune deposits or complement activation (61-68). Of note, differing T-cell infiltrates and B-cell nodules are seen in BPS type 3 C (69).

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 (80-83). 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).

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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 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).

3.2.10 *Conclusions and recommendations: assessment and diagnosis BPS*

Conclusions	LE
BPS has no known single aetiology.	3
Pain in BPS does not correlate with bladder cystoscopic or histologic findings.	2a
BPS Type 3 C is not surely distinguishable by non-invasive means.	2a
Ulcer non-ulcer disease ratios of BPS are highly variable between studies.	2a
The prevalence of BPS-like symptoms is high in population-based studies.	2a
BPS associated non bladder diseases are extremely prevalent, differ in BPS subtypes and correlate with BPS risk.	2a
BPS has a high impact on quality of life.	2a
There is significant overlap of symptoms with other conditions.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	GR
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.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with BPS by subtype and phenotype.	A
A validated symptom and quality of life scoring instrument should be considered for initial assessment as well as for follow-up.	B
BPS associated non bladder diseases should be assessed systematically.	A
BPS associated negative cognitive, behavioural, sexual, or emotional consequences should be assessed.	A

BPS = Bladder pain syndrome.

3.2.11 *References*

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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 recognise 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 noradrenalin, 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 (14) were treated for 4 months with amitriptyline.

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 10mg 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 have a limited role in the treatment of BPS. 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 five 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 (3 100 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

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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 alkalinised 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 alkalinised 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 ($P \leq .01$), whereas the placebo group showed significant improvement in only three domains, ($P \leq .05$) 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 et al. (9) have 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 (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 $C_{max} < 30\%$ 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 sulphoxide (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. DMSO 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). Rossberger 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 (86), BCG treatment failed to demonstrate any benefit.
Another randomised, placebo-controlled, double-blind trial of 260 refractory BPS patients (27) 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 (28), 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 (29).

Vanilloids disrupt sensory neurons (30). Resiniferatoxin (RTX) is an ultrapotent analogue of the chilli pepper extract capsaicin, causing less pain on instillation and therefore no anaesthesia. Chen et al. (31) 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 (32), 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 (33). In a small open-label study with single-dose RTX in patients with frequency and urgency (34), 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) (35). 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 (36) (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 (37).

3.2.13.1 References

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3.2.14 ***Interventional treatments***

Bladder distension. A frequently cited report by Bumpus *et al*. (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, Glemain *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 (2006) 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 five refractory BPS patients, four 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 ± 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

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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). NO 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.

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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 (17) has 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 10 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

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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 unresected 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 ileocaecocystoplasty.

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 (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 urethrotrigonal 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, Navalon *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 Peeker *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 stills 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***

Conclusions	**LE**
None of the present existing treatments have effect on all BPS subtypes or phenotypes.	4
Conventional analgesics have little efficacy. Opioids are effective in controlling BPS pain.	2b
Corticosteroids are not recommended as long-term treatment.	3
Hydroxyzine has limited efficacy shown in RCT and is effective in associated non bladder diseases.	1b
Limited data exist on effectiveness of cimetidine in BPS.	2b
Amitriptyline is effective in pain and related symptoms of BPS.	1b
Oral PPS is effective in pain and related symptoms of BPS.	1a
Oral PPS plus subcutaneous heparin is effective in pain and related symptoms of BPS especially in patients initially low responders to PPS alone.	1b
Only limited data exist on the effectiveness of antibiotics in the treatment of BPS.	2b
Insufficient data for the effectiveness of prostaglandins in BPS exist. Adverse effects are frequent.	3
Global response on cyclosporin A was superior to PPS, but associated with more adverse effects.	1b
Duloxetin has shown no effect and tolerability is poor.	2b
Oxybutynin has limited effect in BPS pain, but data are scant.	3
Only insufficient data exist for the effectiveness of gabapentin in BPS.	3
Only insufficient data exist for the effectiveness of suplatast tosilate in BPS.	3
Preliminary data showed effectiveness of quercetin alone and in multimodal uncontrolled studies.	3
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical PPS is effective based on limited data and may enhance effect of oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical hyaluronic acid may have long term effects in BPS patients with positive intravesical modified KCl test.	2b
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

Recommendations	**GR**
Subtype and phenotype-oriented therapy for BPS is recommended.	A
Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments for BPS.	A
Opioids might be used in BPS in disease flare-ups. Long term application solely if all treatments failed.	C
Corticosteroids are not recommended as long-term treatment.	C
Hydroxyzine is recommended for use in BPS.	A
Consider cimetidine as valid oral option before invasive treatments.	B
Amitriptyline is recommended for use in BPS.	A
Oral PPS is recommended for use in BPS.	A
Treatment with oral PPS plus subcutaneous heparin is recommended especially in low responders to PPS alone.	A
Antibiotics can be offered when infection is present or highly suspected.	C
Prostaglandins are not recommended. Insufficient data on BPS, adverse effects considerable.	C
Cyclosporin A might be used in PPS but adverse effects are significant and should be carefully considered.	B
Duloxetin is not recommended for BPS treatment.	C
Oxybutynin might be considered for the treatment of BPS.	C
Gabapentin might be considered in oral treatment of BPS.	C
Consider intravesical lidocain plus sodium bicarbonate prior to more invasive methods.	A
Consider intravesical PPS before more invasive treatment alone or combined with oral PPS.	A
Consider intravesical heparin before more invasive measures alone or in combination treatment.	C
Consider intravesical hyaluronic acid before more invasive measures.	B
Consider intravesical chondroitin sulphate before more invasive measures.	B
Consider intravesical DMSO before more invasive measures.	A
Consider intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies failed.	C
Consider submucosal injection of BTX-A plus hydrodistension if intravesical instillation therapies failed.	A
Intravesical therapy with Bacillus Calmette Guérin is not recommended in BPS.	A
Intravesical therapy with clorpactin is not recommended in BPS.	A
Intravesical therapy with vanilloids is not recommended in BPS.	C
Bladder distension is not recommendedas atreatment 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 3C only	B

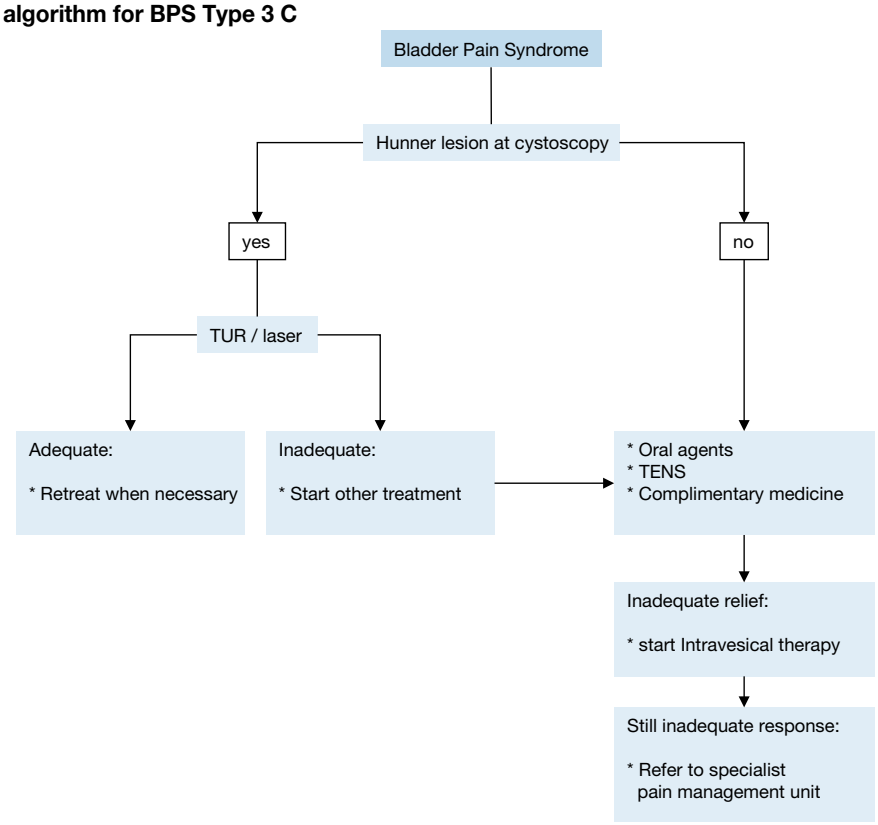
Neuromodulation might be considered before more invasive interventions.	B
Consider bladder training in patients with little pain.	B
Consider manual and physical therapy in first approach.	B
Consider in diet avoidance of triggering substances.	C
Accupuncture is not recommended.	C
Consider psychological therapy in multimodal approach.	B
All ablative organ surgery should be last resort for experienced and BPS knowledgeable surgeons only.	A

PPS = pentosanpolysulphate sodium; DMSO = dimethyl sulphoxide; BPS = bladder pain syndrome.

Figure 6: diagnosis and therapy of BPS

Assessment	Treatment	
Urine culture	Grade A recommended	Standard: Hydroxyzine, Amitriptyline, Pentosanpolysulphate
Uroflowmetry		Intravesical: PPS, DMSO, onabotulinum toxin A plus hydrodistension
Cystoscopy with hydrodistension		
Bladder biopsy	Grade B recommended	Oral: Cimetidine, cyclosporin A
Micturition diary		Intravesical: hyaluronic acid, chondroitin sulphate
Pelvic floor muscle testing		Electromotive drug administration for intravesical drugs
Phenotyping		Neuromodulation, bladder training, physical therapy
ICSI score list		Psychological therapy
	Not recommended	Bacillus Calmette Guerin
		Intravesical Chlorpactin
	Other comments	Data on surgical treatment are largely variable
		Coagulation and laser only for Hunner's lesions

Figure 7: algorithm for BPS Type 3 C



3.2.19 ***References***

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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, which 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, orchalgia and orchiodynia. 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, which 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 epididymis 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 pathognomic for pudendal neuropathy.

3.3.2.4 Post-vasectomy pain syndrome

Post-vasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Post-vasectomy 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. Pathogenetically, it is thought that post-vasectomy 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 post-vasectomy pain is 2-20% among all men who have undergone a vasectomy (7). In men with post-vasectomy 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 non-surgical 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 by 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 orchiectomy 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 post-vasectomy 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 Vaso-vasostomy

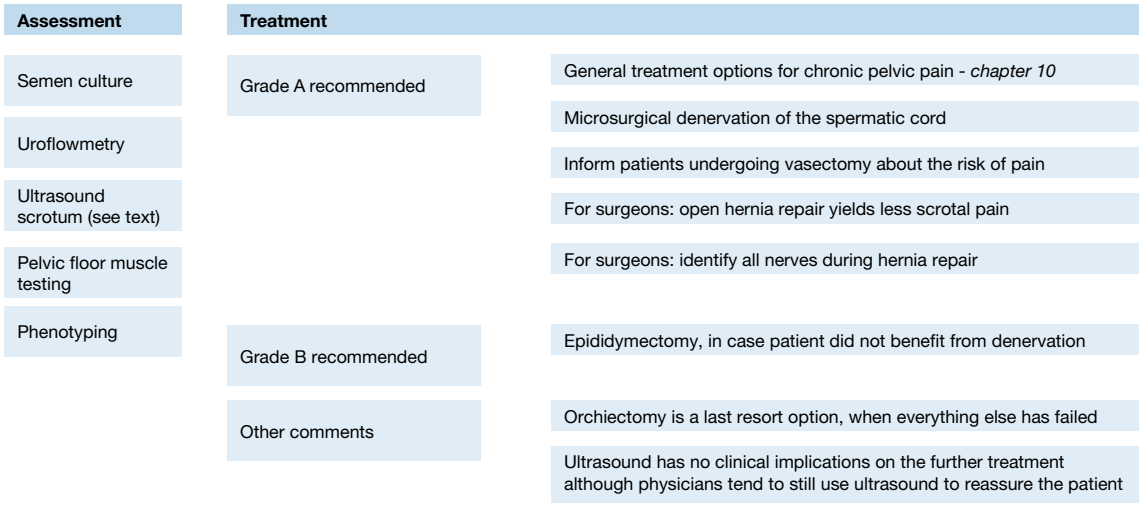
In post-vasectomy pain syndrome, a vaso-vasostomy might help to overcome the obstruction and thereby improve the pain. Some studies have shown good results but the quality of these studies was limited. Results are as high as 69-84% (31,32).

*3.3.5 **Conclusions and recommendations: scrotal pain syndrome***

Conclusions	**LE**
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal content is not of help in diagnostics nor treatment of scrotal pain.	2b
Post -vasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic then after open inguinal hernia repair.	1b
Microsurgical denervation of the spermatic cord is an effective therapy for scrotal pain syndrome.	2b
Vaso-vasostomy is effective in post-vasectomy pain.	2b
Orchiectomy is the last resort in treating scrotal pain syndrome.	4

Recommendations	**GR**
We recommend to start with general treatment options for chronic pelvic pain (see chapter 10).	A
We recommend informing about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	A
To reduce the risk of scrotal pain, we recommend open instead of laparoscopic inguinal hernia repair.	A
We recommend that during inguinal hernia repair all the nerves in the spermatic cord are identified.	A
For patients who are treated surgically, we recommend microsurgical denervation of the spermatic cord.	A
For patients who do not benefit from denervation we recommend to perform epididymectomy.	B
We recommend that orchiectomy is reserved as last resort when every other treatment has failed.	C

Figure 8: assessment and treatment algorithm for scrotal pain syndrome



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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 Arunkalaivanan have concluded that "treatment at its best" is by "behavioral 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. 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.

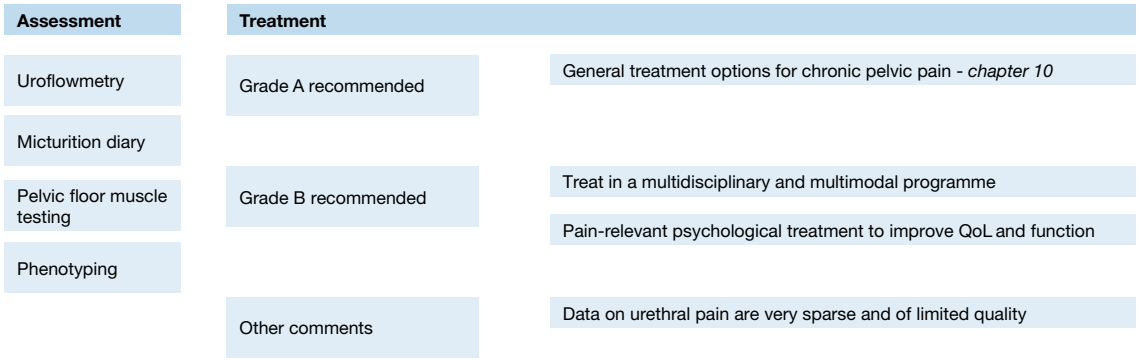
3.4.4 ***Conclusions and recommendations: urethral pain syndrome***

Conclusions	**LE**
Urethral pain syndrome may be a part of BPS.	2a
Urethral pain may be neuropathic hypersensitivity following urinary tract infection.	2b
There is no specific treatment for urethral pain syndrome.	4

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.	4

Recommendations	GR
We recommend to start with general treatment options for chronic pelvic pain (see chapter 10).	A
We recommend that patients with urethral pain syndrome are treated in a multidisciplinary and multimodal programme.	B
When patients are distressed, we recommend referring them for pain-relevant psychological treatment to improve function and quality of life.	B

Figure 9: assessment and treatment algorithm for urethral pain syndrome



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4. GYNAECOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

4.1 Introduction

Chronis 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 post-laparoscopy 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 levo-norgestrol 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, he 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).

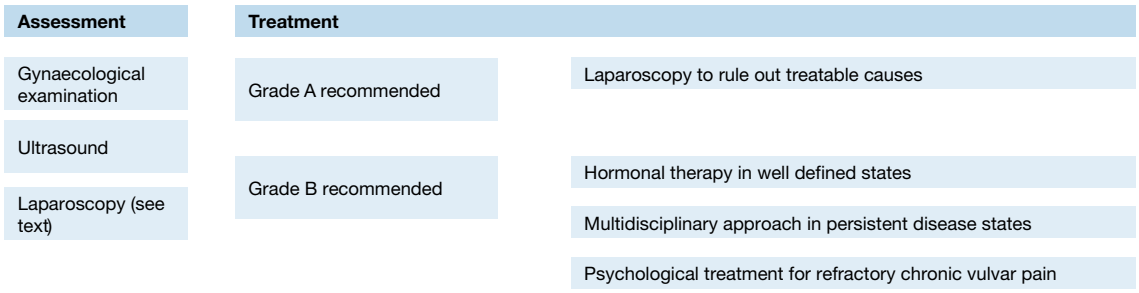
It is only when all the above conditions have been excluded that the physician may declare that the patient has 'unexplained' pelvic pain. Treating these patients remains a challenge for all physicians but quite clearly the best results are obtained from a multidisciplinary approach that considers all possible causes.

*4.6.1 **Conclusions and recommendations: gynaecological aspects of chronic pelvic pain***

Clinical state		**LE**
Clinical history and examination	Mandatory to making a diagnosis	2a
Investigations	Mandatory to making a diagnosis	2a
	Laparoscopy is well tolerated and does not appear to have negative psychological effects	1b
Pain associated with well-defined conditions	*Dysmenorrhoea: effective therapeutic options*	3
	Infection: effective therapeutic option	3
	Endometriosis: effective therapeutic options including medical and surgical care	1b
	Gynaecological malignancy: effective therapeutic options	3
	Injuries related to childbirth: effective therapeutic options	3
	Pain associated with pelvic organ prolapse: effective therapeutic options	3
Vaginal and vulvar pain syndrome	Diagnosis and therapeutic interventions	3
	Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function	1b
Laparoscopy does not appear to have negative psychological effects		1b

Recommendations	GR
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).	A
Provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	B
Provide a multidisciplinary approach to pain management in persistent disease states.	B
Recommend psychological treatment for refractory chronic vulvar pain.	B
Use alternative therapies in the treatment of chronic gynaecological pelvic pain.	C

Figure 10: assessment and treatment gynaecological aspects in chronic pelvic pain



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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 “highly likely” and “possible” levator ani syndrome 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***

CPP 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 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***

CPP 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_2O. 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 H20) 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 topic 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 gastroenterology, urology, gynaecology 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. CPP 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*

Conclusions on functional anorectal pain.	**LE**
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a
Biofeedback is the preferred treatment for the chronic anal pain syndrome.	1a
Electrogalvanic stimulation is less effective than biofeedback.	1b
Botulinum toxin is efficient in CPP with spasms.	1b
Sacral neurostimulation is effective in pelvic pain.	3
Inhaled salbutamol is effective in intermittent chronic anal pain syndrome.	3

Recommendations for functional anorectal pain	**GR**
Functional testing is recommended in patients with anorectal pain.	A
Biofeedback treatment is recommended in patients with pelvic pain and dyssynergic defecation.	A
Botulinum toxin in women with pelvic pain and electrogalvanic stimulation can be considered in the chronic anal pain syndrome.	B
Sacral neuromodulation is recommended in the chronic anal pain syndrome.	C
Inhaled salbutamol is recommended in the intermittent chronic anal pain syndrome.	C

Figure 11: assessment and treatment algorithm for anorectal pain syndrome

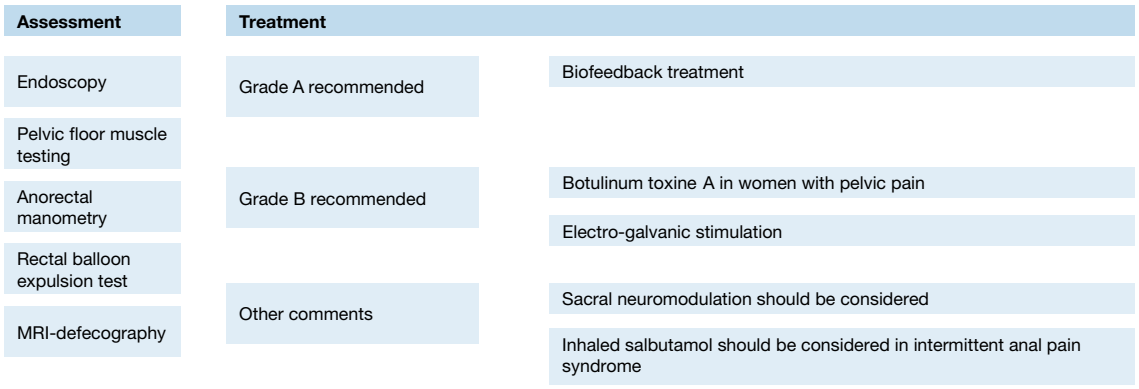
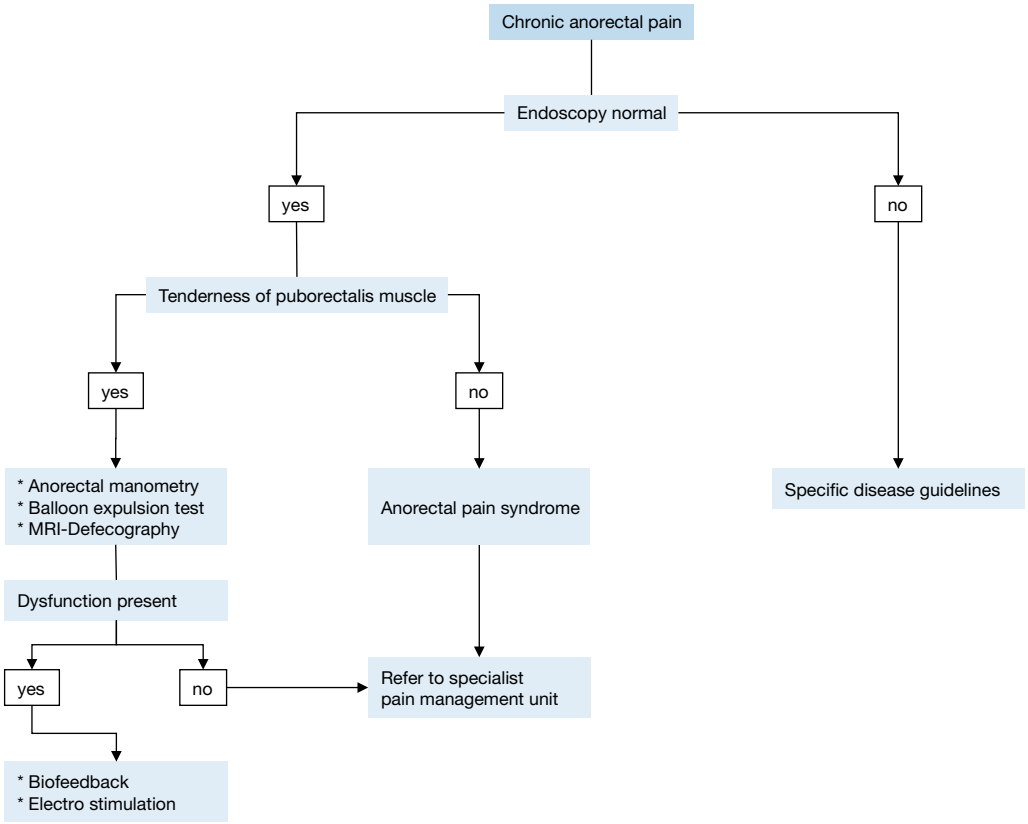


Figure 12: diagnosis algorithm for chronic anorectal pain



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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 nervoussystem (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 provide a source of 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 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 central nervous system 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 sacrotuberal ligament and ischeal 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 superiour 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 annoccoccygeal 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)

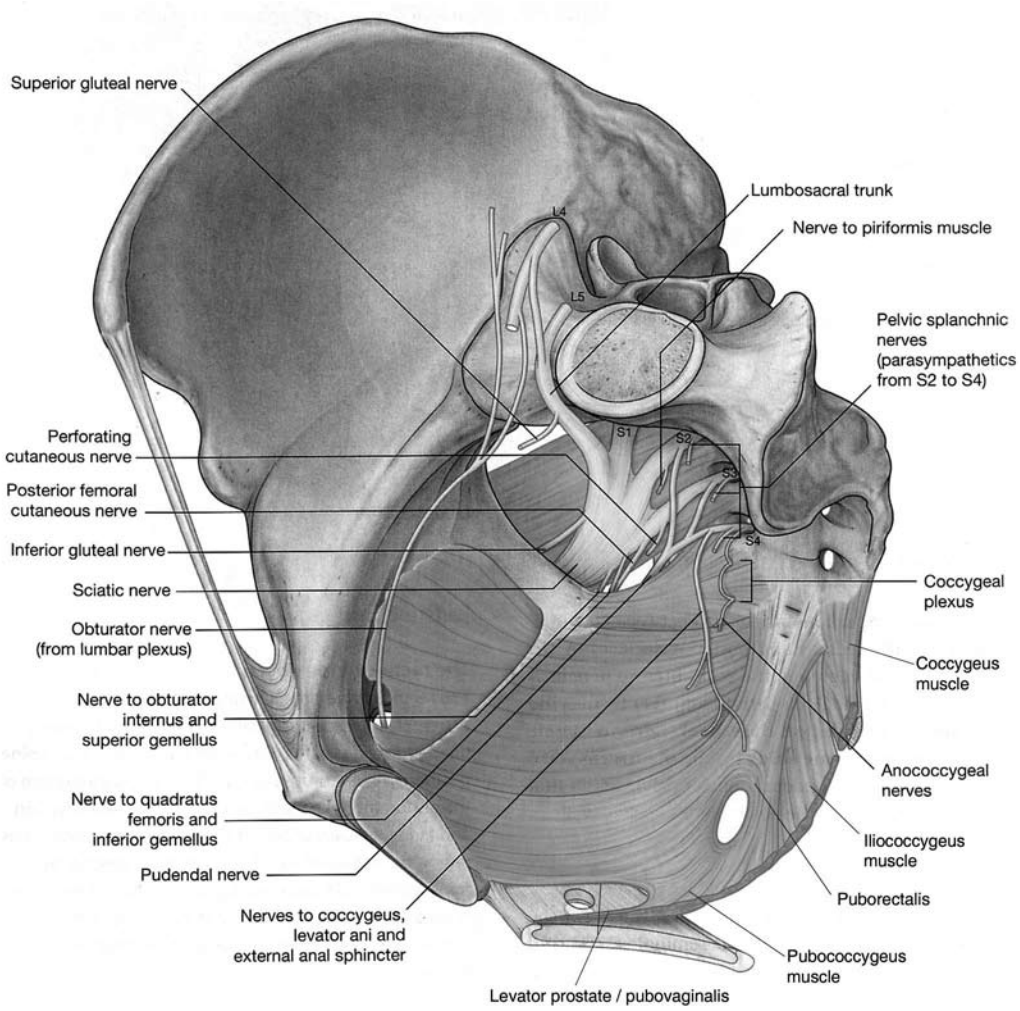
The anatomy may be variable, however, the three roots that form the pudendal nerve usually merge anterior to the sacrum and inferior to the piriformis muscle.
The pudendal nerve leaves the pelvis via the greater sciatic notch to enter the subgluteal region. In the posterior subgluteal triangle (the area 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 sacral the 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 Etiology of nerve damage

*6.3.1 **Anterior groin nerves - etiology 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 - etiology 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) (9,10).

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 pregnancy 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 where as 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 that 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); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (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 dysparunia, 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, catrostophising 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, allodynia 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 abdominus or paraspinal muscles).

6.4.2.6 Investigations

MRI 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 bulbocavernosal 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. We have already 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***

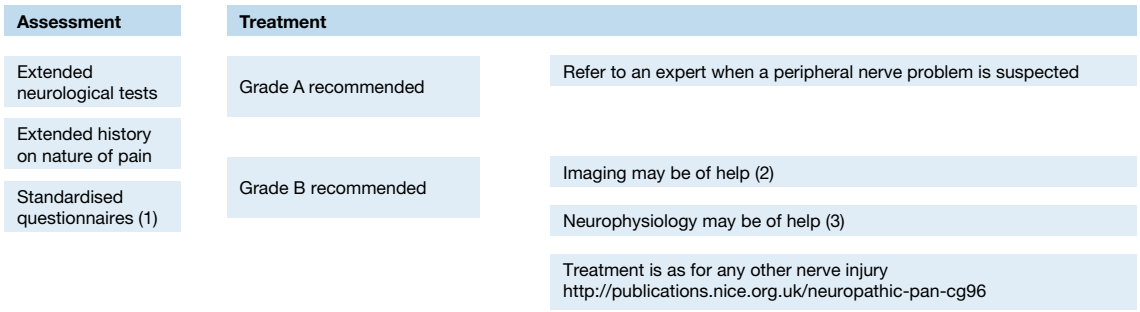
Pudendal neuralgia represents a peripheral nerve injury and as such should respond to neuromodulation by implanted pulse generators. However, it is important that the stimulation is perceived in the same site as the perceived pain. Spinal cord stimulation (SCS) may be effective for thoraco-lumbar afferents. 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 multidisciplinarycare (49-51).

6.6 Conclusions and recommendations: pudendal neuralgia

Conclusions	**LE**
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.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1
There are multiple treatment options with varying levels of evidence.	1

Recommendations	GR
It is important to rule out confusable diseases.	A
If a Peripheral Nerve Pain Syndrome is suspected, early referral should occur to an expert in the field, working within a multidisciplinary team environment.	B
Imaging and neurophysiology may help with the diagnosis, but the gold standard investigation is an image and nerve locator guided local anaesthetic injection.	B
Neuropathic pain guidelines are well established. Standard approaches to management of neuropathic pain should be utalised.	A

Figure 14: assessment and treatment algorithm for peripheral nerve pain syndrome



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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, ones 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're 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 centers" 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 man the penis will become limp and in woman the lubrication will stop, laeding 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 (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). CPP 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 (24). 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 (25).

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 (26), and that weak muscles may provide insufficient activity necessary for vaginal friction or blood flow, and inhibit orgasmic potential (27). It has also been proposed that sexual pleasure is enhanced for both partners by genital responses provided by contraction of the levator ani (28). 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 (28). 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 (29).

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% (30,31). Goetsch recently reported her findings that physical therapy may serve as important adjunct to surgery for "vulvar vestibulitis" (vulvar pain syndrome) (32).

7.4 CPP 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 (33).

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 (34) 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 (35). Post-ejaculation pain is not mentioned in this questionnaire.

In the 1980s an association between PPS and sexual dysfunction was postulated (36). 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. Where as 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 (37,38).

In a Chinese study of men with PPS 1768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) 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 (39,40). ED was prevalent in 27.4% of Italian men aged 25-50 (41), 15.2% among Turkish men

(significantly higher than control group) (17) and 43% among Finnish men with PPS (42). 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 (43,44). Recently, a significant correlation between "chronic prostatitis", PPS symptoms (measured by NIH-CPSI) and ED (measured by IIEF) was confirmed (45), while other studies using the same questionnaires were not able to confirm such a correlation (35,46). Some studies also report ejaculatory dysfunction, mainly premature ejaculation (6,30,39,40). 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" (47). The reported prevalence of PE varies widely in PPS patients, but unlike ED the prevalence does not increase with age (40).

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 (17). Screponi et al. (2001) reported the high incidence of prostatic inflammation symptoms in men with PE (48). PE 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 been shown significantly 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 (49,50).

Furthermore, there are reports which highlight the appearance of ejaculatory pain in patients with PPS (51), while some studies suggested PPS symptoms improvement by increased ejaculatory frequency and sexual activity (52,53).

The presence of pelvic pain may increase the risk for erectile dysfunction independently of age (44). On the other hand, cross-sectional data suggest no improvement of LUTS by an increased frequency of ejaculation (38). 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 (54). 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 (37-40,55).

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 (37,54). PPS 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 (56). 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 (57). Aubin et al. found that men appeared open to the initiation of sex and assumed their partners were sexually satisfied (58).

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 central nervous system plays an important role in this mechanism.

7.5 CPP and sexual dysfunction of the female

CPP 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. CPP leads to substantial impairment in QoL and several sexual dysfunctions (58-61).

It seems reasonable to expect that pain, extreme fatigueness , depressive mood and paindrugs will effect womens 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 behavior, non-sensuality, and complaints of "vaginismus" (62).

CPP 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 (20). Collett and colleagues (63) 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 (64). Satisfaction with the sexual relationship appears to be associated with higher marital functioning (65). 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 (65).

In community-based studies in the UK (7), New Zealand (59) and Australia (66), 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 (63,67,68). The study of Veritt et al. show 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 (68). 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 (67-69).

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 (70).

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 (19).

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 (19).

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 (71-75). 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 counseling during their treatment course (76). Specific behavioral 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 behavioral changes involve pre- and postcoital voiding, application of ice packs to the genital or suprapubic area (76,77), and use of vaginal dilators before penile penetration. An alternative is to use natural dilators such as different fingers or sex toys. Hypoallergenic nonirritating 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 (78). In patients with an overactive pelvic floor, referral for physical therapy, myofascial release, and internal pelvic floor muscle massage may offer relief (79).

7.7 In summary

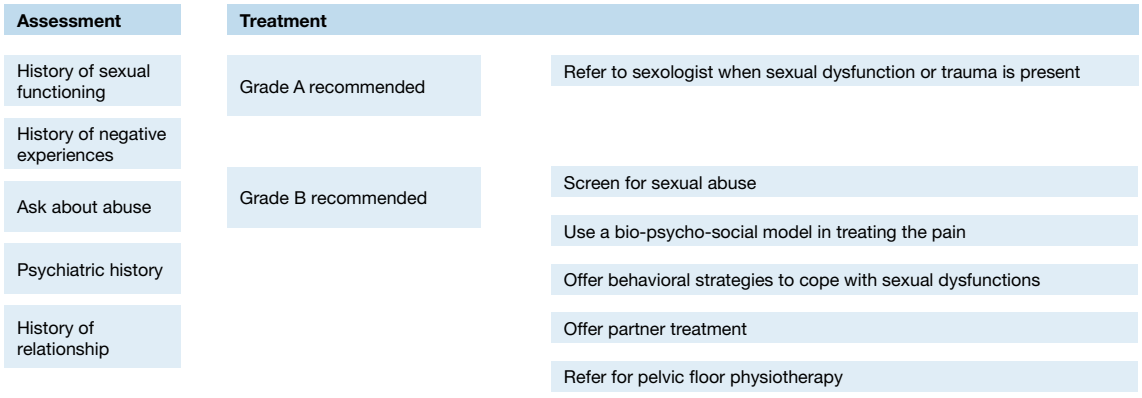
Problems with sexual functioning resulting from CPP have to be addressed and assessed by the health-care professional. The attention directed toward these patients must be focused not only on the disease but also on the woman as a whole. As treatment solely of the underlying disease is not acceptable, 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

Conclusions	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Patients who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of PPS.	2b
Sexual dysfunctions are prevalent in patient with PPS.	2b
In men with PPS the most prevalent sexual complains are erectile dysfunction and ejaculatory dysfunctions.	3
In females with CPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and “vaginismus”.	2a
Vulvar Pain Syndrome is associated with BPS.	3
Women with BPS suffer significantly more from fear of pain, dyspareunia and less desire.	2a
Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.	3
Chronic pain can cause disturbances in each of the sexual response cycle phases.	2b
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complains.	2b

Recommendations	GR
Clinicians may screen for abuse in patients presenting with symptoms suggestive for prostate pain syndrome without suggesting a causal relation with the pain.	B
The biopsychosocial model should be applied in the evaluation of the effect of prostate pain syndrome on the sexual function of the patient.	B
The biopsychosocial model should be incorporated in research in the role of chronic pelvic pain in sexual dysfunction.	B
Behavioral strategies should be offered to the patient and his/her partner to cope with sexual dysfunctions.	B
We recommend training of the pelvic floor muscles to improve quality of life and sexual function.	B

Figure 15: assessment and treatment algorithm for sexological aspects in chronic pelvic pain



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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 co-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 musculosketal 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 physican-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 has 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 has 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). Ehlert 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 healthcare, 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 healthcare 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 (1) at the pain itself, with the intended outcome of reducing pain and its consequent impact on life, or (2) at adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction.

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 (50) 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. 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 (51) 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. The only RCTs in CPP used elements of this approach in combination with medroxyprogesterone acetate (MPA) or placebo (52). Combination of 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. (53) have compared emotional disclosure by writing about pain with writing about positive events as a control. 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.

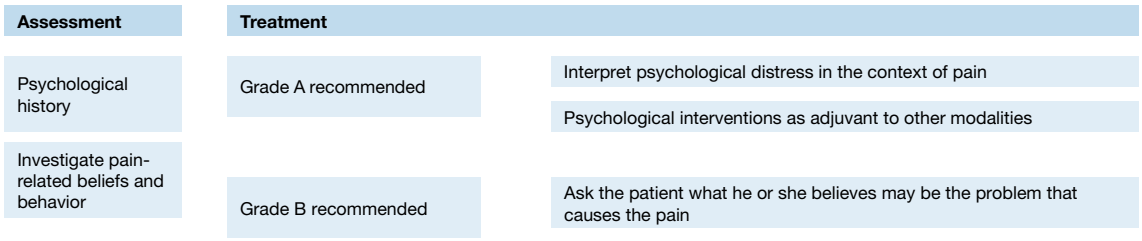
In a different intervention, Fenton et al. (54) have conducted a small RCT of transcranial direct current stimulation compared to sham stimulation. Pain reduction was greater in the treatment group, in the first week only, as was reduction in disability.

8.5 Conclusions and recommendations: psychological aspects of CPP

Conclusions	LE
There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.	2b
Current or recent sexual abuse should be assessed as possible contributory factors in pelvic pain.	2a
Psychological intervention in general can produce benefits in pain, mood, and quality of life, depending on its content and focus.	1a
Psychologically informed physical therapy can improve pain and function.	1b
Combined exercise and cognitive behavioural therapy with medroxyprogesterone acetate can reduce pain in a majority of women with pelvic pain.	1b
Transcranial direct current stimulation may reduce pain in the short term.	1b

Recommendations	GR
Psychological distress is common in pelvic pain in women but should be interpreted in the context of pain.	A
We recommend asking the patient what she thinks may be wrong to cause pain, to allow the opportunity to inform and reassure as appropriate.	B
We recommend trying psychological interventions in combination with medical and surgical treatment, or alone.	A

Figure 16: assessment and treatment algorithm for psychological aspects of chronic pelvic pain



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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 central nervous system 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 central nervous system 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 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. EMG 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 has become a 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 CPP syndrome 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 defecation. 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.

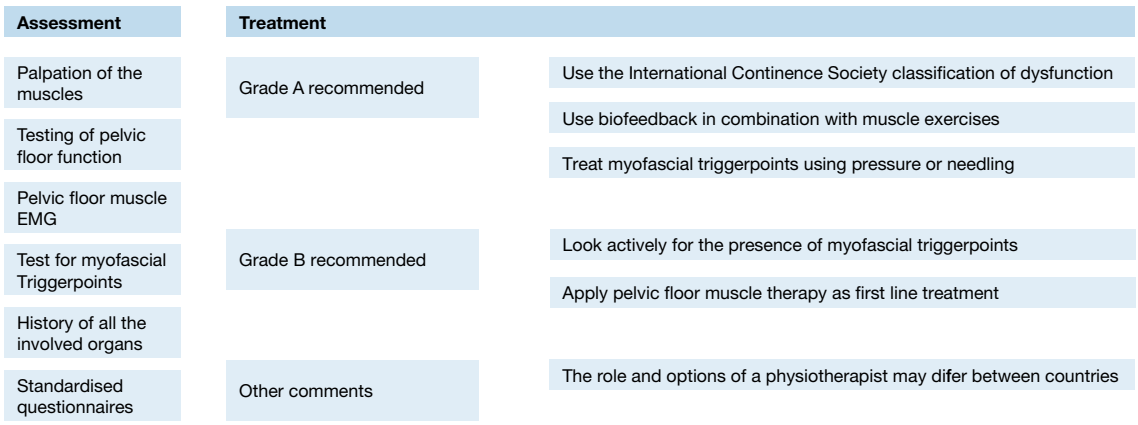
9.7 Conclusions and recommendations: pelvic floor function

Conclusions	**LE**
The ICS classification is suitable for clinical practice.	2a
Overactivity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a

The overactivity of the pelvic floor muscles is an input to the central nervous system causing central sensitisation.	2b
There is no accepted standard for diagnosing myofascial trigger points.	2a
There is a relation between the location of trigger point and the region where the pain is perceived.	3
Myofascial treatment is effective in prostate- and bladder pain syndrome.	1b
Biofeedback improves the outcome of myofascial therapy for pelvic floor dysfunction.	1a
Trigger point release is effective in treating muscle and referred pain, but there is no preference from one method over another.	1a

Recommendations	**GR**
We recommend the use of the ICS classification on pelvic floor muscle function and dysfunction.	A
In patients with chronic pelvic pain syndrome we suggest to actively look for the presence of myofascial trigger points.	B
In patients with chronic pelvic pain syndrome we suggest to apply pelvic floor muscle treatment as first line treatment.	B
In patients with an overactive pelvic floor we recommend biofeedback as therapy adjuvant to muscle exercises.	A
When myofascial trigger points are found we recommend treatment by pressure or needling.	A

Figure 17: assessment and treatment pelvic floor function



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10. GENERAL TREATMENT OF CHRONIC PELVIC PAIN

10.1 Introduction

Chronic pelvic pain (CPP) 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 above.

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, and 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 inhibiter (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 2.4g/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 then 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 on line 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 (24); a situation in which patients taking opioids, paradoxically, become more sensitive to painful stimuli. This is another reason for these drugs to be used in a controlled fashion for long-term management of non-malignant pain.

*10.4.1 **Recommendations for use of opioids in chronic/non-acute urogenital pain***

Recommendations
All other reasonable treatments must have been tried and failed.
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).
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.
The patient should undergo a trial of opioids.
The dose required needs to be calculated by careful titration.
The patient should be made aware (and possibly give written consent): • That opioids are strong drugs and associated with addiction and dependency. • Opioids will normally only be prescribed from one source (preferably the family doctor). • The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period. • 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. • Inappropriate aggressive behaviour associated with demanding the drug will not be accepted. • Hospital specialist review will normally occur at least once a year. • The patient may be requested to attend a psychiatric/psychological review. 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.
Morphine is the first-line drug, 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.

*10.4.2 **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.

*10.4.3 **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., iliostomy). 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 noradrenalin reuptake inhibition. It is too early to assess its real value in the armamentarium for pain management.

10.5 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 practioners 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 practioners 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.

10.6 Transcutaneous electrical nerve stimulation (TENS)

Despite the popularity of TENS and the number of trials undertaken, a systematic review has been unable to provide an evidence base for this technique (28). It is clear that further more rigorous trials should be undertaken to provide some clarity for a commonly used intervention.

10.7 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.

10.8 Summary

CPP 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.

10.9 Recommendations for the medical treatment of CPP

Agent	Pain Type	LE	GR	Comment
Paracetamol	Somatic pain	1a	A	Evidence based on arthritic pain with good benefit
NSAIDs	Pelvic pain with inflammatory process (e.g. dysmenorrhoea)	1a	A	Good evidence for their use
	Central mechanisms (e.g. endometriosis)	1a	A	No good evidence for their use
Antidepressants including tricyclic antidepressants, venlafaxine and duloxetine	Neuropathic pain	1a	A	Effective. No specific evidence for CPP.
Anticonvulsants gabapentin, pregabalin	Neuropathic pain, fibromyalgia	1a	A	Effective
Gabapentin	Women with CPP	2b	B	Effective
Topical capsaicin	Neuropathic pain	1a	A	Some evidence of benefit
Opioids	Chronic non-malignant pain	1a	A	Beneficial in a small number of patients
Nerve blocks		3	C	Have a role as part of a broad management plan
TENS		1a	A	No good evidence of benefit
Neuromodulation	Pelvic pain	3	C	Role developing with increasing research.

Figure 18: algorithm for the use of neuropathic analgesics

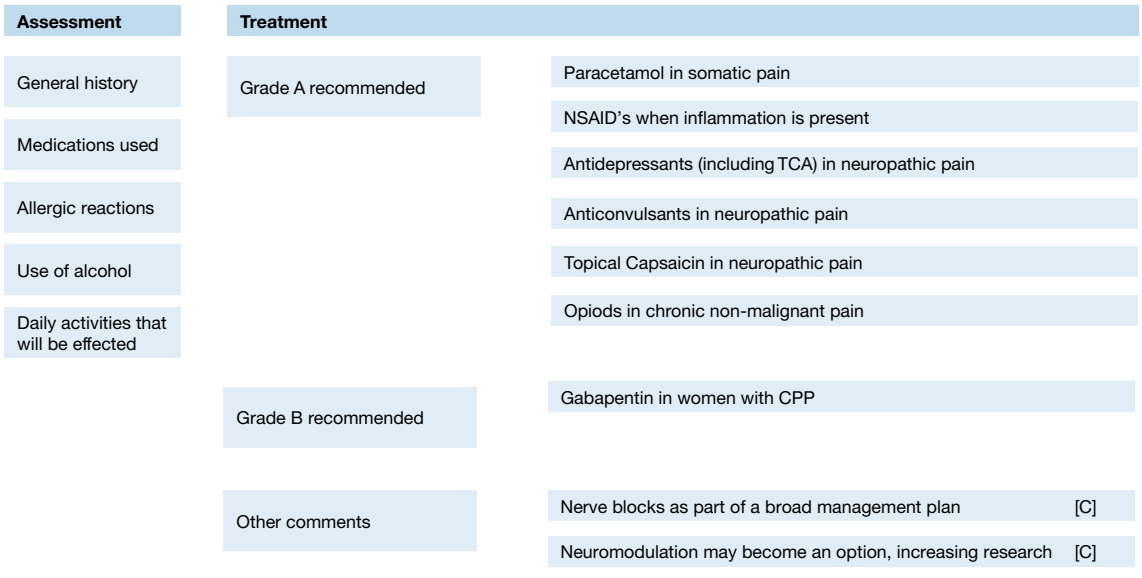
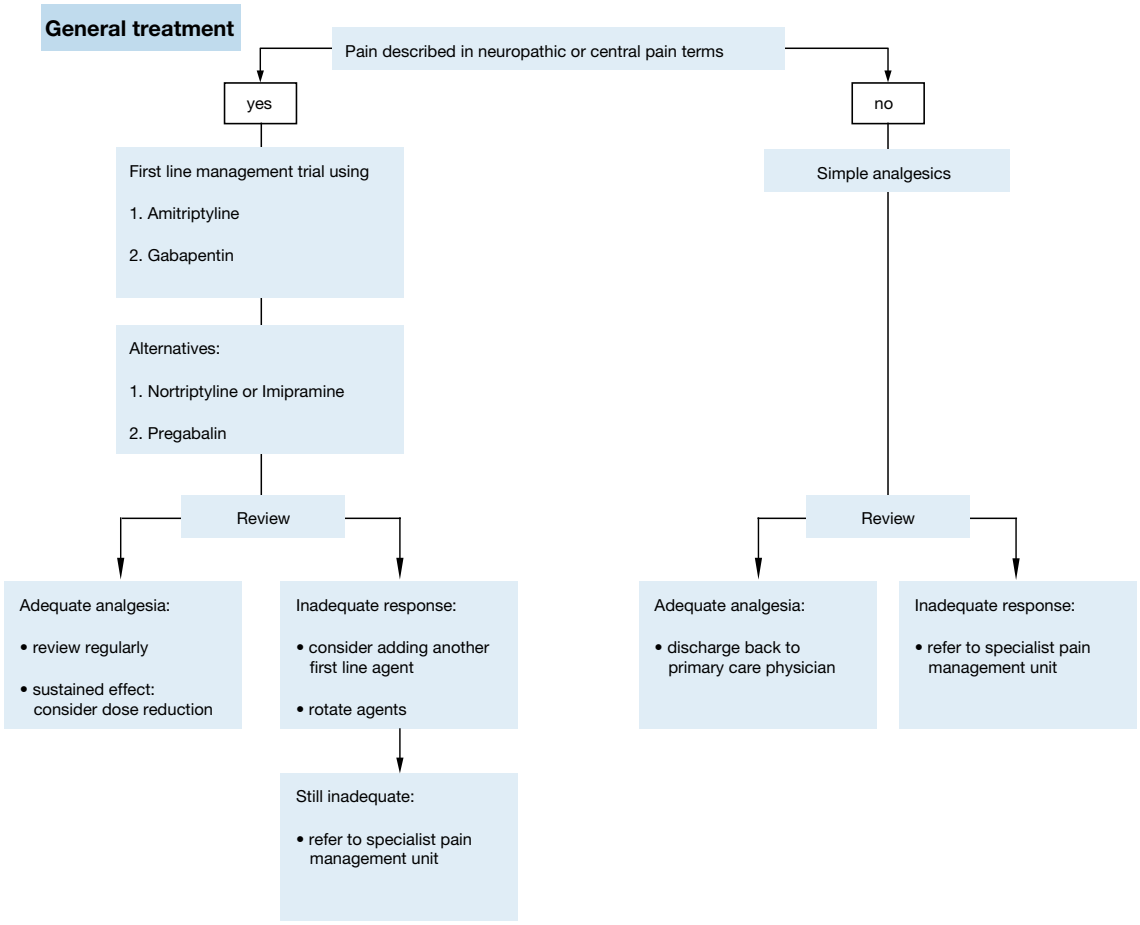


Figure 19: treatment algorithm for general treatment



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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AMPA	amino-methylene-phosphonic acid
ATP	Adenosinetriphosphate
BCG	Bacillus Calmette Guérin
BDNF	brain-derived neurotrophic factor
BPS	bladder pain syndrome
BTX-A	Botulinum toxin A
CBT	cognitive behavioural therapy
CFS	chronic fatigue syndrome
CHRP	calcitonin gene-related peptide
CI	confidence interval
CNS	central nervous system
CPP	chronic pelvic pain
CPPS	chronic pelvic pain syndrome
CRH	corticotrophin-releasing hormone
CyA	Cyclosporin A
DMSO	Dimethyl sulphoxide
DNIC	diffuse noxious inhibitory control
DRG	dorsal root ganglion
EH	excisional haemorrhoidectomy
ESSIC	European Society for the Study of BPS
FM	fibromyalgia
FSS	functional somatic syndrome
GAG	glycosaminoglycan
HBO	Hyperbaric oxygen
HIF	hypoxia inducible factor
IASP	Association for the Study of Pain
IBS	irritable bowel syndrome
ICDB	Interstitial Cystitis Data Base
ICSI	Interstitial Cystitis Symptom Index
IPPS	International Prostate Symptom Score
ISSVD	Society for the Study of Vulvovaginal Disease
LUTS	lower urinary tract symptoms
MAPP	Multi-disciplinary Approach to the study of chronic Pelvic Pain research
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NBS	non-bladder syndromes
NGF	nerve growth factor
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIH-CPSI	NIH Prostatitis Symptom Index
NMDA	N-methyl-D-aspartate
NO	nitric oxide
PAG	periaqueductal grey
PID	pelvic inflammatory disease
PNS	pudendal nerve stimulation
PNS	peripheral nervous system
PPMT	pre-post-massage test
PPS	prostate pain syndrome
QoL	quality of life
RBL	rubber band ligation
RCT	randomised controlled trial
RTX	Resiniferatoxin
RUR	transurethral resection
TUNA	transurethral needle ablation
VAPS	visual analogue pain scale

Conflict of interest

All members of the Chronic Pelvic Pain 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 kept on file in the European Association of Urology Central Office database. 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 Transplantation

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European
Association
of Urology

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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 contains not only urologists but also an immunologist (Prof. Dr. Süsal) and a nephrologist (Prof. Dr. Budde). Besides medical and technical aspects, the Guidelines Group 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

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

Table 2: Grade of recommendation

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

**modified from Sackett et al. (1)*

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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 in 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
It is the right of individuals to donate as well as to receive an organ.
Commercially motivated renal transplantation is unacceptable. It has been widely prohibited by law and is strongly opposed by the International Society of Transplantation.
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.
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.
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.
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.

Because ethical values cannot be measured using the 'scientific' basis of levels of evidence, grades of recommendation are not given.

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2.2 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 transplant rates in different European countries (1).

Table 3: Kidney transplant rates in 2010 (1)

Country	Deceased donor kidneys (pmp)	Living-donor kidney (pmp)	Total kidneys (pmp)
Austria (ET)*	38.1	6.9	45
Belgium (ET)* (2008)	38.6	4.2	42.8
Bulgaria	5.14	1.71	6.85
Croatia (ET)*	49.8	4.51	54.31
Cyprus (2008)	34	49	83
Czech Republic	31.1	1.6	32.7
Denmark (ST)**	23	18.1	41.1
Estonia	26.1	3	29.1
Finland (ST)**	30.7	2.06	32.76
France (2007)	42.03	3.5	45.8
Georgia (2008)	0	1.5	1.5
Germany (ET)*	27.8	8.1	35.9
Greece (2009)	10.6	3.0	13.0
Hungary	26.4	4.19	30.59
Iceland (ST)**	No data	15.74	15.74
Ireland (2007)	32.6	1.2	33.8
Italy	25.1	3	28.1
Latvia	27.8	0.9	28.7
Lithuania	19.1	2.4	21.5
Luxembourg (ET)*	12.05	No data	12.05
Malta (2009)	15	12.5	27.5
Moldova (2007)	0	0.6	0.6
Netherlands (ET)*	22.7	28.5	51.2
Norway (ST)**	36.9	16.9	53.8
Poland	24.85	1.3	26.15
Portugal	49.1	4.8	53.9
Romania	5.68	4	9.68
Slovak Republic (08)	27.4	3.6	31
Slovenia (ET)*	30.5	0	30.5
Spain (2009)	45.2	5	48.2
Sweden (ST)**	21.6	17.9	39.5
Switzerland	23.1	14.7	37.8
Ukraine (2009)	0.5	1.9	2.4
United Kingdom	23	16.6	39.6

pmp = per million population.
* ET = Country member of the Eurotransplant.
** ST = Country member of the Scandia Transplant.

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

care physicians and transplant co-ordinators also need to access the register routinely to identify potential deceased donors.

Recommendation	GR
In all countries without presumed consent law, efforts should be increased to recruit donors through an opting-in register or by carrying donor cards.	C

*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.

Recommendation	GR
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.	C

*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).

Recommendation
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.

*2.2.4 **Non-heart-beating donor (NHBD)***

Non-heart-beating donors 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.

Recommendations	GR
The use of NHBDs should be expanded significantly.	B
Transplant staff should create policies for recently dead admissions to casualty departments to be used as NHBDs.	B
Local coroners should be consulted regarding the legal implications.	B

*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).

Recommendations	GR
The use of carefully selected donors over 60 years of age should be maintained and encouraged as a continuing source of deceased donor kidneys.	B
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.	B

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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

During referral process
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.
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.
If legally permitted, living unrelated donors should be encouraged.
More general methods
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.
Ethical methods, such as showing appreciation for organ donation.
Organisational methods, such as medical leave for organ donation and reimbursement of all costs to the donor.

Recommendations	**GR**
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.	C
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 Honor', limited reimbursement, medical leave, priority access to organ for transplant, donor insurance).	C
All nephrologists who care for ESRD patients should explore the living donor option with the family when a patient first presents with ESRD.	

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).

Recommendations	**GR**
Multiple renal artery or grafts with anatomical anomalies are not absolute contraindications. Decisions should be made on an individual basis.	C
Laparoscopic right kidney nephrectomy is as safe as left kidney nephrectomy in terms of complications and graft survival.	A

2.3.1.2 Laparoscopic living-donor nephrectomy (LLDN)

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

Advantages	**Disadvantages**
Less post-operative pain	Graft loss or damage during 'learning curve'
Minimal surgical scarring	Pneumoperitoneum may compromise renal blood flow
Rapid return to full activities	Longer operative time and work (about 4 weeks)
Shorter hospital stay	
Magnified view of renal vessels	

Recommendations	**GR**
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.	A
Laparoscopic nephrectomy increases the number of individuals willing to donate. It should be used only by appropriately trained and experienced surgeons.	C

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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).

Recommendations	**GR**
ABO-incompatible transplantation is a promising procedure undergoing clinical evaluation.	C
Due to its experimental nature, it should be performed in experienced centres under scientific documentation.	C
Patients should be counselled about potential risks and alternatives.	C

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 Missmatch programme, cross-over transplantation) should be considered to allow a timely transplantation of these patients with standard immunosuppressive protocols (15) (LE: 4).

Recommendation	GR
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.	C

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).

Recommendation	GR
Living related and unrelated donation should be encouraged within national laws.	B

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).

Recommendations	GR
Legislation in every European country forbids payment for organs.	C
Donation of an organ should remain a gift of live without any financial impetus.	C

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*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).

Recommendation	**GR**
Paired kidney exchange and cross-over renal transplantation if permitted by national law is a way of increasing the number of kidney transplants.	C

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).

Recommendations	**GR**
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.	B
There should be a national insurance plan that provides life and disability insurance for all living donors.	B

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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

Human immunodeficiency virus-1, -2 (HIV-1, HIV-2)
Hepatis C (HCV)
Hepatitis B surface antigen (HBsAg), anti-HBc; acute hepatitis (liver enzymes)
Cytomegalovirus (CMV)
Epstein-Barr virus (EBV), only in paediatric recipients
Active syphilis
Viral infection, sepsis, tuberculosis, infections of unknown aetiology
Family history of (or clinical signs that may be caused by) Creutzfeldt-Jacob disease

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

HCV-positive donor
In an HCV-positive recipient, transplant is allowed following informed consent.
In an HCV-negative recipient, there is a high risk of disease transmission. However, transplant may be possible in emergency situations following informed consent.
HBsAg-positive donor

In an HBsAg-positive recipient (if HDV antigen is negative), transplant is allowed after informed consent.
In an HBsAg-negative recipient with high anti-HBs antibody titre and HBc positivity, transplant is allowed after informed consent.
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 ≥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 gonadotropin (hCG) must be measured to exclude chorioncarcinoma 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 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).

Recommendations	**GR**
Any brain death comatose subject should be considered a potential organ donor, without age limits.	C
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: - Contact between relatives and a well-trained, sensitive professional is very important in establishing favourable public opinion on organ donation. - Individuals who objected to donation during life must always be excluded.	
Any donor organ affected by a potentially transmittable pathology (infections, neoplasias) must be carefully evaluated considering the risk-benefit ratio for the recipient.	B
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.	C

*2.4.9 **References***

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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

Infuse 3L of University of Wisconsin (UW) solution into the aorta before organ recovery.
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.
After the heart is removed and the liver is to be retrieved, careful attention should be given to ensure the following: • 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. • 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. • 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.
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.
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.
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).

Table 9: Important considerations in kidney retrieval

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.
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.
It is useful to rewash each kidney until the effluent is free of blood before packaging.
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.
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.
Mass clamping of the hepatoduodenal ligament can be performed to minimise flushing of the liver. In a donor < 3-4 years, the surgeon must make sure the aortic cannula does not occlude the renal artery orifices.

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.

Recommendations	GR
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.	C
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.	B
In multiple organ recovery, it is essential there is good co-ordination and co-operation between the surgical teams.	C

*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

Better results (both long- and short-term) compared to deceased donor grafts
Consistent early function and easier management
Avoidance of long waiting time for transplantation
Less aggressive immunosuppressive regimens
Emotional gain to donor
Global increase of the kidney transplant rate

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

Absolute contraindications
Age < 18 years
Uncontrolled hypertension
Diabetes mellitus
Proteinuria (> 300 mg/24 h)
Abnormal GFR for age

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

Approach	Description
Classic transperitoneal	Through a midline or through a left or right subcostal incision.
Sub- or supra-costal extraperitoneal	Can be either left- or right-sided.
Dorsal lumbar	Perform incision either underneath the 12th rib, resecting the 12th rib, or above the 12th rib (extraperitoneal, extrapleural).
Laparoscopic	Can be transperitoneal or retroperitoneoscopic. The transperitoneal approach is more common in the USA and Scandinavia.

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

Patient's preparation	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).
Patient's position on the operative table	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.

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).

Recommendations	**GR**
The use of living donors has been associated with higher success rates than seen with deceased donor donation. Living donation allows some patients to avoid long waiting times and even dialysis.	B
An independent assessment of the donor's renal function by a nephrologist or a specialised team is mandatory in all cases.	B
It is advisable to obtain a psychiatric or independent medical evaluation of the donor's motivation, fitness, and their ability to understand the risks of the operation.	B
It is the surgeon's responsibility to ensure that the donor is medically, as well as psychologically, suitable for the procedure; the donated organ is healthy; and the expectation of success in the recipient is reasonable.	B
The donor should always be left with the 'better' kidney. Kidney removal through a transperitoneal approach has a higher number of splenic and intestinal complications compared with other surgical alternatives.	B
Open-donor nephrectomy should be performed by an extraperitoneal approach through a subcostal or dorsal lumbotomy incision.	B
Laparoscopic donor nephrectomy (either trans- or retro-peritoneal) should only be performed by those trained in the procedure.	B
Hand-assisted laparoscopic donor nephrectomy minimises warm ischaemia time compared to classic laparoscopic procedures.	B

2.5.3 ***References***

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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*

Control of cell-swelling during hypothermic ischaemia
Maintenance of intra- and extra-cellular electrolyte gradient during ischaemia
Buffering acidosis
Providing energy reserve
Minimising oxidative reperfusion injury

**From references 1-6.*

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
UW-solution and HTK-solution are standard storage solutions and equally effective for both multiorgan-donors and kidney-only donors.	A
Celsior-solution seems to be equally effective.	B
Keep cold and warm ischaemia times as short as possible for any renal transplant.	A

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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).

Recommendation	GR
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.	B

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 exstrophy, 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 an 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 continent 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

Autosomal-dominant polycystic kidney disease (ADPKD)
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)
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
Suspected renal or urothelial cancer
Urolithiasis
No strong evidence for removal of native kidneys in urolithiasis
Nephrectomy is necessary if there is a possible risk of infection due to stones

Recommendations	**GR**
In abnormal urogenital tract, meticulous pre-transplant work-up is necessary, with urodynamics being the key investigation.	B/C
If pharmacological therapy or intermittent catheterisation fails or is not possible, urinary diversion is necessary using catheterisable pouches, conduits or cystoplasties.	B/C
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.	B/C

ADPKD = autosomal dominant polycystic kidney disease

3.1.4 References

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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. isoniasid 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 haemaglutination (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	GR
Active infection, which may exacerbate after transplantation causing life-threatening infection, is a contraindication to transplantation.	B
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).	B
Routine screening examination of all patients in all subspecialties is not necessary.	B

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	GR
In severe co-morbidity or non-compliance, a thorough and individual assessment should be performed.	C

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	GR
Pre-transplant work-up should focus on the presence of cardiac disease.	B
In patients with a high risk of cardiac disease, an extensive work-up is strongly recommended to firmly rule out coronary artery disease.	B
Perform any revascularisation before transplantation.	B

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	GR
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). Furthermore, 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	GR
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	GR
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	GR
A careful examination of coagulopathies in patients at risk in order to prevent early post-transplant thrombotic events is recommended.	C

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	GR
Diseases that might influence post-transplant course should be identified during pre-transplant work-up and if possible treated before transplantation.	C

*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	GR
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.	B

*3.2.4 **Recurrence risk (original renal disease)***

An 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	**GR**
Recurrence of the original disease is common, but graft loss due to recurrence is infrequent.	C
Only a few rare diseases with a high recurrence rate leading to early graft loss are a contraindication for renal transplant.	C
Patients with the risk of recurrent diseases should be counselled before transplantation, especially before living related kidney transplant.	C

*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***

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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.

Recommendations	GR
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.	B
The second post-transplant year is the ideal period.	B

*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

Haemodynamic changes
Hypertension
Impairment of renal function (5-10) (LE: 2a)
Rejection (11)
Urinary tract infections

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.

Recommendations	GR
After kidney transplantation pregnancy is possible and well tolerated for most patients with normal graft function.	B
However, pregnant transplanted women always must be considered at high risk and their care requires the co-operation of the obstetrician, nephrologist, and urologist.	B

*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 fetal 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 fetal infections (12).

Recommendation	GR
Care during pregnancy should focus on control of proteinuria, hypertension (pre-eclampsia affects 30% of patients), renal function, rejection, and infection.	B

*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).

Recommendations	GR
Cyclosporine and tacrolimus do not seem to increase the risk of teratogenicity and they are currently used with or without steroids and azathioprine.	B
Treatment with mycophenolate (mycophenolate mofetil or mycophenolate sodium) or m-TOR inhibitors (sirolimus or everolimus) is not recommended.	B

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, fetal 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 fetal 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.

Recommendations	GR
If there is no premature condition or fetal distress, vaginal delivery can be considered.	B
Breastfeeding is not recommended because of the potential risk of ingesting immunosuppressive agents.	B

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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

Kidney
Place the kidney on a sterile iced bed
Check for the absence of renal tumours
Tie all that is cut near the hilus (lymphostasis)
Vein
The right kidney should be removed, together with the infra renal vena cava for lengthening the renal vein on
the back table (1)
Artery
Preserve the aortic patch and check the intima of the renal ostium
In severe atheroma in the ostium, remove the aortic patch
In multiple arteries, back table reconstruction could be necessary (2,3)
Ureter
Preserve peri-pyelic and proximal peri-ureteral fat in the ‘golden triangle’
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 intravescial 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	GR
It is essential not to neglect transplant preparation. This is a crucial step in the transplantation process.	C
Take care with lymphostasis into the recipient and during the graft preparation.	C

Vascular anastomosis sites should take into account the differences in vessel length.	C
JJ-stent may be used routinely.	C
Check the arterial and venous status before transplant.	C
Iliac fossa may be an alternative in children less than 20 kg provided the graft is small enough.	C

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 lake 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 can 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**
Use a short ureter and keep the peri-ureteral fat around the hilus (29).	C
Avoid ligature of polar artery because of the risk of parenchymal and ureteral necrosis.	C
Prophylactic use of JJ-stent prevents major urinary complications (8).	A

*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	GR
Importance of procurement technique quality.	C
Preserve when possible the aortic patch; otherwise, use a punch perforator to create a large arterial opening.	C
Look for a possible intimal rupture before performing anastomosis.	C
Avoid plication of the artery.	C
Sudden anuria should lead to Doppler,	C

*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	GR
Lengthen the right renal vein with the infra renal vena cava.	C
Carry out a large venous anastomosis.	C
Avoid post-operative drop in blood pressure.	C
If there is a history of thrombosis., check for hypercoagulation or Leiden factor V mutation.	C
Sudden anuria should lead to Doppler.	C

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.

Recommendations
The anti-reflux tunnel for the uretero-vesical anastomosis should be 3-4 cm long.
Avoid lower urinary tract infections.
Endoscopic treatment might be the first option for the treatment of symptomatic reflux.

*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
Treat hyperparathyroidism in the recipient.
Use absorbable threads for the urinary anastomosis.
Treat urinary obstructions and infections.
Check calciuria.

*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	GR
Avoid very deep biopsy reaching the renal hilum.	C

*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	GR
Strict lymphostasis should be maintained by clips or ligatures of the lymphatic vessels of the transplant and during dissection of the iliac vessels.	C

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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).

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5. MATCHING OF DONORS AND RECIPIENTS

Recommendations	GR
The ABO blood group and the HLA-A, -B, and -DR phenotypes should be determined for all candidates awaiting kidney transplantation.	B
To avoid hyper-acute rejection, a lymphocyte cross-match test must be performed before each kidney and combined kidney/pancreas transplantation.	B

5.1 Histocompatibility (HLA) 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 HLA-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 (4,5):

- 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 (6).
- 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.

5.2 Cross-matching

To avoid hper-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-positive 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 cytometric cross-match may exclude unnecessarily a high number of patients from transplantation (1,7). 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 HLA-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 (8). 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 (9). 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 (6).

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%) (10). 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 transplantations, even without splenectomy (11).

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.

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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 prescibing 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 hypomagnesemia (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 fulfils 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 immunosuppresive 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).

Recommendations	**GR**
Rejection prophylaxis with Calcineurin-inhibitors represents current best practice pending publication of long-term results using newer agents.	A
The choice of Calcineurin-inhibitors depends on the immunological risk, recipient characteristics, concomitant immunosuppression, and socio-economic factors.	A
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).	A

*6.2.2 **Mycophenolates***

The mycophenolates, MMF and EC-MPS, are based on mycophenalic 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 centers 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	**GR**
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.	A
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.	A
Mycophenolate drug monitoring cannot be recommended for all patients due to limited evidence supporting its benefit.	A

6.2.3 ***Azathioprine***

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprione, 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).

Recommendations	GR
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 azathiprine in combination therapy with CNIs and steroids.	A

*6.2.4 **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 peroid. (1-3,45,54,57) (LE: 3).

Recommendations	GR
Initial steroid therapy remains the standard in perioperative and early posttransplant period.	A
There is increasing evidence that steroids may be safely stopped in most patients after 3-12 months on combination therapy with Calcineurin-inhibitors and myco phenalic acid.	A
Steroid-free long-term therapy is inherently associated with a reduction of steroid-induced side effects.	A

*6.2.5 **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).

6.2.5.1 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 themself 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 effcacy, due to the highly synergisitic potential of this combination therapy (57-60) (LE: 1b).

6.2.5.2 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).

6.2.5.3 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

CNI = Calcineurin-inhibitors

*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).

Recommendations	GR
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 staring 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	GR
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.	A
Formal evidence for improved patient and graft outcome is lacking, although recent large clinical trials suggest such a benefit.	A

6.2.8 ***References***

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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)

History of previous rejection episodes
Previous transplantations, especially when graft loss has occurred due to acute rejection
Non-compliance with immunosuppressive treatment
Some virus infections, e.g. CMV

CMV = cytomegalovirus.

Table 20: Main types of rejection (1-7)

Hyper-acute rejection (HAR)
Antibody-mediated rejection is caused by pre-formed anti-HLA or anti-AB (blood group) antibodies
Now rare due to donor-recipient ABO matching and routine pre-transplant cross-matching between donor cells and recipient serum
Acute cellular rejection (ACR)
Much more common than HAR, occurring in 10-40% of transplants
Usually occurs from 5 days' post transplant
Most likely within the first 3 months, though may occur after this time
Usually responds well to steroid bolus treatment
Acute humoral rejection (AHR)
Much less frequent than ACR, occurring in 5-20% of transplants
Most likely within the first 3 months' post transplant
Presence of certain histological features and/or positive C4d immunostaining and/or anti-HLA antibodies
Worse prognosis than ACR because more difficult to treat
Chronic allograft rejection (CAR)
Rare, slowly progressive, immunological process
Certain non-specific histological features and/or anti-HLA antibodies
Requires clear strong evidence for a solely chronic immunological process

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 (HAR)

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	GR
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.	B
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.	B
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).	B

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	GR
Renal transplant practitioners must be continuously aware of the possibility of acute rejection, particularly during the first 6 months after renal transplant.	B
During hospitalisation, regular blood and urine samples should be taken for renal and haematological studies in addition to regular ultrasound examinations.	B
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.	B
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.	B

There should be routine access to ultrasound-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a clear-cut diagnosis of rejection or other type of allograft dysfunction.	B
Staff and facilities on renal transplant units should be sufficiently equipped to admit a patient with acute rejection immediately to allow rapid diagnosis and treatment.	B
Patients who suffer acute cellular rejection should be tested as soon as possible for anti-HLA IgG antibodies reactive with the graft.	B

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	**GR**
Treatment with steroid bolus therapy is recommended.	B
In severe or steroid-resistant rejection, consider intensified immunosuppression, including high-dose steroid treatment, conversion to tacrolimus, and T-cell depleting agents.	B

7.3.2 ***Treatment of acute humoral rejection (AHR)***

Acute humoral rejection 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	**GR**
Treatment of acute hormonal injection should include early antibody elimination.	B
In addition, steroid bolus therapy, conversion to tacrolimus, T-cell depleting agents and intravenous immunoglobulin treatment are used frequently.	B
Anti-CD20 (rituximab) may be efficacious. However, firm evidence on efficacy and side-effects are lacking.	B

7.4 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy (IF/TA)

Many patients lose their grafts due to chronic allograft dysfunction (9). Histology will usually reveal a chronic process of 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 (9). 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	**GR**
During the years of follow-up after renal transplantation, regularly monitor serum creatinine, creatinine clearance, blood pressure, and urinary protein excretion.	A
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.	
If a specific cause for deteriorating renal function can be identified, appropriate treatment should be instituted.	A
If unspecific IF/TA is confirmed, begin appropriate medical treatment (e.g. control of hypertension, proteinuria).	A
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).	
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 (< 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.	A

7.5 References

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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 infraclinical 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 multiform) 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

Low-grade astrocytoma
Pituitary adenomas
Epidermoid cysts
Colloid cysts of the third ventricle
Pilocytic astrocytoma, ependymoma
Low-grade oligodendroglioma (Schmidt A and B)
Choroid plexus papilloma
Ganglionic cell tumour (ganglioma, gangliocytoma)
Benign meningioma
Craniopharyngioma
Haemangioblastoma (not associated with Von Hippel Lindau syndrome)
Acoustic Schwannoma
Pineocytoma
Well-differentiated teratoma

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).

Recommendations	**GR**
Donors with active cancer or history of metastatic cancer and cancers with a high risk of recurrence should not be considered as possible donors.	C
A prior history of neoplasia is no longer an absolute contraindication for organ donation.	C

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	GR
Any active tumour in the recipient is an absolute contraindication for kidney transplantation because of the risk of dissemination and fatal outcome.	C
The waiting period before transplant in recipients with a history of malignancy depends on the type, TNM stage and grade of the tumour, and recipient's age and general health.	C
Recipients with tumours that have a low recurrence rate can be considered for immediate transplantation after successful treatment.	C
Close follow-up is mandatory particularly after transplantation.	C

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

Sun exposure: skin cancer
Analgesic abuse: urothelial cancer
Acquired multicystic renal disease: renal cancer
Immunosuppressants, e.g. CNIs and lymphocyte-depleting antibodies
Viral infections, e.g. EBV, herpes 8 virus, human papillomavirus, HBV, HCV, HEV

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 HHV8 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 preferrable over CNIs, which seem to promote the appearance of Kaposi´s sarcoma (19) (LE: 3).

Recommendations	GR
Oral and written information on the risk of skin cancer and protective measures should be given.	C
Dermatological examination before, and at least annually after, transplantation is mandatory.	C
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.	C

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	GR
Use of induction therapy with T-cell depleting agents should be restricted whenever possible.	C
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.	C

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 greter 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 cardiothorarcic abnormalities (28) (LE: 4).

Recommendations	**GR**
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.	B/C
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.	B/C

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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 this risk factors should be instituted;
- The physician should also focus on the adequate prophylaxis, detetction and treatment of concomitant diseases (e.g. bone disease, anemia) and infections.

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10. GRAFT AND PATIENT SURVIVAL

Recommendations	LE	GR
Graft survival following unselected kidney transplantation should be at least 85% after 1 year and 70% after 5 years (1,2) (Figure 1).	3	B
Patient survival following unselected kidney transplantation should be at least 90% after 1 year and 85% after 5 years (1,2) (Figure 2).	3	B

Figure 1: Improvement of graft survival following kidney transplantation during the last two decades

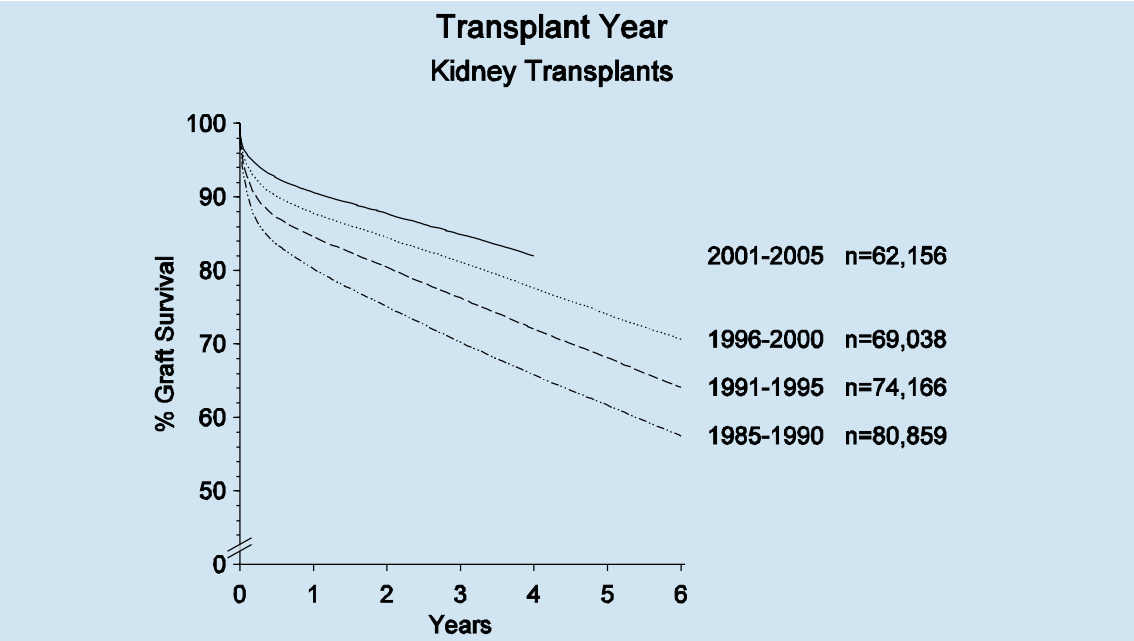

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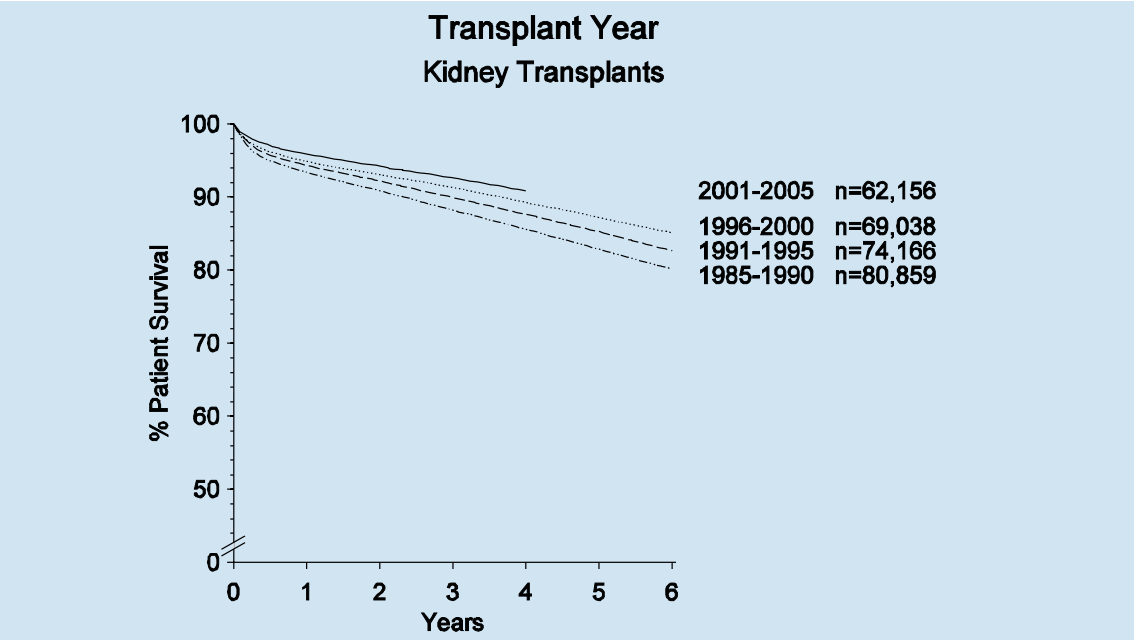
Figure 2: Improvement of patient survival following kidney transplantation during the last two decades



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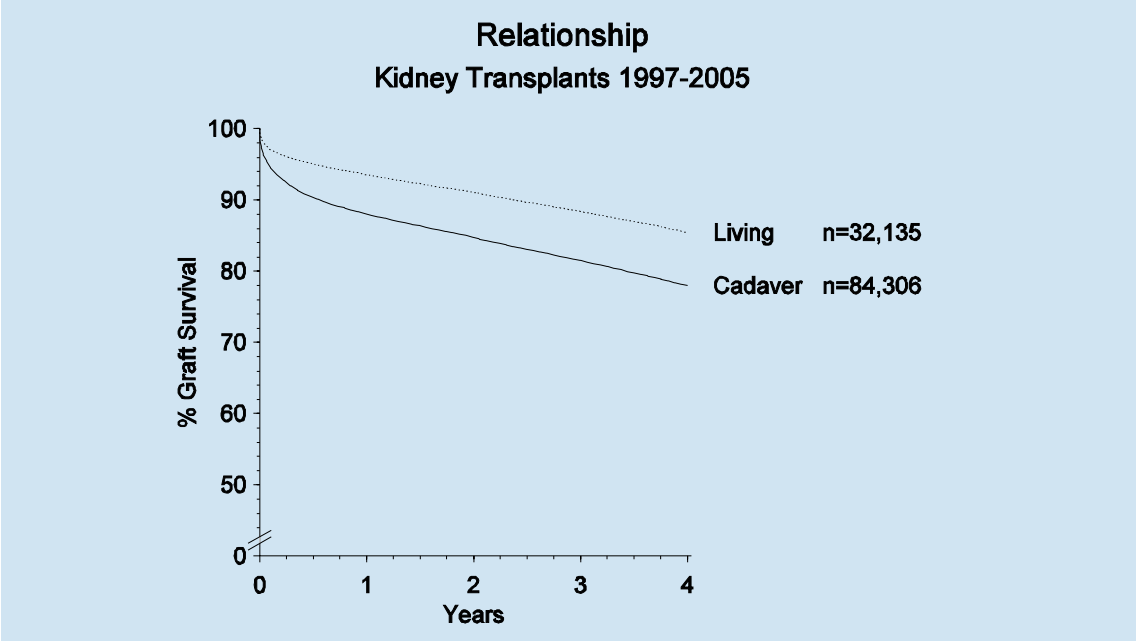
This general outcome following kidney transplantation depends on several criteria that are discussed below:

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



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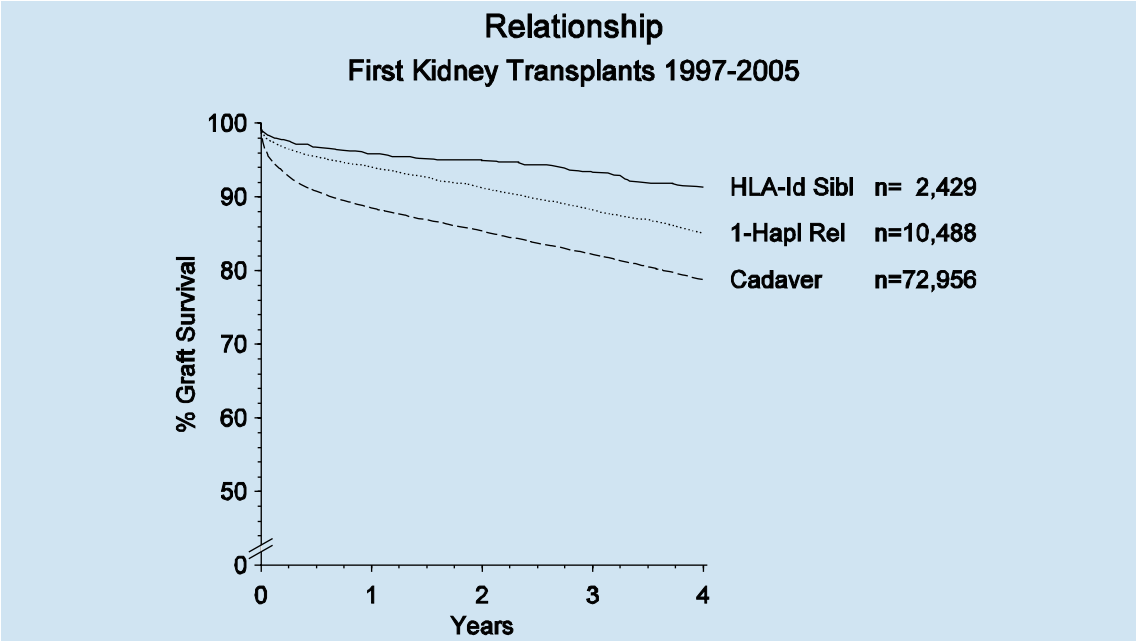
The 1-year graft survival of living-donor kidney is in mean 97% for HLA-identical siblings and 95% for 1-haplotype-identical related donors compared to 88% for deceased-donor kidneys (Figure 4). The 3-year graft survival of living-donor kidney is in mean 95% for HLA-identical siblings and 90% for 1-haplotype-identical related donors compared to 83% for deceased- donor kidneys (Figure 4).

Figure 4: Graft survival following deceased- and living-donor kidney transplantation.



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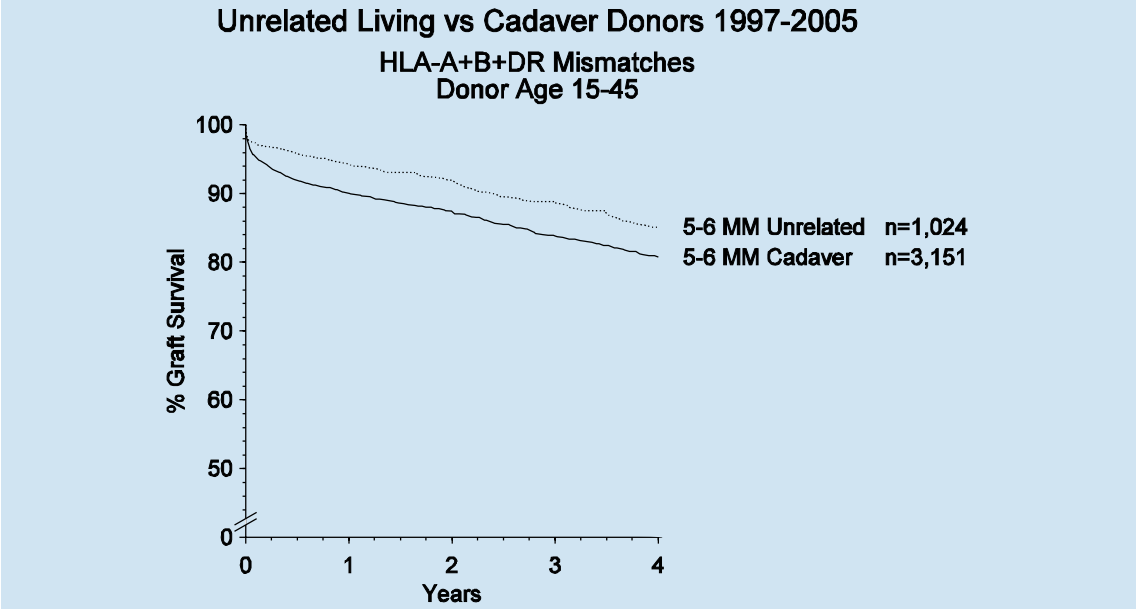
Excellent graft outcomes have been reported in unrelated living-donor transplantation, even if the donor-recipient pairs were poorly HLA-matched (3). CTS data show that poorly matched kidneys from unrelated living donors demonstrate a much better outcome than poorly matched kidneys from deceased donors. 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



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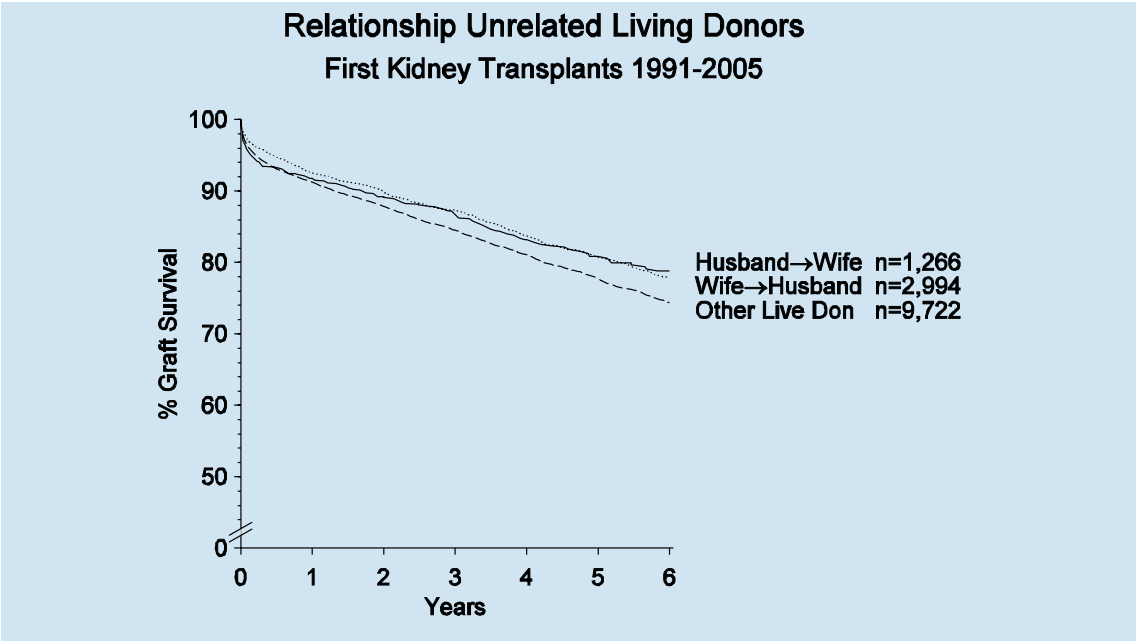
Husband-to-wife and wife-to-husband transplantations performed between 1991 and 2005 show virtually identical results with a 3-year graft survival of 87% (Figure 6). If a wife recipient has been pregnant, the outcome may be worse (3).

Figure 6: Graft survival in living unrelated kidney transplantation



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10.1.2 ***Patient survival***

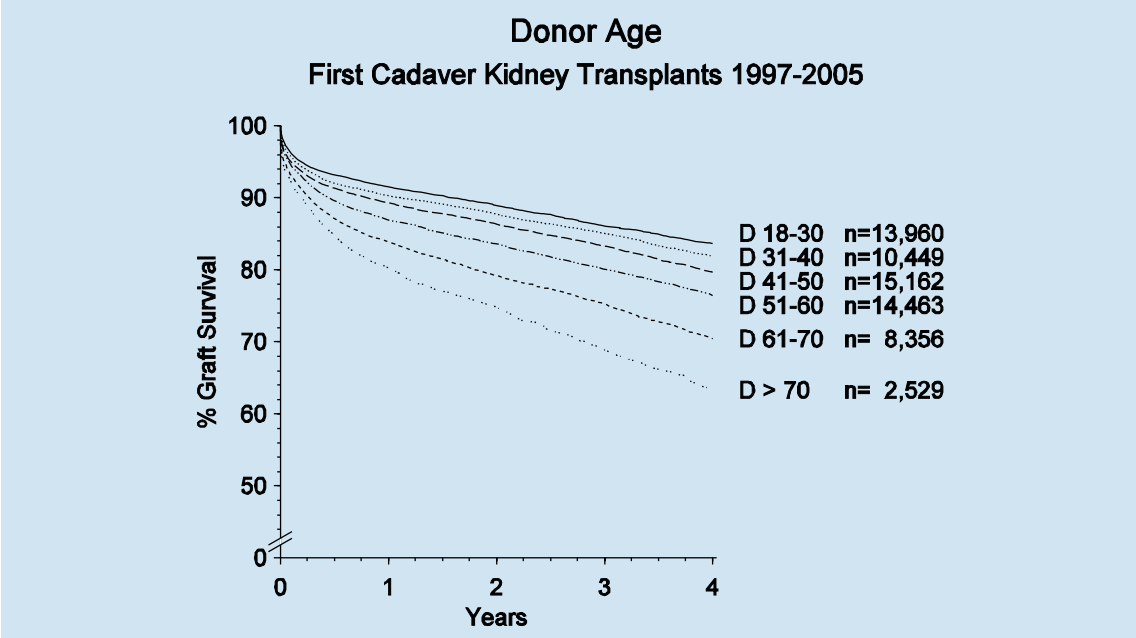
Nowadays, patient survival following living-donor kidney transplantation is about 98% after 1 year and 90% after 5 years. This is better than patient survival following deceased donor kidney transplantation with a 1-year survival rate of 95% and a 5-year survival rate of about 80% (1,2).

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).

Figure 7: Impact of donor's age on graft survival in deceased-donor kidney transplantation



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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 HLA-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

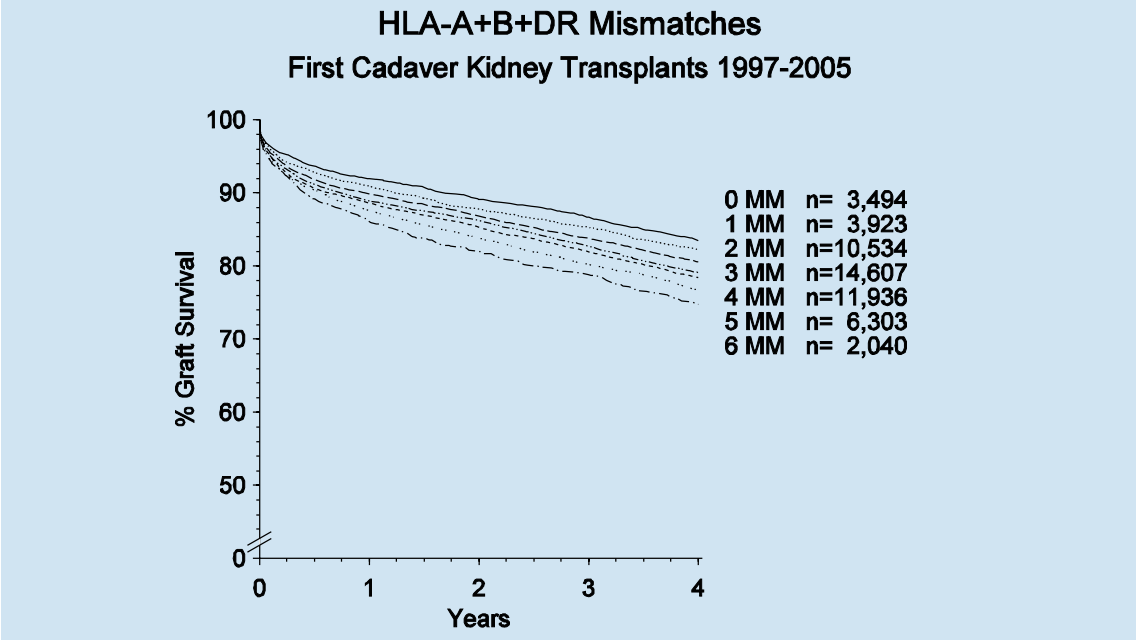

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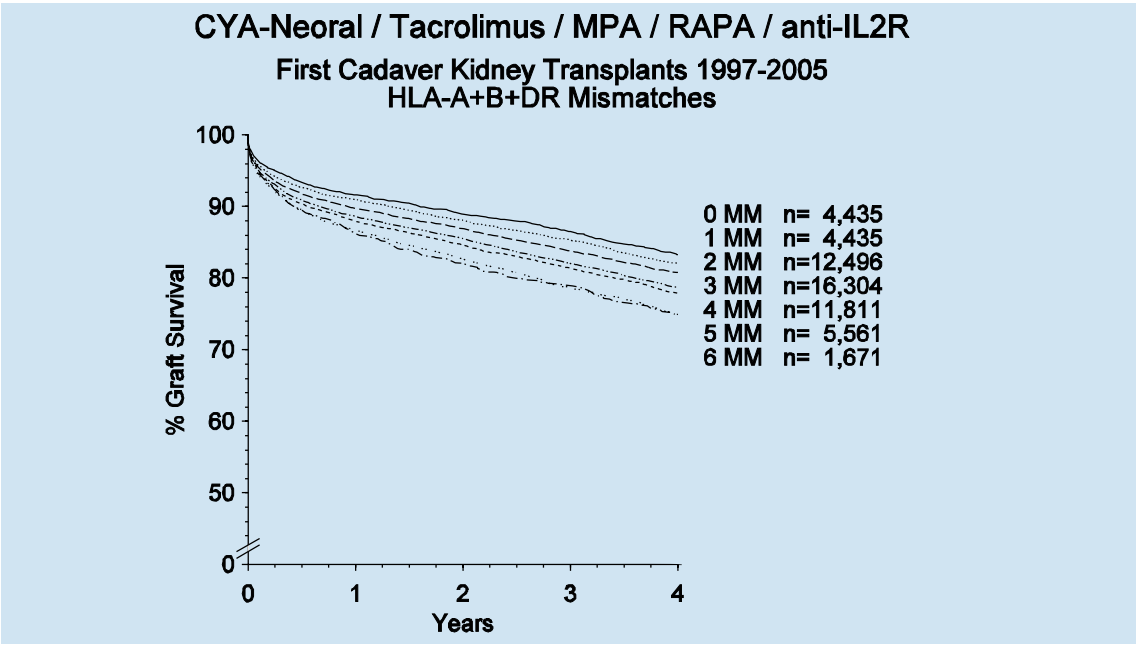
Figure 9: Impact of HLA compatibility on kidney graft survival under 'modern-day' immunosuppression



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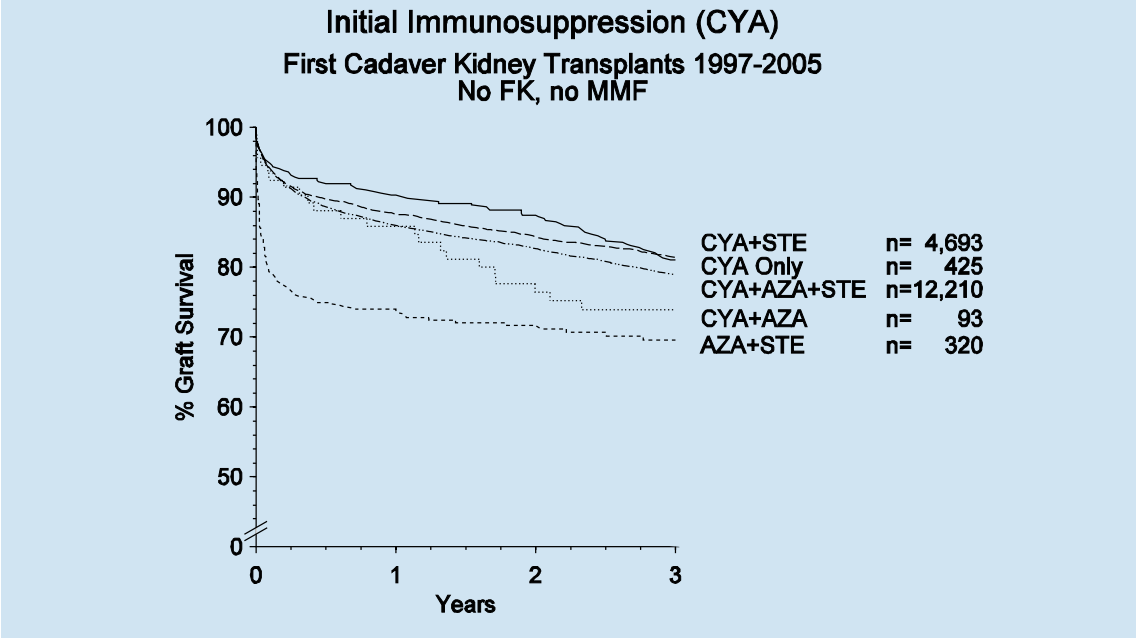
CYA = cyclosporine A; MPA = mycophenolate mofetil; RAPA = rapamycin.

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



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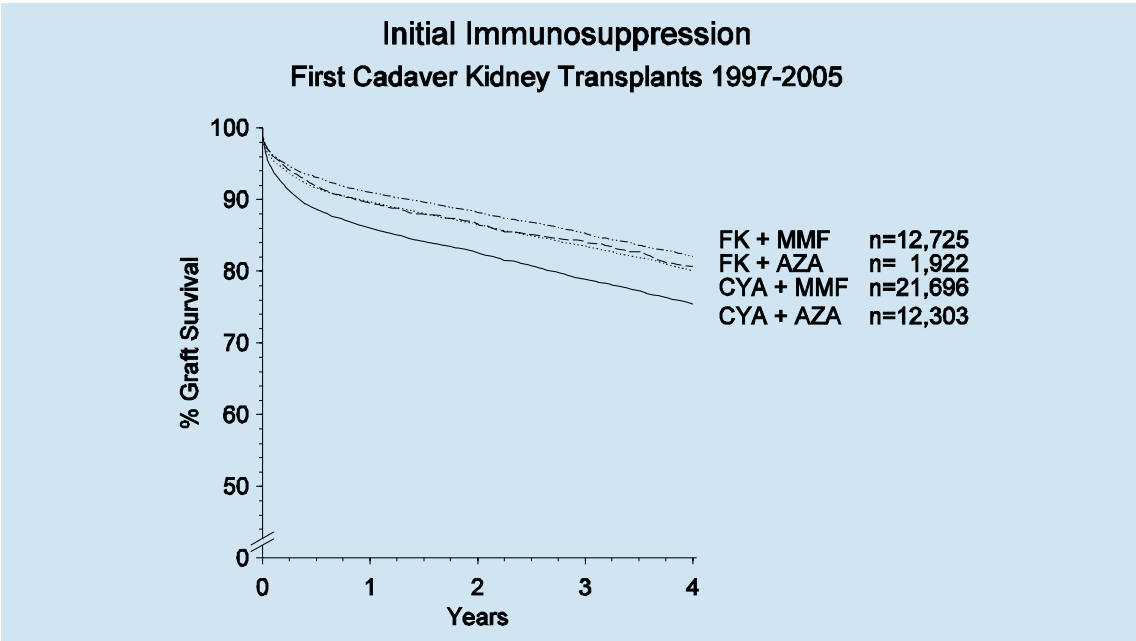
FK: FK506; MMF: mycophenolate mofetil; CYA = cyclosporine A; AZA = azathioprine; STE = steroids.

Figure 11: Influence of different immunosuppressive agent combinations on graft survival following kidney transplantation



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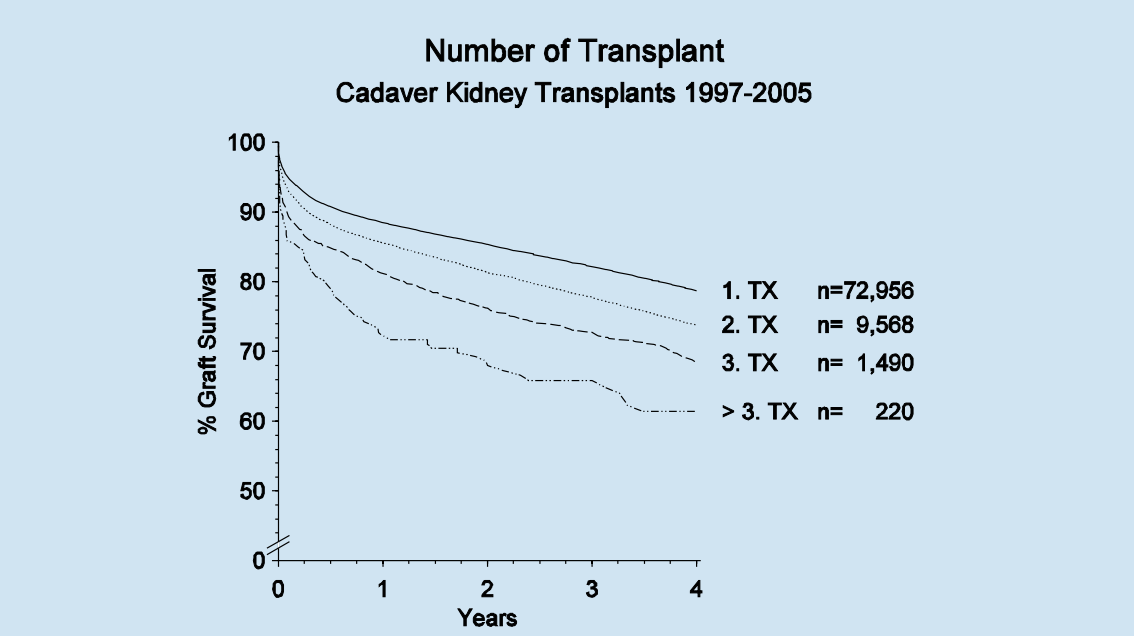
CYA = cyclosporine A; FK: FK506; AZA = azathioprine; MMF: mycophenolate mofetil.

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



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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

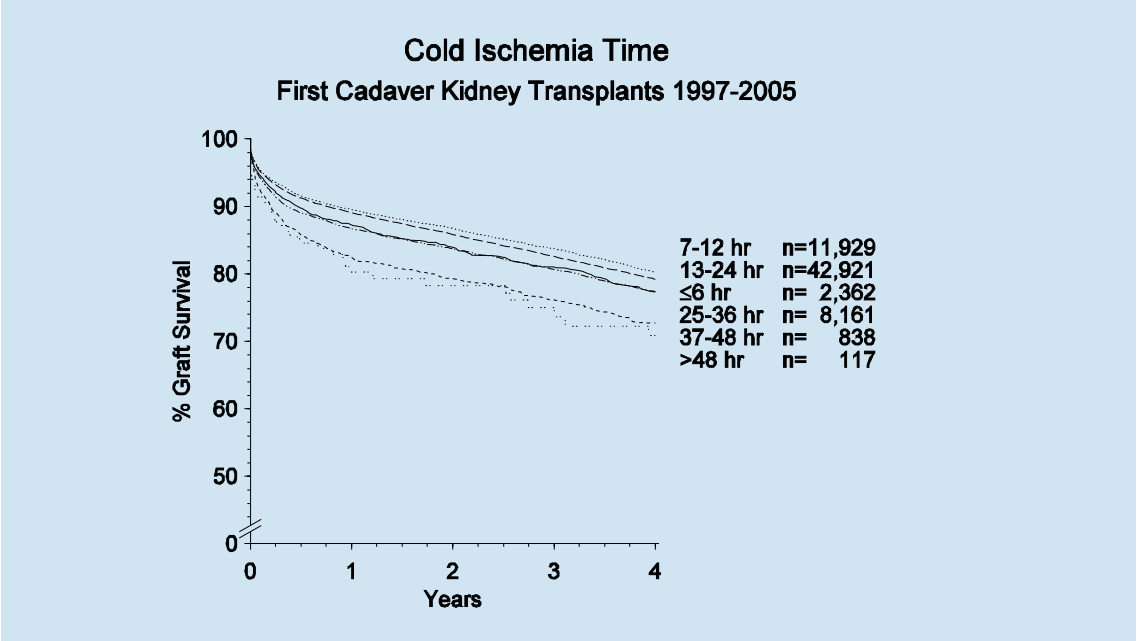

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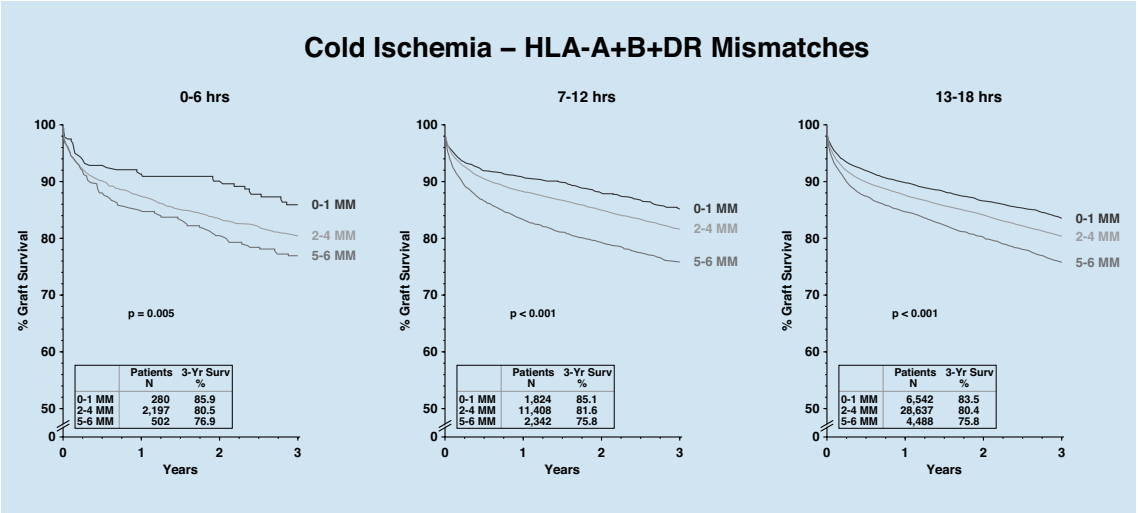
Figure 14: HLA-match dependent impact of cold ischaemia time on graft survival in deceased-donor kidney transplantations performed between 1990 and 2005



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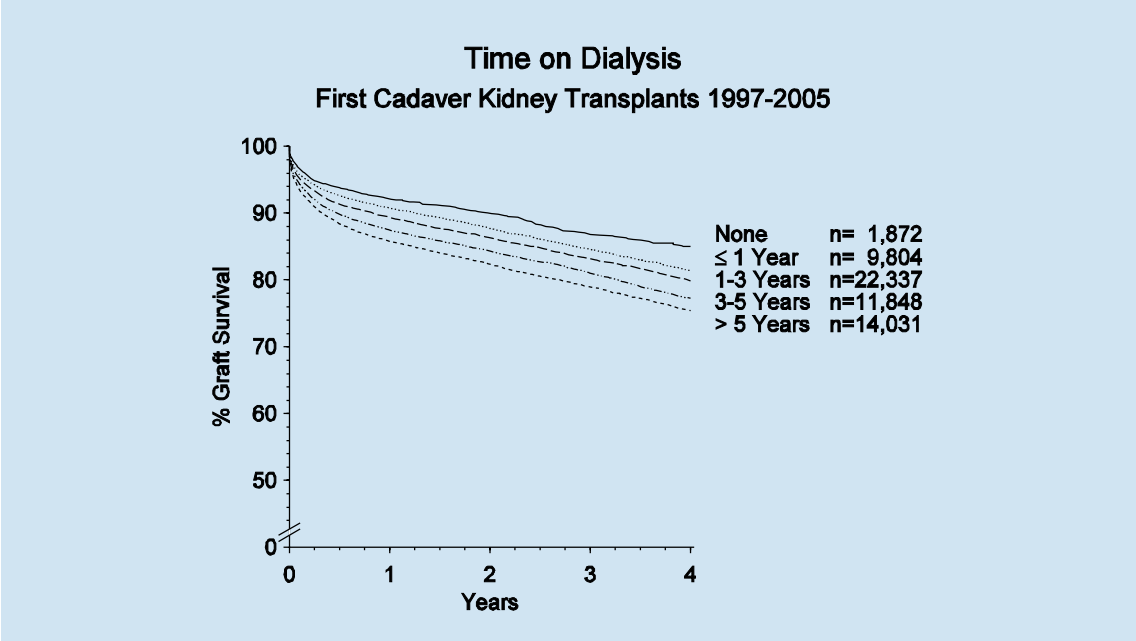
10.7 Time on dialysis

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



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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
CTS	Collaborative Transplant Study
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	mycophenalic acid
MRI	magnetic resonance imaging
NHBD	non-heartbeating donor

OKT3	anti-CD3 monoclonal antibody
OLDN	open live donor nephrectomy
PRA	panel-reactive antibody
PSA	prostate-specific antigen
PTLD	post-transplantation lymphoproliferative disease
RAPA	rapamycin
RCC	renal cell carcinoma
ST	Scandia Transplant
STE	steroids
TA	tubular atrophy
TB	Tuberculosis
TNM	Tumour Node Metastasis
TRAS	Transparant Renal Artery Stenosis
UNOS/OPT	United Network for Organ Sharing/The Organ Procurement and Transplantation Network
UW	University of Wisconsin (solution)
VATER	Vertebrae, Anus, Trachea, Esophagus, and Renal
WHO	World Health Organization

Conflict of interest
All members of the Renal Transplantation Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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

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O. Traxer, A.S. Merseburger (chairman)

European
Association
of Urology

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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.

*1.2.2 **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.

*1.2.3 **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)

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

Modified from Sackett et al. (3)

Table 2: Grade of recommendation (GR)

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

Modified from Sackett et al. (3)

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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_{max}), post-void residual urine volume (PVR) and maximal detrusor pressure (Pdetmax) 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

Active crystal	Abbreviation	Wavelength (nm)	Technique	Acronym
Holmium	Ho:YAG	2140	Holmium laser ablation	HoLAP
			Holmium laser resection of prostate	HoLRP
			Holmium laser enucleation of prostate	HoLEP
Neodym	Nd:YAG	1064	Visual laser ablation of prostate	VLAP
			Contact laser ablation of prostate	CLAP
			Interstitial laser coagulation (of prostate)	ILC
Kalium titanyl phosphate	KTP:Nd:YAG (SHG)	532	Photoselective vaporisation of prostate	PVP
Lithium borat	LBO:Nd:YAG (SHG)	532	Photoselective vaporisation	PVP
Thulium	Tm:YAG	2013	Thullium laser vaporisation of prostate	ThuVAP
			Thulium laser vaporesection of prostate	ThuVARP
			Thulium laser vapoenucleation of prostate	ThuVEP
			Thulium laser enucleation of prostate	ThuLEP
Diode lasers	-	830	Interstitial laser coagulation of prostate	ILC
		940	Vaporisation	-
		980	Vaporisation	-
		1318	Vaporisation	-
		1470	Vaporisation	-

2.3 Historical use of lasers

*2.3.1 **Nd:YAG laser***

The Nd:YAG laser has a wavelength of 1.064 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).

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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:

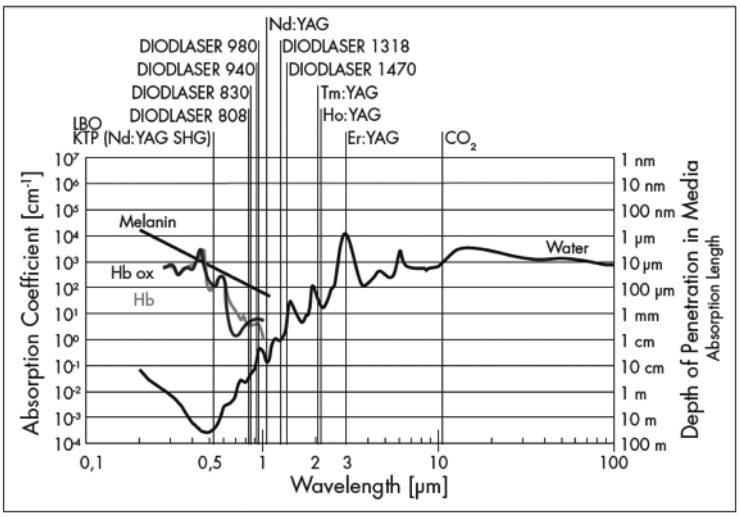
- KTP (kalium titanyl phosphate, KTP:Nd:YAG [SHG]) and LBO (lithium borat, LBO:Nd:YAG [SHG]) lasers;
- Diode lasers (various);
- Holmium (Ho):YAG (yttrium-aluminum-garnet) lasers;
- Thulium (Tm):YAG (yttrium-aluminum-garnet) lasers.

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 occured 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 occured 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 vaporise, 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 vaporising effect on the next tissue layer (4).

Figure 1: Wavelength of different laser types, depth of penetration in media and absorption coefficient



Er:YAG = Erbium: yttrium-aluminum-garnet laser; Ho:YAG = Holmium: yttrium aluminium garnet; KTP = potassium titanyl-phosphate; LBO = lithium triborate; Nd:YAG = Neodymium-doped: yttrium aluminium garnet; Tm:YAG = Thulium: yttrium aluminium garnet.

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:YG) ($p < 0.05$). 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

Study	Bach et al. 2010 (8)		Heinrich et al. 2010 (7)		Wendt-Nordahl et al. 2008 (6)		
Laser Type	Tm:YAG		KTP	LBO	Tm:YAG	KTP	HF (TURP)
Wavelength (nm)	2013	2013	532	532	2013	532	
Power setting (W)	70	120	80	120	70	80	160
Tissue ablation rate (g/10 min)	9.80	16.41	3.99	7.01	6.56 ± 0.69	3.99 ± 0.48	8.28 ± 0.38
Bleeding rate (g/min)	0.11	0.15	0.21	0.65	0.16 ± 0.07	0.21 ± 0.07	20.14 ± 2.03
Coagulation zone (mm)	0.36	0.40	0.667	0.835	0.2647	0.669	0.287

KTP kalium titanyl phosphate; LBO lithium borate;Tm Thulium:YAG Laser.

*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 an 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 (Q_{max}) than the KTP PVP laser (14). Another study comparing KTP PVP with OP showed equivalence in Q_{max} 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 Q_{max} 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

Reference	Laser source (power)	Follow-up (mo)	Patients (n)	Mean prostate size (mL)	PSA reduc-tion (%)	Change in symptoms (%)	Change in Q_{max} (mL/s) (%)	PVR change (%)	LE
Bouchier-Haydes et al. 2006 (13)	KTP PVP	12	38	42.4	n.a.	49.83	+12.1 (167)	81.63	1b
	TURP		38	33.2	n.a.	50.23	+9.2 (149)	68.90	
Horasanli et al. 2008 (14)	KTP PVP	6	39	86.1	31.8	30.68	+5.8 (157)	87.05	1b
	TURP		37	88	44.6	68.31	+13.8 (225)	73.98	
Tasci et al. 2008 (17)	KTP PVP	24	40	108.4	56.8	82.66	+13.5 (307.7)	83.69	2a
	TURP		41	104.2	78.7	83.33	+12.8 (306.4)	84.91	
Skolarikos et al. 2008 (15)	KTP PVP	18	65	93	61.2	50	+7.4 (186)	84.53	1b
	OP		60	96	68.2	59.52	+7.0 (187.5)	86.51	
Al-Ansari et al. 2010 (16)	LBO	36	60	61.8	38.4	60.29	+9.6 (239)	78.9	1b
	TURP		60	60.3	62.5	65.9	+13.6 (312.5)	80.2	

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 on 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 stricture 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 larger prostates and PSA levels > 6.1 ng/mL (34), but this finding has not been supported by other studies (25,30). Bladder neck strictures seem to occur more often in patients with prostate glands < 40 mL (7.8 vs 3.6%, $p < 0.05$) (25).

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*

Conclusions	LE
In patients with small to moderate-sized prostates, TURP remains the standard of care.	1a
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.	1b
Over a follow-up of 3-5 years, re-treatment rates appear comparable to those with TURP.	1b (at 3 yr) 4 (at 5 yr)
KTP PVP and LBO PVP are safe and effective for patients receiving anticoagulation medication or patients in retention.	4

Recommendations	GR
KTP/LBO PVP is a treatment alternative for patients with BOO and BPE for small and medium glands.	A
KTP/LBO PVP can be offered as an alternative to TURP for patients with refractory urinary retention.	B
KTP/LBO PVP can be offered to patients using anticoagulant medication.	B
KTP/LBO PVP is a safe method for volume reduction in large size prostate glands.	A

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*

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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 (8.99g/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

Study	**Wezel et al. 2010 (3)**				**Seitz et al. 2009 (5)**			**Seitz et al. 2009 (7)**	
Laser Type	Diode			LBO	Diode	Diode	KTP	Diode	
Wavelength (nm)	1318	1470	980	532	1470	1470	532	940	940
Power setting (W)	100	80	200	120	50	100	80	200	60
Fibre confirmation	bare fibre	side fire	side fire	side fire	side fire	side fire	side fire	side fire	side fire
Animal model	ppk	ppk	ppk	ppk	ppk	bp	ppk	cp	ppk
Tissue ablation rate (g/10 min)	12.34*	5.27§	8.99§	7.0	n.a.	4.0&	n.a.	15.168	n.a.
Output power efficacy (g/W/10 min)	0.124	0.066§	0.045§	0.058	n.a.	[0.038; 0.042]i	n.a.	0.07584	n.a.
Bleeding rate (g/min)	0.35$	0.24*	0.27*	0.65	0.17	n.a.	0.19	n.a.	0.21
Tissue necrosis (mm)	4.62*	1.3§	4.18*	0.84	3.39t	2.30t	1.27	4.25	n.a.

§ 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];
i mean [0.038-0.042];
t 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 vaporizing 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_{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 7: Results of diode lasers with regard to improvement of urodynamic parameters, symptom score and PSA reduction

Reference	Laser source (power, W)	Follow-up	Patients (n)	Mean prostate size (mL)	PSA reduction (%)	Change in symptoms (%)	Change in Q_{max} (mL/s) (%)	PVR change (%)	LE
Seitz et al. 2007 (12)	1470 (50 W)	12	10	47.8	-42	-69.32	13.5 (251.68)	-88.93	3b
Chen et al. 2010 (10)	980 (200/ 150W)	6	55	66.3	-58.82	-75.62	13.7 (349.01)	-87.74	3b
Erol et al. 2009 (11)	980 (132/80 W)	6	47	51.4	-30.31	-54.99	9.4 (205.97)	-58.11	3b
Ruszat et al. 2009 (9)	980 (n.a.)	6	55	64.7	-58.13	-75.93	5.1 (147.66)	-85.55	3b
	LBO PVP		65	67.4	-45	-57.89	11.3 (191)	-80.64	
Chiang et al. 2010 (14)	980 (200 W)	12	55	66.3	-42.19	-84.26	14 (425.58)	-86.37	1b
	LBO PVP		84	60.3	-58.82	-83.08	11.2 (303.64)	-85.40	

PSA = prostate-specific antigen; Q_{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

Recommendation	LE	GR
In patients presenting with BOO and BPE and who have bleeding disorders or are receiving anticoagulants, diode laser treatment is an alternative.	1b	C

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 is 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 morcelator, to the holmium laser enuclation 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 vaporise 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). Q_{max} 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 vaporisation 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 discusses 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 Q_{max} 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 Q_{max} at 12-month follow-up. Compared with TURP, significantly higher Q_{max} 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 H_2O) decreased significantly more compared to TURP (70 vs 40.7 cm H_2O; 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

Ref.	Laser source/ Technique	Follow-up (mo)	Patients (n)	Mean prostate size (mL)	PSA reduction (%)	Change in symptoms (%)	Change in Q_{max} (mL/s) (%)	PVR change (%)	LE
Mottet et al. 1999 (25)	HoLAP	12	23	39	n.a.	-70	11.1 (226)	n.a.	1b
	TURP		13	34	n.a.	-80	9.6 (229)	n.a.	
Elmansy et al. 2010 (26)	HoLAP	36	46	33.1	-0.40	-71	11 (264)	-0.81	1b
	KTP		42	37.3	-0.28	-64	12.10 (289)	-0.80	
Westenberg et al. 2004 (30)	HoLRP	48	61	44.3	n.a	-76	13.6 (253)	n.a.	1b
	TURP		59	44.6	n.a.	-75	9.4 (203)	n.a.	
Kuntz et al. 2004 (40)	HoLEP	18	60	114.6	n.a.	-90	23.60 (721)	-97	1b
	TURP		60	113	n.a.	-90	24.40 (778)	-98	
Kuntz et al. 2004 (41)	HoLEP	12	100	53.5	n.a.	-92	23 (569)	-98	1b
	TURP		100	49.9	n.a.	-82	21.80 (469)	-88	
Briganti et al. 2006 (42)	HoLEP	24	60	73.30	n.a.	-83	n.a.	n.a.	1b
	TURP		60	58.20	n.a.	-83	n.a.	n.a.	
Gupta et al. 2006 (43)	HoLEP	12	18	57.9	n.a.	-78	19.20 (527)	-83	1b
	TURP		16	59.8	n.a.	-76	19.95 (487)	-77	
Naspro et al. 2006 (44)	HoLEP	24	41	113.27	n.a.	-61	11.36 (245)	n.a.	1b
	TURP		39	124.21	n.a.	-63	11.79 (242)	n.a.	
Wilson et al. 2006 (45)	HoLEP	24	31	77.8	n.a.	-77	12.6 (250)	n.a.	1b
	TURP		30	77.0	n.a.	-78	11.0 (233)	n.a	
Montorsi et al. 2008 (46)	HoLEP	12	52	70.3	n.a.	-81	16.9 (306)	n.a.	1b
	TURP		48	56.2	n.a.	-82	17.20 (326)	n.a.	
Gilling et al. 2008 (38)	HoLEP	72	71	58.5	n.a.	-67	10.9 (235)	n.a.	3a
Kuntz et al. 2008 (39)	HoLEP	60	60	114.6	n.a.	-86	20.5 (639)	-96	1b
	OP		60	113	n.a.	-86	20.8 (678)	-98	

PSA = prostate-specific antigen; Q_{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 mobidity 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 incontince 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 occured 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. Peristing *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 sphicter 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 retograde 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***

Recommendations	LE	GR
HoLAP can be offered to patients with BOO or BPE with small- to medium-sized prostates.	1b	A
HoLRP can be offered to patients with BOO or BPE with small- to medium-sized glands.	1b	A
HoLEP can be offered to any patient with BOO and BPE.	1a	A
HoLEP can be offered to patients in chronic urinary retention.	2b	B
HoLEP can be offered to patients on anticoagulant or antiplatelet medication.	2b	B

BOO = bladder outlet obstruction; BPE = benign prostatic enlargement

3.4.13 ***References***

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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 264.7 ± 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 vaporisation of the prostate (ThuVaR);
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 is 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 vaporisation of the prostate

ThuVaR is a solely vaporising 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 vaporisation 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 vaporisation 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 vaporisation 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 Thu:YAG is similar to the Ho:YAG with regard to its shallow tissue and water penetration and haemostasis, vaporisation capacity is significantly increased by the continuous-wave emitting mode. Therefore, tissue ablation is not only achieved by resection, but also by simultaneous vaporisation.

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 ThuVARP 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

Trial	Laser source/ Technique	Follow-up	N	Mean prostate size (mL)	PSA reduc-tion (%)	Change in symp-toms (%)	Change in Q_{max} (mL/s) (%)	PVR change (%)	LE
Mattioli et al. 2008 (2)	ThuVAP	12	99	45*	n.a.	-67*	14.8 (289)*	-88.9*	4
	ThuVARP		101						
Xia et al. 2008 (6)	ThuVARP	12	52	59.2	n.a.	-84	15.7 (296)	-94.4	1b
	TURP		48	55.1	n.a.	-81	15.8 (290)	-92.8	
Fu et al. 2009 (7)	ThuVARP	12	58	49.8	n.a.	-85.4	14.9 (329)	-84.3	2b
	TURP		42	48.2	n.a.	-81.1	15.5 (312)	-84.8	
Bach et al. 2007 (8) 2009 (9)	ThuVARP	18	54	30.3	n.a.	-67	12.8 (258]	-86	2b
Fu et al. 2008 [10]	ThuVARP	12	72	65.8	-69.4	-72.6	15.1 (364)	-65.7	2b
Szlauer et al. 2009 [11]	ThuVARP	9	56	50.0	-56.1	-56	13.8 (270)	-62.4	2b
Shao et al. 2009 (13)	ThuVEP	6	52	40.3	- 40.8	-70	14.9 (350)	- 80	1b
	HoLEP		46	37.3	- 35.7	-60	15.5 (330)	- 80	
Bach et al. 2010 (12,14)	ThuVEP	18	88	61.3	n.a.	-63	15.7 (664)	-72.4	2b
Bach et al. 2011 (18)	ThuVEP	12	90	108.59	- 88	-79.7	18.7 (326)	-90.8	

* for both groups.

PSA = prostate specific antigen; PVR = postvoid residual urine volume; LE = level of evidence; ThuVAP = thulium laser vaporisation of the prostate; ThuVARP = Tm:YAG vaporesection; ThuVEP = Tm:YAG vapoenucleation; 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 secondlook 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***

Conclusions	**LE**
ThuVARP showed equivalent effectivity 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).	1b
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.	1b
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.	4

Recommendations	LE	GR
ThuVARP is an alternative to TURP for small- and medium-sized prostates.	1b	A
ThuVARP and ThuVEP are suitable for patients at risk of bleeding or taking anticoagulant medication.	3b	C
ThuVEP can be offered as an alternative to TURP, to HoLEP and OP for large size prostates.	1b, 2b	B

3.5.5 ***References***

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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 (LE: 3/4). 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 is 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

Ref.	Study design	LE	Patients (n)	Surgical technique	Operation time (min)	Compli-cations	Follow-up (mo)	Recurrence (%)		
								Local	Out of field	Overall
Ho:YAG (holmium) laser										
Das et al. 1998 (5)	Prospective	3	23	Photoablation + biopsy	18.6	1 recather-isation	n.a.	n.a.	n.a.	n.a.
Saito 2001 (2)	Retrospective	3	35	En bloc + biopsy	n.a.	None	n.a.	n.a.	n.a.	n.a.
Soler-Martinez et al. 2007 (19)	Prospective	3	36	Biopsy + photoablation	14 (5-17)	None	3, 6, 12	n.a.	n.a.	14, 22, 25
Zhu et al. 2008 (10)	Prospective	2	101	En bloc	30.7 (±16.1)	1 perfora-ted bladder	34 (18, 43)	n.a.	n.a.	n.a.
Xishuang et al. 2009 (11)	Prospective	2	64	En bloc	16.5 (±3.8)	1 urethral stricture	24	n.a.	n.a.	LR 15 IR 34.6 HR 31.7
Zhong et al. 2010 (21)	Retrospective	3	25	En bloc	21.5 (±12.5)	None	12, 24	n.a.	n.a.	12.5, 26, 6
Tm:YAG (thulium)										
Gao et al. 2008 (3)	Prospective	3	32	En bloc	25 (15-35)	None	3, 6, 12	3, 7, 11	6, 17, 21	9, 22, 28
Zhong et al. 2010 (21)	Retrospective	3	34	En bloc	29.1 (±16.5)	None	12, 24	n.a.	n.a.	17.6, 29.9
Yang et al. 2009 (7)	Prospective	3	9	En bloc	7 (5-15)	1 perfora-ted bladder	7.5 [6,9]*	0	n.a.	-

LE = level of evidence; n.a. = not applicable.

4.3 Conclusions and recommendation for laser treatment of bladder cancer

Conclusions	LE
The use of lasers is feasible for resection, coagulation and enucleation of non-muscle invasive bladder tumours.	3
Transurethral resection of the bladder remains the gold standard.	1a
In laser coagulation of tumours, no tissue for pathological staging is obtained.	
Long-term recurrence and progression rates are unknown for this novel technique.	
Currently, no data are available to indicate superiority of one device over another in bladder pathology.	
Complications are generally directly related to the laser's wavelength (penetration depth) and surgical technique.	

Recommendation	GR
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.	C

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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 in 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

Reference	Patients (n)	Treatment	Laser beam	Hilar clamping	Comments or adverse effects	LE
Barzilay et al. 1982 (1)	4	Partial nephrectomy (3), bivalving of kidney (1)	CO_2 laser beam	Yes	Open	3
Rosemberg 1985 (2)	3	Partial nephrectomy	CO_2 laser beam	Yes	Open	3
Malloy et al. 1986 (3)	3	Partial nephrectomy	Nd:YAG laser	No	Open	3
Korhonen et al. 1993 (4)	5	Partial nephrectomy	Nd:YAG laser	Yes	Open	3
Merguerian et al. 1994 (5)	3	Partial nephrectomy	Nd:YAG laser and KTP laser	Yes	Open	3
Gruschwitz et al. 2008 (6)	5	Partial nephrectomy	2.0-µm continuous wave laser	No	Open	3
Lotan et al. 2002 (7)	3	Partial nephrectomy	Ho:YAG laser	No	Laparoscopic/ smoke accumulation and splashing of blood on camera	3
Hodgson et al. 2008 (8)	2	Partial nephrectomy	KTP laser	No	Robotic / hilar clamping was necessitated in one occasion	3

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***

Conclusions	LE
Current data on nephron-sparing surgery using laser energy as an ablative method remain inconclusive.	
Preliminary results indicate that laser-assisted laparoscopic PN without the need for hilar clamping is feasible.	3
No major complication has been reported in humans.	3
Laser-assisted PN is a promising alternative in renal surgery, which is worth further evaluation in clinical trials.	

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

References	Patients (n)	Treatment	Laser beam	Comments or adverse effects	LE
Gianduzzo et al. 2007 (9)	5	LNSRP	1064 nm Nd:YAG laser	Laparoscopic	3

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***

Conclusions	LE
Data are sparse and safe conclusions cannot be drawn yet.	
Preliminary results indicate that laser-assisted LNSRP is feasible and could possibly enhance neuro-vascular bundle preservation.	3
Laser-assisted LNSRP remains experimental.	

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

Reference	Patients (n)	Disease	Laser beam	Comments	LE
de Jode et al. 1999 (12)	3	Inoperable renal tumours	Nd:YAG laser	Percutaneously or MRI-guided	3
Dick et al. 2002 (13)	9	Inoperable renal tumours	Nd:YAG laser	Percutaneously or MRI-guided	3

6.1 Conclusions and recommendation for laser treatment of small renal masses

Conclusions	LE
Data are poor and safe conclusions cannot be drawn yet regarding oncological outcome and safety.	**4**
Renal tumour interstitial laser ablation remains experimental.	**4**

Recommendation	GR
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.	C

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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 [Gdor 2008]. 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 calculi 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

Reference	Patients (n)	Disease	Success rate	Mean follow-up (mo)	Comments
Lin et al. 2009 (2)	19	Benign ureteral strictures	52.6%	40.2	Stricture length and severity of hydronephrosis correlated with successful outcome
Gnessin et al. 2009 (3)	35	Benign ureteral strictures	82% symptomatic, 78.7% radiographic	27	Success rate was higher for nonischemic strictures (100% vs 64.7%, p = 0.027). Most failures occur within less than 9 months after surgery
Fu et al. 2009 (4)	18	Benign ureteral strictures, 6 cases complicated with ureteral calculus	88.8%	10.7	Post-operatively, an orthopaedic ureteral stent was left in place for 3-6 months
Corcoran et al. 2009 (5)	9	Benign ureteral strictures (20% idiopathic, 80% after calculi management or abdominal surgery)	85%	25.2	Laser urethrotomy was followed by balloon dilation in most cases
Gdor et al. 2008 (6)	13	Ureteral strictures associated with ureteral calculi (impacted ureteral calculi in 4)	62%	21	In case of impacted ureteral calculi, success rate was 56%. Without a history of impacted calculi, success rate was 75%
Hibi et al. 2007 (7)	20		80%	60.5	All failures occurred within 18 months
Lane et al. 2006 (8)	19	Non-obliterative iatrogenic ureteral strictures	68.4%	36	Failure was uniformly evident within the first 3 months
Razdan et al. 2005 (9)	17	Ureteral strictures of varying causes		40,8	
Kourambas 2001 (10)	7	Ureteral strictures	91%	3	
Singal et al. 1997 (1)	22	Ureteral strictures from a variety of causes and including ureteroenteric anastomoses	76%	9	Failure was uniformly evident within the first 3 months
Watterson et al. 2002 (11)	23	Ureterointestinal strictures	56%	36	Some recurrences occurred 16 months or longer postoperatively
Laven et al. 2001 (12)	19	Ureterointestinal strictures	57%	20.5	

7.3 Conclusions and recommendations for retrograde laser endoureterotomy

Conclusions	LE
Retrograde laser endoureterotomy is a feasible and safe treatment option for ureteral strictures.	3
Open surgical revision remains the gold standard.	1a
Ureteral strictures of different aetiologies appear to respond differently to treatment.	2b
In selected cases, success rate can reach 90%.	
Ureteroenteric anastomosis strictures respond poorly to laser endoureterotomy.	3
Late stricture recurrence should be expected until as long as 18 months post-operatively.	3

Recommendations	GR
Retrograde endoureterotomy should be considered a first-line treatment option for ureteral strictures.	C
Longer follow-up is needed.	C

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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 (7) (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. Rarely do more serious measures, such as conversion to open surgery, 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

Reference	Patients (n)	Disease	Success rate	Mean follow- up (mo)	Comments
Acher et al. 2009 (2)	15	Failed pyeloplasty	100%	6	No complications reported
Stilling et al. 2009 (3)	44	Primary (n=37) and secondary (n=7) UPJO	Symptom relief complete 66%; improved 23%	27.5	Strict inclusion criteria
Savoie et al. 2009 (4)	27	Primary (n=16) and secondary (n=11) UPJO	70%	35	Median time to failure: 2.7 months
Braga et al. 2007 (5)	10	Failed pyeloplasty in children	60% radiographic relief	47	Age < 4 years and narrowed ureteral segment greater than 10 mm were associated with a poor outcome

Doo et al. 2007 (6)	47	UPJO	67.5%	37.3	Median time to failure: 7.7 months
Rassweiler et al. 2007 (7)	113	Extrinsic as well as intrinsic UPJO	72.6% (85.7% intrinsic vs 51.4% extrinsic)	63 months	Complication rate of 5.3%
Ponsky et al. 2006 (8)	37	Primary and secondary UPJO	74.2%	75.6	No major complications reported
Geavlete et al. 2007 (9)	30	Failed pyeloplasty (n=17); failed endopyelotomy (n=13)	83.3% (at 18 months)	31	
el-Nahas et al. 2006 (10)	20	Primary and secondary UPJO	85%	29.9	10% complication rate
Minervini at al. 2005 (11)	30	UPJO	80% (at 10 months)	24	12.5% complication rate
Seveso et al. 2005 (12)	16	Primary (n=10) and secondary (n=6) UPJO	81%	18	One case of intra-operative haemorrhage
Matin et al. 2003 (13)	46	Primary (n=40) and secondary (n=6) UPJO	65.4% symptomatic and 73.1% radiographic	23.2	No intra-operative complications; 11.1% post-operative complications
Hibi et al. 2002 (14)	5	UPJO	80%	12.8	
Giddens et al. 2000 (15)	23	Primary and secondary UPJO	83%	10	Repeat laser incision successful in 50% of primary failures
Biyani et al. 2000 (16)	22	Primary (n=16) and secondary (n=4) UPJO	75%	34	Success rate tends to be poor in patients with poor renal function
Renner et al. 1998 (17)	34	Primary (n=27) and secondary (n=7) UPJO	85%	18	Minor complications in 15%
Conlin et al. 1998 (18)	21	UPJO	81%	12	
Biyani et al. 1997 (19)	8	Primary (n=5) and secondary (n=3) UPJO	87.5%	12.4	

UPJO = ureteropelvic junction obstruction.

8.3 Conclusions and recommendations for laser treatment for UPJO

Conclusions	**LE**
Retrograde laser endopyelotomy is a feasible and safe treatment option for the treatment of uteropelvic junction obstruction.	3
Open or laparoscopic pyeloplasty remains the gold standard.	1a
In selected cases, success rate can reach 90%.	
Treatment morbidity is minimal and major complications are rare.	3
Treatment failure may occur up to 1 year post-operatively.	3

Recommendations	GR
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

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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

Reference	Patients (n)	Disease	Success rate %	Mean follow-up (mo)	Comments
Guo et al. 2010 (2)	238	Urethral strictures	81.9%	6	2-micron thulium laser
Guo et al. 2008 (3)	198	Urethral strictures (n = 179) or atresia (n = 13)	81.7%	6	2 micron thulium laser
Xiao et al. 2008 (4)	34	Urethral strictures	94.7%	3-18	Holmium laser: 4 received urethral dilation and 2 underwent a second holmium laser urethrotomy

Eltahawy et al. 2008 (5)	24	Anastomotic stenosis following radical prostatectomy, 79% recurrent-resistant to other treatment modalities	83%	24	Holmium laser + steroid injection
Futao et al. 2006 (6)	28	Paediatric patients with urethral strictures (n=25) and urethral atresias (n=3)	89.3%	(2-48)	Ho:YAG
Hossain et al. 2004 (7)	30	Short segment anterior urethral stricture	90%	6	Ho:YAG
Dogra et al. 2004 (8)	29	Urethral stricture (< 2.5 cm)	65.51% excellent, 31.03% acceptable	15	Ho:YAG
Gürdal et al. 2003 (9)	21	Recurrent benign urethral strictures 5-20 mm in length	52%	24	Nd:YAG
Dogra et al. 2003 (10)	61	Obliterative post-traumatic urethral strictures in children	100%	24	Nd-YAG
Matsuoka et al. 2002 (11)	31	Ureteral stricture of varying lengths	74%		Ho:YAG
Dogra et al. 2002 (12)	65	Post-traumatic urethral strictures	95.3%	9-44	Nd- YAG
Kamal 2001 (13)	22	Urethral strictures (8 recurrent)	54% (78.5% in non recurrent strictures)	26.7	Diode laser
Schmidlin et al. 1997 (14)	20	Anterior urethral strictures	81%	6	KTP
Becker et al. 1995 (15)	900	Urethral strictures (most iatrogenic)	30%	15.2	Argon
Faerber et al. 1994 (16)	12	Paediatric urethral strictures	83%	12	Nd-YAG
Turek et al. 1992 (17)	37	Benign urethral strictures	59% complete, 20.5% partial success	9.7	KTP
Vicente et al. 1990 (18)	15	Benign urethral strictures	73.3%	12	Cold knife + Nd:YAG laser
Bloiso et al. 1988 (19)	115	31 short strictures 36 bladder neck 48 complicated	96.7% (short strictures); 100% (bladder neck); 22.91% (complicated)	10 (short strictures); 7 (bladder neck); 14 (complicated)	Nd:YAG

Ho:YAG = Holmium: yttrium aluminium garnet; KTP = potassium titanyl-phosphate laser; Nd:YAG = neodymium-doped yttrium aluminium garnet

9.3 Conclusions and recommendations for transurethral laser urethrotomy

Conclusions	**LE**
Transurethral laser urethrotomy is a feasible and safe treatment option for the treatment of urethral strictures.	3
Cold-knife optical urethrotomy remains the gold standard.	1a
Success rates as high as 100% are reported in selected cases	3
Treatment morbidity is minimal and major complications are rare.	3

Recommendations	GR
Transurethral laser urethrotomy could be one of the first-line treatment options for benign urethral strictures.	C

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10. LASER CLINICAL APLICATIONS 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 is 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, which 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 use 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***

	LE
Pulsed lasers are an effective and safe treatment for UUT stones, using endoscopes.	
Lasers present a safe option for defragmenting stones in the upper urinary tract.	1

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

Conclusion	**LE**
Nephro-ureterectomy is still the gold standard for UUT urothelial tumours	1a

Recommendations	**GR**
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	B
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	C

10.5 References

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11. 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-aluminum-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 nevrovascular bundle
OP	open prostatectomy
PN	partial nephrectomy
PSA	prostate specific antigen
PVP	photoselective vaporisation of the prostate
PVR	postvoid residual urine
Q_{max}	urinary peak flow
QoL	Quality of Life
Tm:YAG laser	Thulium:Yttrium-Aluminium-Garnet laser
ThuVAP	Thulium laser vaporisation of the prostate
ThuVaR	Tm:YAG Vaporisation of the prostate
ThuVARP	Tm:YAG Vaporesection
ThuVEP	Tm:YAG Vapoenucleation
ThuLEP	Tm:YAG laser enucleation of the prostate
TUR	transurethral resection
TURP	transurethral resection of the prostate
TURB	TUR of the bladder
UPJO	ureteropelvic junction obstruction
UTI	urinary tract infection

Conflict of interest

All members of the New Technologies Guidelines working group 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 kept on file in the European Association of Urology Central Office database. 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

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European Association of Urology

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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)

Criteria	Requirement
Method of accruing data defined	Prospective or retrospective accrual of data are indicated
Duration of follow-up indicated	Report clarifies the time period of postoperative accrual of complications such as 30 days or same hospitalisation
Outpatient information included	Study indicates that complications first identified following discharge are included in the analysis
Definition of complications provided	Article defines at least one complication with specific inclusion criteria
Mortality rate and causes of death listed	The number of patients who died in the postoperative period of study are recorded together with cause of death
Morbidity rate and total complications indicated	The number of patients with any complication and the total number of complications are recorded
Procedure-specific complications included	
Severity grade utilised	Any grading system designed to clarify severity of complications including major and minor is reported
Length-of-stay data	Median or mean length of stay indicated in the study
Risk factors included in the analysis	Evidence of risk stratification and method used indicated by study

Table 2: Clavien-Dindo grading system for the classification of surgical complications (11)

Grades	Definitions
Grade I	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.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade III-a	Intervention not under general anaesthesia
Grade III-b	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction

Grade V	Death of a patient
Suffix “d”	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.

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 urological procedures using the Clavien-Dindo system

Study title: .....

Published in:
☐ European Urology ☐ Journal of Urology ☐ BJU International ☐ Urology
☐ World Journal of Urology

Year of publication:
☐ 1999/2000 ☐ 2009/2010 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

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 urological 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

Classification	Clinical validation	Simplicity	Severity grading
Clavien-Dindo	Yes	Easy	I-V
MSKCC	Yes	Easy	5
Accordion contracted extended	No	Easy	 4 6
NSQIP	Yes	Complex	Major/minor
NCT-CTC	Yes	Complex	5

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), and (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 Web site (http://www.accordionclassification.wustl.edu).

Table 4: Accordion severity classification of postoperative complications: contracted and expanded classification (17)

Contracted classification	Expanded classification
1. Mild complication 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.	1. Mild complication 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.
2. Moderate complication Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.	2. Moderate complication Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.
3. Severe complication All complications requiring endoscopic or interventional radiology or re-operation, as well as complications resulting in failure of one or more organ systems.	3. Severe: invasive procedure without general anaesthesia Requires management by an endoscopic, interventional procedure or re-operation* without general anaesthesia
4. Death Postoperative death	4. Severe: operation under general anaesthesia Requires management by an operation under general anaesthesia
	5. Severe: organ system failure†
	6. Death Postoperative death

**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 Web site (www.ctep.info.nih.gov).

Table 5: National Cancer Institute Common Toxicity Criteria grading system for the adverse effects of cancer treatment (17)

Grade	Definition of effects
Grade 1	Minimal and usually asymptomatic that do not interfere with functional endpoints (interventions or medications are generally not indicated for these minor effects).
Grade 2	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).
Grade 3	Severe and very undesirable. There are usually multiple, disruptive symptoms (more serious interventions, including surgery or hospitalisation, may be indicated).
Grade 4	Potentially life threatening, catastrophic, disabling, or result in loss of organ, organ function, or limb.

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

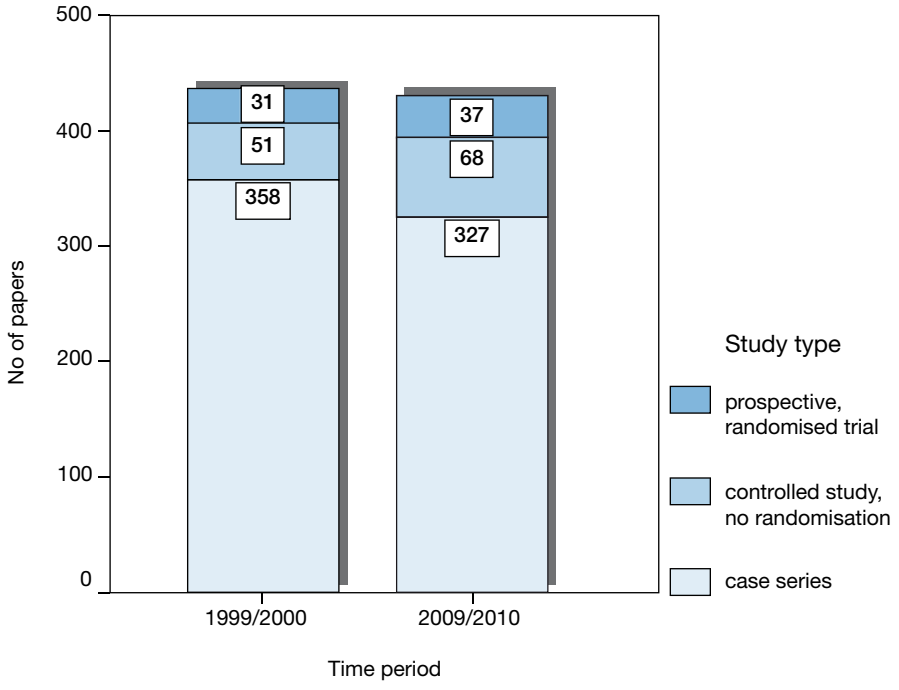


Fig. 2: Comparative distribution of papers reporting complications after urologic procedures by number of Martin criteria met and time frame

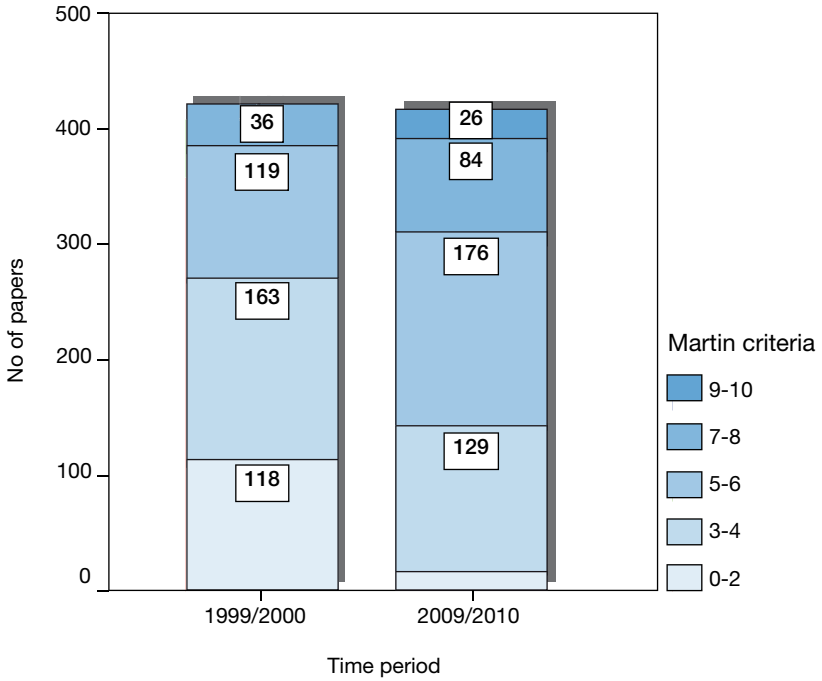
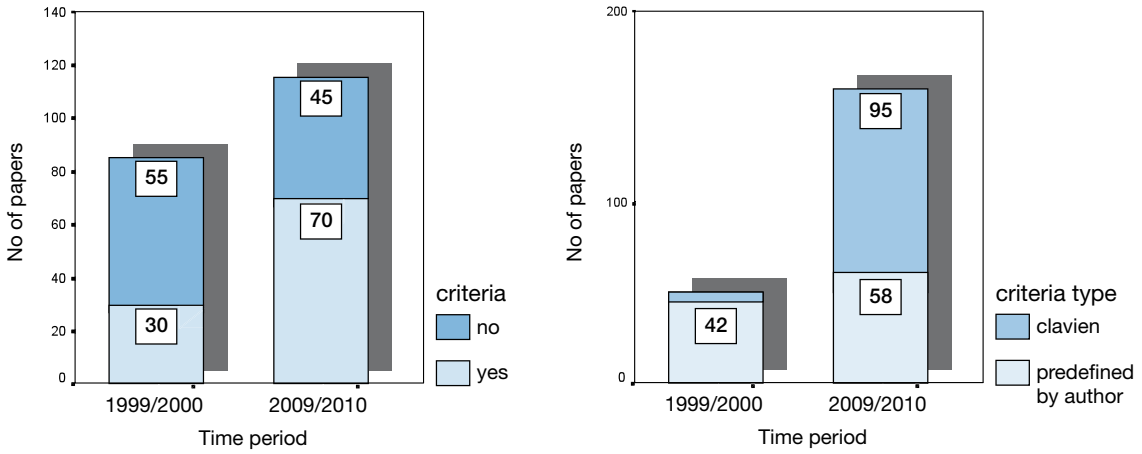


Fig. 3: Comparative distribution of papers reporting complications after urologic procedures by time frame and whether standardised criteria were used (left), and in case they were, whether the Clavien-Dindo system was used (right)



3.3 Assessment of the Clavien-Dindo system for reporting complications after urologic procedures

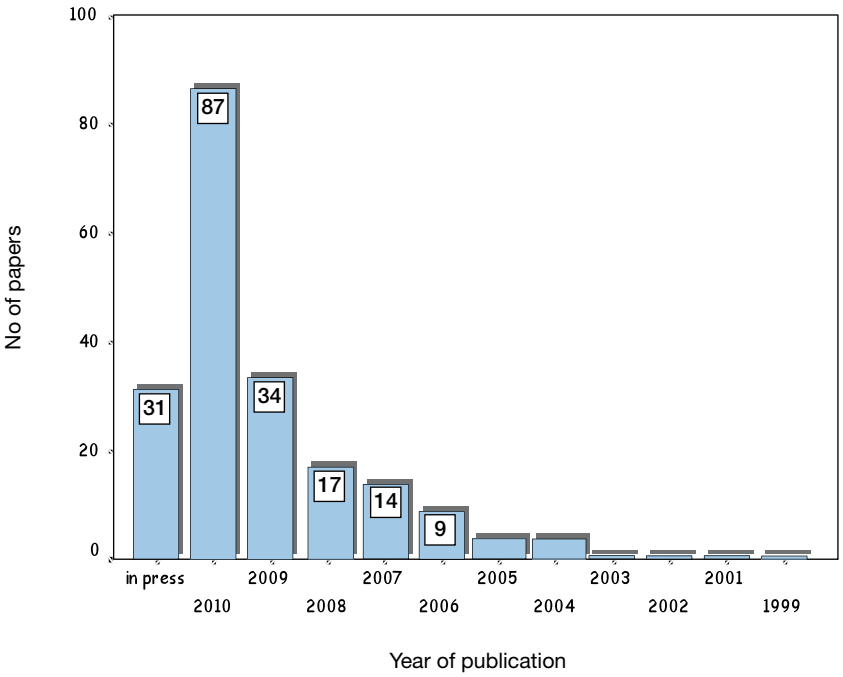
The literature search identified 204 papers published in:

- 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 within 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.

Theses 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, a fact 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

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6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ARF	acute renal failure
ASA	American Society of Anesthesiologists
CNS	central nervous system
CTC AE	Common Terminology criteria for Adverse Events
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
IC(U)	intensive care (unit)
ICS	International Continence Society
IF	impact factor
IUGA	International Urogynecological Association
MSKCC	Memorial Sloan-Kettering Cancer Centre classification
NSQIP	National Surgical Quality Improvement Programme
NCT-CTC	National Cancer Institute Common Toxicity Criteria
O/E	ratio of observed versus expected
VA	US Veterans Administration

Conflict of interest

All members of the ad hoc EAU Guidelines working group on Reporting and Grading Complications after Urologic Surgical Procedures have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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.