European Association of Urology

Pocket Guidelines

2021 edition

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Introduction

Over the course of the past year, we have faced a truly unprecedented healthcare crisis. The COVID-19 pandemic has tested the resources and capacity of health systems around the world and our normal working patterns have been radically altered. Despite these challenges, the EAU Guidelines Office has continued to function and we are honoured to present the 2021 edition of the European Association of Urology (EAU) Guidelines. We would like to take this opportunity to thank all members of the Guidelines Office who have worked tirelessly over the course of the past twelve months to make this update possible. The EAU Guidelines remain the most comprehensive, continuously updated, guidelines available for urologists and clinicians from related specialties.

Last year an additional burden was placed on panel members over and above the yearly update of the EAU Guidelines. In response to the COVID-19 pandemic, a Guidelines Office Rapid Reaction Group (GORRG), composed of highly experienced Board and Panel members was established. The GORRG groups initial remit was to provide rapid guidance, underpinned by the best knowledge available, on adapting EAU Guidelines recommendations to the COVID-19 pandemic. Thanks to the efforts of all panel members, the publication of the EAU Adapted Guidelines for the COVID-19 Era was achieved in a very short period and published in April 2020. Moving forward, the GORRG will expand on their initial remit to address a wider range of important topics directly impacting urological practice.

For the 2021 edition of the EAU Guidelines, we are proud to present two new EAU Guidelines on Non-Neurogenic Female Lower Urinary Tract Symptoms (LUTS) and Urethral Strictures. The Guidelines on Non-Neurogenic Female LUTS provide a concise overview of the evidence-base related to assessment and treatment of female LUTS as reflected in clinical practice and expands on the previous EAU Incontinence Guideline. The Guidelines on Urethral Strictures aim to provide a comprehensive overview of urethral strictures management in male, female and transgender patients.

The yearly publication of the EAU Guidelines would not be possible without the unwavering support of the EAU Executive Committee and Management team, our highly valued Guidelines Panels and young Guidelines Associates, the Guidelines Office Staff, our EAU membership and every user of the Guidelines globally. So, on behalf of the EAU Guidelines Office Board, thank you for your support and inspiration.

We hope you enjoy using the 2021 update of the EAU Guidelines!

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Level of evidence and grading systems
For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];

2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

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 [3]*

References

1. Guyatt, G.H., et al. What is "quality of evidence" and why is it important to clinicians? BMJ, 2008. 336: 995.
2. Guyatt, G.H., et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008. 336: 924..
3. Phillips, B., et al. Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
4. Guyatt, G.H., et al. Going from evidence to recommendations. BMJ, 2008. 336: 1049.

EAU GUIDELINES ON NON-MUSCLE-INVASIVE (TaT1, CIS) BLADDER CANCER

(Limited text update March 2021)

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Epidemiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in the male population worldwide, while it drops to the 10th position when both genders are considered. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women.

Staging and classification systems

The 2017 TNM (Tumour, Node, Metastasis Classification) is used for staging (Table 1). For grading, both the 1973 and 2004/2016 WHO grading classifications are used (Table 2).

Table 1: TNM Classification 2017

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 stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional 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 regional 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	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

Two grading systems, the WHO 1973 and the WHO 2004/2016, are currently available for routine clinical use. To facilitate their application in daily practice, these Guidelines provide recommendations for tumours classified based on both grading systems.

Carcinoma *in situ*

Carcinoma *in situ* is a flat, high-grade, non-invasive urothelial carcinoma, and classified into the following clinical types:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Table 2: WHO grading in 1973 and in 2004/2016

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004/2016 WHO grading system *(Papillary lesions)*
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

Variants of urothelial carcinoma and lymphovascular invasion

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, sarcomatoid) have a worse prognosis than pure HG urothelial carcinoma. The presence of lymphovascular invasion (LVI) in transurethral resection of the bladder (TURB) specimens is associated with worse prognosis.

Recommendations for bladder cancer classification	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO classification systems.	Weak
Do not use the term "superficial bladder cancer".	Strong

Diagnosis

A comprehensive patient history is mandatory. Haematuria is the most common finding. Physical examination does not reveal NMIBC.

Recommendations for the primary assessment of non-muscle invasive bladder cancer	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography (CT)-intravenous urography during the initial work-up in patients with haematuria.	Strong

Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

Papillary (TaT1) tumours

The diagnosis of papillary bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the tissue resected during TURB. Transurethral resection of the bladder is a crucial procedure in the diagnosis and treatment of TaT1 tumours and should be performed systematically in individual steps (see recommendations below). A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis.

The technique selected depends on the size of the lesion, its location and experience of the surgeon. In selected cases, due to the risk of tumour persistence and understaging after initial TURB, a second resection (2nd TURB) is recommended.

Carcinoma *in situ*

Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of bladder biopsies taken from suspicious areas or as mapping biopsies from normal looking mucosa (for details, please consult the extended guidelines). Carcinoma *in situ* cannot be eradicated by TURB and further treatment is mandatory.

Recommendations for transurethral resection of the bladder (TURB), biopsies and pathology report	**Strength rating**
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak

Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia. This step may be omitted in case non-invasive or early treatment for invasive disease is planned; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong

Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma *in situ* is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if 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.	Strong
Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas are present in the prostatic urethra at this time, these need to be biopsied as well.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak

The TURB protocol must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a 2nd TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a 2nd TURB within 2–6 weeks after the initial resection. This 2nd TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a 2nd TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS, and detrusor muscle.	Strong

Predicting disease recurrence and progression and defining risk groups

After TURB, patients should be stratified, according to prognostic factors, into risk groups which will facilitate treatment recommendations (see Table 3). For individual prediction of the risk of tumour progression at different intervals after TURB, application of the 2021 EAU NMIBC Risk Calculator (www.nmibc.net) is strongly recommended.

For bacillus Calmette-Guérin (BCG)-treated patients, separate scoring models and risk groups have been created by the CUETO and the EORTC, respectively. For prediction of tumour recurrence in individual patients, the 2006 EORTC scoring model and calculator may be used.

Recommendations for stratification of non-muscle invasive bladder cancer	Strength rating
Stratify patients into 4 risk groups according to Table 3. A patient's risk group can be determined by using the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, use The EAU NMIBC 2021 scoring model.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with bacillus Calmette-Guerin (BCG).	Strong

Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (2016 EORTC model is calculated for 1-3 year of maintenance, CUETO model for 5 to 6 months of BCG).	Strong

Table 3: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems

- Only one of the two grading systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both grading systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973, as it has a higher prognostic value.
- The category of LG tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are*:
  - age > 70;
  - multiple papillary tumours;
  - tumour diameter > 3 cm.

Risk Group	Description
Low Risk	• A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient < 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors*
Intermediate Risk	Patients without CIS who are not included in either the low-, high- or very high-risk groups

High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group.
	Stage, grade with additional clinical risk factors*: • Ta LG/G2 or T1 G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1 G2 (no CIS) with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors*:** • Ta HG/G3 and CIS with all 3 risk factors • T1 G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

The scoring model is based on an individual patient meta-analysis, but does not consider patients with primary CIS (high risk) or with recurrent tumours, as well as some pathologic parameters like variant histology (*micropapillary, plasmocytoid, sarcomatoid, small-cell, neuroendocrine*) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with some variant histology of urothelial carcinoma or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high- or very high-risk groups according to their other prognostic factors.

Disease management

Adjuvant treatment

Since there is considerable risk for recurrence and/or progression of tumours after TURB, adjuvant intravesical therapy is recommended for all stages (TaT1, and CIS).

- **Immediate single post-operative instillation of chemotherapy** within six hours after TURB can reduce the recurrence rate in patients with low-risk and selected intermediate-risk tumours. The difference of efficacy between individual drugs (mitomycin C, epirubicin, or doxorubicin) has not been confirmed.
- **Further chemotherapy** instillations can improve recurrence-free survival in intermediate-risk tumours, but do not prevent progression. These instillations are associated with minor side-effects.
- **Intravesical immunotherapy with BCG** (induction and maintenance) is superior to intravesical chemotherapy in reducing recurrences and in preventing or delaying progression to muscle-invasive bladder cancer.

The individual choice of further intravesical adjuvant therapy depends on the patient's risk (Table 3). In patients at highest risk of progression, RC should be considered.

Bacillus Calmette-Guérin (BCG) failure

Several categories of BCG failures, broadly defined as any disease recurrence following BCG therapy, have been proposed.

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1G3/HG tumour is present at 3 months (LE: 3).
2. If TaG3/HG tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance (LE: 4).
3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance (LE: 1b). If CIS (without concomitant papillary tumour) identified at 3 months, is still present after re-induction/a first maintenance course (at 6 months). In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases.
4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response (LE: 3).
BCG-unresponsive tumour
BCG unresponsive tumours include all BCG refractory tumours and those who develop T1Ta/HG BCG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure** (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment.

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

** *Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

General recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS	Strength rating
Counsel smokers with confirmed NMIBC to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder should be based on the risk groups shown in Table 3. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, one immediate chemotherapy instillation is recommended.	Strong
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	Strong

In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side-effects and problems connected with BCG shortages.	Strong
In patients with very high-risk tumours, discuss immediate radical cystectomy (RC).	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
Offer a RC to patients with BCG unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferentially in clinical trials).	Weak
Recommendations – technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak

Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

Guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification

Recommendations	Strength rating
EAU risk group: Low	
Offer one immediate instillation of intravesical chemotherapy after TURB.	Strong
EAU Risk Group: Intermediate	
In all patients either one-year full- dose Bacillus Calmette-Guerin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURB.	Strong
EAU risk group: High	
Offer intravesical full-dose BCG instillations for one to three years or radical cystectomy (RC).	Strong
EAU risk group: Very High	
Consider RC and offer intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC.	Strong

Table 4: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC).
	2. Enrollment in clinical trials assessing new treatment strategies.
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG-relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation.
	2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. Radical cystectomy.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; LG = low-grade.

Follow-up

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed-up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk.

Recommendations for follow-up in patients after transurethral resection of the bladder	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	Weak
Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk and very high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong

During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1–2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT (UTUCs)

(Limited text update March 2021)

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Epidemiology

Upper urinary tract urothelial carcinomas (UTUCs) are uncommon and account for only 5-10% of urothelial carcinomas (UCs). They have a similar morphology to bladder carcinomas and nearly all UTUCs are urothelial in origin.

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

Staging and grading systems

The UICC 2017 TNM (Tumour, Node, Metastasis Classification) for renal pelvis and ureter is used for staging (Table 1).

Tumour grade

The 2004/2016 WHO classification distinguishes between non-invasive tumours:

- papillary urothelial neoplasia of low malignant potential;
- low-grade papillary urothelial carcinomas;
- high-grade papillary urothelial carcinomas.

As well as define flat lesions (carcinoma *in situ*) and invasive carcinoma.

Upper urinary tract tumours with low malignant potential are very rare.

Table 1: TNM Classification 2017

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 muscularis
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 greatest dimension

N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Diagnosis

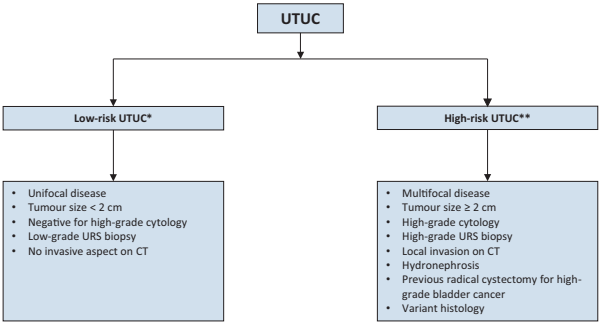
UTUCs are diagnosed using imaging, cystoscopy, urinary cytology and diagnostic ureteroscopy. Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques. In case conservative management is considered, a pre-operative ureteroscopic assessment is needed.

Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform a computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy and biopsy if imaging and cytology are not sufficient for the diagnosis and/or risk stratification of the tumour.	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/computed tomography may be used when CT is contra-indicated.	Weak

Prognosis

Invasive UTUC usually have a very poor prognosis. The main factors to consider for risk stratification are listed in Figure 1.

Figure 1: Risk stratification of non-metastatic UTUC

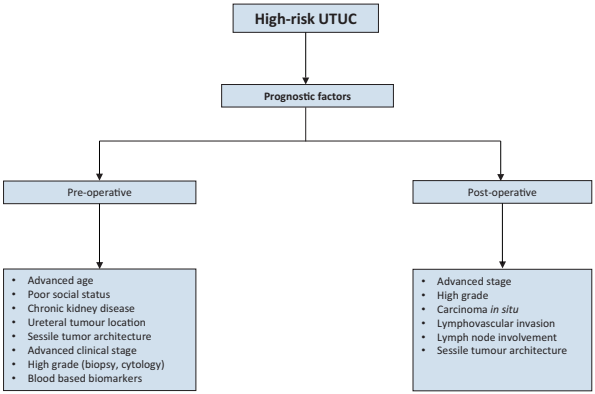


CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
**All these factors need to be present.*
***Any of these factors need to be present.*

Risk stratification

As tumour stage is difficult to assess clinically in UTUC, it is useful to "risk stratify" UTUC between low- and high-risk tumours to identify those patients who are more likely to benefit from kidney-sparing treatment. Those factors can be used to counsel patients regarding follow-up and administration of peri-operative chemotherapy (see Figures 1 and 2). Currently, no prognostic biomarkers are validated for clinical use.

Figure 2: UTUC prognostic factors included in prognostic models



UTUC = upper urinary tract urothelial carcinoma.

Recommendation	Strength rating
Use prognostic factors to risk-stratify patients for therapeutic guidance.	Weak

Disease management *(see also Figures 3 & 4)*

Localised disease

Kidney-sparing surgery

Kidney-sparing surgery for low-risk UTUC consists of surgery preserving the upper urinary renal unit and should be discussed in all low-risk cases, irrespective of the status of the contralateral kidney.

Kidney-sparing surgery potentially allows avoiding the morbidity associated with open radical surgery without compromising oncological outcomes and kidney function.

Kidney-sparing surgery can also be considered in select patients with serious renal insufficiency or solitary kidney (i.e., imperative indications).

Recommendations	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong
Offer kidney-sparing management (distal ureterectomy) to patients with high-risk tumours limited to the distal ureter.	Weak
Offer kidney-sparing management to patients with solitary kidney and/or impaired renal function, providing that it will not compromise survival. This decision will have to be made on a case-by-case basis in consultation with the patient.	Strong

The instillation of bacillus Calmette-Guérin or mitomycin C in the urinary tract by percutaneous nephrostomy, or via a ureteric stent is technically feasible after kidney-sparing management, or for treatment of carcinoma *in situ*. However, the benefits have not been confirmed.

High-risk non-metastatic disease

Radical nephroureterectomy

Open nephroureterectomy (RNU) with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location.

- In high-risk patients, neoadjuvant chemotherapy has been associated with significant downstaging at surgery and ultimately survival benefit as compared to RNU alone.

- Adjuvant chemotherapy was only associated with an OS benefit in patients with pure urothelial carcinoma and the main limitation of using adjuvant chemotherapy for advanced UTUC remains the limited ability to deliver full dose cisplatin-based regimen after RNU, given that this surgical procedure is likely to impact renal function.
- In patients with regional lymph node invasion who are cisplatin-unfit after RNU, induction chemotherapy with radiological evaluation and consolidating surgery is a treatment option.
- A single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2-10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU.

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer post-operative systemic platinum-based chemotherapy to patients with muscle-invasive UTUC.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

Metastatic disease

Radical nephroureterectomy has no benefit in metastatic (M+) disease but may be used in palliative care. As UTUCs are urothelial tumours, platinum-based chemotherapy should provide similar results to those in bladder cancer. Currently, insufficient data are available to provide any recommendations. Radiotherapy is no longer relevant nowadays, neither as a sole treatment option, nor as an adjunct to chemotherapy.

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
Do not offer carboplatin or non-platinum combination chemotherapy.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemo-therapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong

Offer checkpoint inhibitor (atezolizumab or nivolumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong

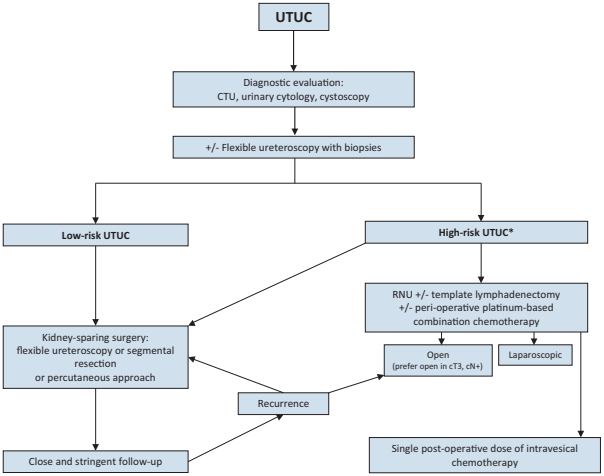
GC = gemcitabine plus cisplatin; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

Follow-up after initial treatment

In all cases, there should be strict follow-up after radical management to detect metachronous bladder tumours, as well as invasive tumours, local recurrence and distant metastases. When kidney-sparing surgery is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence.

Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly, for five years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every six months for two years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy (URS) at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at three and six months, and then yearly.	Weak
Perform URS and urinary cytology *in situ* at three and six months.	Weak

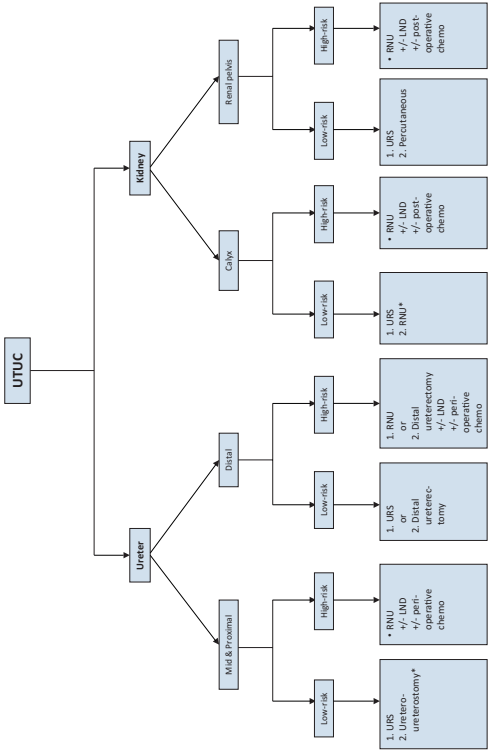
Figure 3: Proposed flowchart for the management of UTUC



** In patients with a solitary kidney, consider a more conservative approach.*

CTU = computed tomography urography; RNU = nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

Figure 4: Surgical treatment according to location and risk status



1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy;
UTUC = upper urinary tract urothelial carcinoma.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

(Limited text update March 2021)

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Introduction

Optimal treatment strategies for Muscle-invasive Bladder Cancer (MIBC) require the involvement of a specialist multidisciplinary team and a model of integrated treatment strategies to avoid fragmentation of patient care.

Staging and grading systems

The 2017 TNM (Tumour, Node, Metastasis Classification) is used for staging (Table 1). For grading, the 1973 and 2004/2016 WHO grading classifications are used.

Table 1: TNM Classification 2017

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	Microscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional 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 a common iliac lymph node(s)	

M - Distant Metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastasis

Pathology of MIBC

Determination of morphological subtypes can be helpful in assessing the prognosis and treatment options of high-grade urothelial carcinomas (UCs) (grade II or grade III) as discussed in these guidelines. The following differentiations are used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. micropapillary urothelial carcinoma;
4. nested variant (including large nested variant) and microcystic urothelial carcinoma;
5. plasmacytoid, giant cell, signet ring, diffuse, undifferentiated;
6. lymphoepithelioma-like;
7. small-cell carcinomas;
8. sarcomatoid urothelial carcinomas;
9. neuroendocrine variant of urothelial carcinoma;
10. some urothelial carcinomas with other rare differentiations.

Recommendations for the assessment of tumour specimens	Strength rating
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4a and pT4).	Strong
Record margins with special attention paid to the radial margin, prostate, ureter, urethra, peritoneal fat, uterus and vaginal vault.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphatic or blood vessel invasion.	
Record the presence of carcinoma *in situ*.	
Record the sampling sites, as well as information on tumour size when providing specimens to the pathologist.	

Recommendations for the primary assessment of presumably invasive bladder tumours*	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	Strong

In men with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intra-operative frozen section can be omitted.	Strong
In men with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied *a priori*, unless an intra-operative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	Strong
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.	Strong
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

* *For general information on the assessment of bladder tumours, see the EAU Guidelines on Non-muscle-invasive Bladder Cancer.*

Recommendations for staging of MIBC	**Strength rating**
In patients with confirmed muscle-invasive bladder cancer, use computed tomography (CT) of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation.	Strong

Use magnetic resonance urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	Strong
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	Strong
Use CT to diagnose pulmonary metastases. Computed tomography and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	Strong

Assess health status

Recommendations for the use of comorbidity scales	**Strength rating**
Base the decision on bladder-sparing treatment or radical cystectomy in older/ frail patients with invasive bladder cancer on tumour stage and frailty.	Strong
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting.	Strong

Markers

Prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data, but until long-term follow-up data from phase III randomised controlled trials are available, many questions currently remain open.

Recommendations for markers	Strength rating
Evaluate PD-L1 expression (by immunohistochemistry) to determine the potential for use of pembrolizumab or atezolizumab in previously untreated patients with locally advanced or metastatic urothelial cancer who are unfit for cisplatin-based chemotherapy.	Weak
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy).	Weak

Disease Management

Neoadjuvant therapy

Neoadjuvant cisplatin-containing combination chemotherapy (NAC) improves overall survival (OS) (5-8% at five years), irrespective of the type of definitive treatment used. Patients may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0, ≤ ypT1, ypN0 and negative surgical margins.

Currently, no tools are available to select patients who have a higher probability of benefitting from NAC. Response after two cycles of treatment is related to outcome. In the future, genetic markers in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.

Checkpoint inhibitors have shown significant benefit in patients with unresectable and metastatic bladder cancer in the salvage setting and in platinum-ineligible PD-L1+ patients as first-line treatment, but data are still immature.

Recommendations for neoadjuvant therapy	**Strength rating**
Offer neoadjuvant chemotherapy (NAC) for T2–T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

Recommendations for pre- and post-operative radiotherapy in MIBC	**Strength rating**
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant radiation in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak

Radical cystectomy and urinary diversion

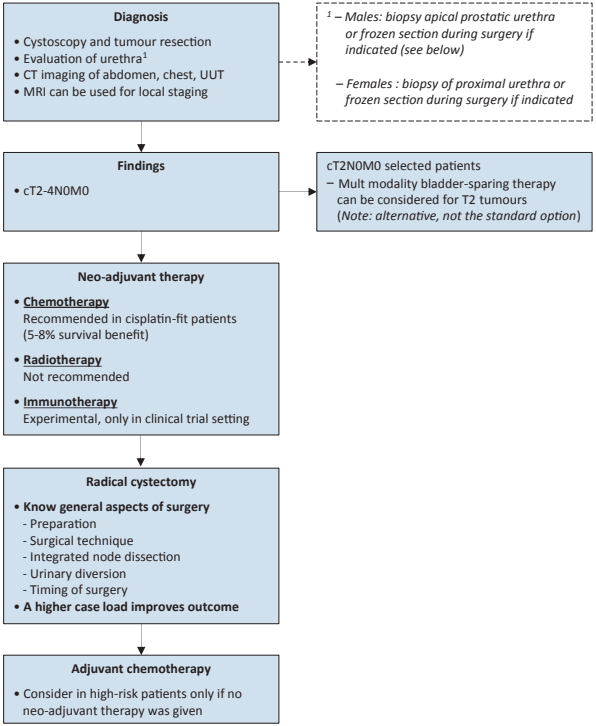
Contraindications for orthotopic bladder substitution are positive margins at the level of urethral dissection, positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate (in men).

Recommendations for radical cystectomy and urinary diversion	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
Do not offer sexual-preserving radical cystectomy to men as standard therapy for MIBC.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong

Select men for sexual-preserving techniques based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong
Do not offer pelvic organ-preserving radical cystectomy to women as standard therapy for MIBC.	Strong
Offer sexual-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select women for sexual-preserving techniques based on: • absence of tumour in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma.	Strong
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time to bowel recovery.	Strong
Offer pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong
Offer RC to patients with T2–T4a, N0M0 disease or high-risk non-muscle-invasive bladder cancer.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

Recommendations for laparoscopic/ robotic-assisted laparoscopic cystectomy	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

Figure 1: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; UUT = upper urinary tract.

Bladder-sparing treatments for localised disease

Transurethral resection of bladder tumour

Transurethral resection of bladder tumour alone is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if restaging biopsies are negative for residual tumour.

External beam radiotherapy

External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or as part of a trimodality bladder-preserving approach.

Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation due to extensive local tumour growth.

Chemotherapy and best supportive care

Complete and partial local responses have been reported with cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients.

Trimodality treatment

In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy. Delaying surgery can compromise survival rates.

Recommendations for bladder-sparing treatments for localised disease	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong
Offer surgical intervention or trimodality bladder-preserving treatments (TMT) to appropriate candidates as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer TMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option or not acceptable.	Strong

Surgically non-curable tumours

Palliative radical cystectomy for metastatic disease

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

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms.	Weak

Adjuvant chemotherapy

Recommendation	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Only offer immunotherapy with a checkpoint inhibitor in a clinical trial setting.	Strong

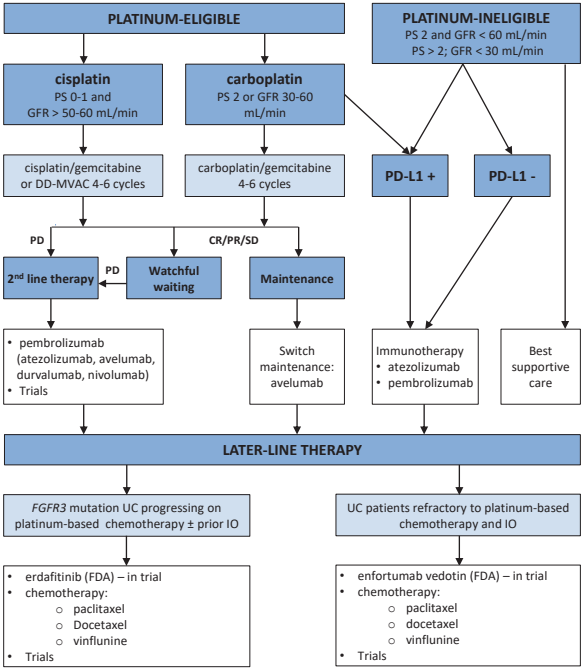
Metastatic disease

Recommendations	Strength rating
First-line treatment for platinum-fit patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
In patients unfit for cisplatin but fit for carboplatin use the combination of carboplatin and gemcitabine.	Strong
In patients achieving stable disease, or better, after first-line platinum-based chemotherapy use maintenance treatment with PD-L1 inhibitor avelumab.	Strong
First-line treatment in patients unfit for platinum-based chemotherapy	
Consider checkpoint inhibitors pembrolizumab or atezolizumab.	Weak

Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemo-therapy for metastatic disease. If this is not possible, offer atezolizumab, nivolumab (EMA, FDA approved); avelumab or durvalumab (FDA approved).	Strong
Further treatment after platinum- and immunotherapy	
Offer treatment in clinical trials testing novel antibody drug conjugates (enfortumab vedotin, sacituzumab govitecan); or in case of patients with FGFR3 alterations, FGFR tyrosine kinase inhibitors.	Strong

GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptor; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin.

Figure 2: Flow chart for the management of metastatic urothelial cancer*



**Treatment within clinical trials is highly encouraged.*
BSC = best supportive care; CR = complete response; DD-MVAC = dose dense methotrexate vinblastine doxorubicin cisplatin; EV = enfortumab vedotin; FDA = US Food and Drug Administration; FGFR = pan-fibroblast growth factor receptor tyrosine kinase inhibitor; GFR = glomerular filtration rate; IO = immunotherapy; PR = partial response; PS = performance status; SD = stable disease.

Health-related quality-of-life (HRQoL)

Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.

Recommendation	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with MIBC.	Strong
Discuss the type of urinary diversion taking into account a patient preference, existing comorbidities, tumour variables and coping abilities.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON PRIMARY URETHRAL CARCINOMA

(Limited text update March 2021)

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Epidemiology

Primary Urethral Carcinoma is a rare cancer, accounting for < 1% of all genitourinary malignancies. The age-standardised ratio is 4.3/million in men and 1.5/million in women, with a male to female ratio of 2.9:1.

Aetiology

Predisposing factors in males include urethral strictures, chronic irritation after intermittent catheterisation/ urethroplasty, external beam irradiation therapy, radioactive seed implantation, chronic urethral inflammation following sexually transmitted diseases (especially human papilloma virus) and lichen sclerosus. In females, urethral diverticula and recurrent urinary tract infections have been associated with the development of primary urethral carcinoma.

Staging and Grading systems

The 2017 TNM classification (8th edition) is used for the staging of urethral carcinoma. Of note, a separate staging system exists for urothelial carcinoma (UC) of the prostatic urethra.

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial (transitional cell) carcinoma of the prostate	
Tis pu	Carcinoma *in situ*, involvement of prostatic urethra
Tis pd	Carcinoma *in situ*, involvement of prostatic ducts
T1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
T2	Tumour invades any of the following: prostatic stroma, corpus sponsiosum, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder or rectum)
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes

M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Histopathology

Urothelial carcinoma of the urethra is the predominant histological type in men with primary urethral carcinoma followed by squamous cell carcinoma (SCC) and adenocarcinoma (AC).

In women, recent studies report higher rates of adenocarcinoma, followed by SCC rather than UC. Specimen handling should follow the general rules as published by the International Collaboration on Cancer Reporting.

Recommendation for staging and grading	Strength rating
Use the 2017 TNM classification and 2004/2016 WHO grading systems for pathological staging and grading of primary urethral carcinoma.	Strong

Diagnosis

Diagnosis of primary urethral carcinoma is based on clinical examination, urine cytology, urethroscopy with biopsy and cross-sectional imaging for the assessment of the primary tumour, lymph nodes (LNs) and distant organs. Patients with clinically enlarged inguinal or pelvic LNs often exhibit pathological LN metastasis.

Recommendations	Strength rating
Use urethrocystoscopy with biopsy and urinary cytology to diagnose urethral carcinoma.	Strong
Assess the presence of distant metastases by computed tomography of the thorax and abdomen/pelvis.	Strong
Use pelvic magnetic resonance imaging to assess the local extent of urethral tumour and regional lymph node enlargement.	Strong

Prognosis

The majority of patients are diagnosed late, with local symptoms due to advanced disease and the prognosis is poor.

Risk factors for survival include age, race, tumour stage, grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and the type and modality of treatment.

Disease management

Localised disease in males

Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours. Therefore, optimising treatment of distal urethral carcinoma has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. Penis-preserving surgery for tumours confined to the corpus spongiosum (stage ≤ T2) using various reconstructive techniques has been investigated. In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence when complete circumferential assessment of the margins shows no evidence of disease.

Recommendations	Strength rating
Offer distal urethrectomy as an alternative to penile amputation in localised distal urethral tumours, if surgical margins are negative.	Weak
Ensure complete circumferential assessment of the proximal urethral margin if penis-preserving surgery is intended.	Strong

Localised disease in females

In women with distal tumours, urethra-sparing surgery and local radiotherapy (RT) present alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.

Recommendations	Strength rating
Offer urethra-sparing surgery, as an alternative to primary urethrectomy, to women with distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Offer local radiotherapy, as an alternative to urethral surgery, to women with localised urethral tumours, but discuss local toxicity.	Weak

Multimodal therapy in advanced disease in both genders

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with the option of additional RT. Multimodal therapy is often underutilised in locally advanced disease. It confers an overall survival benefit in primary urethral carcinoma of urothelial origin.

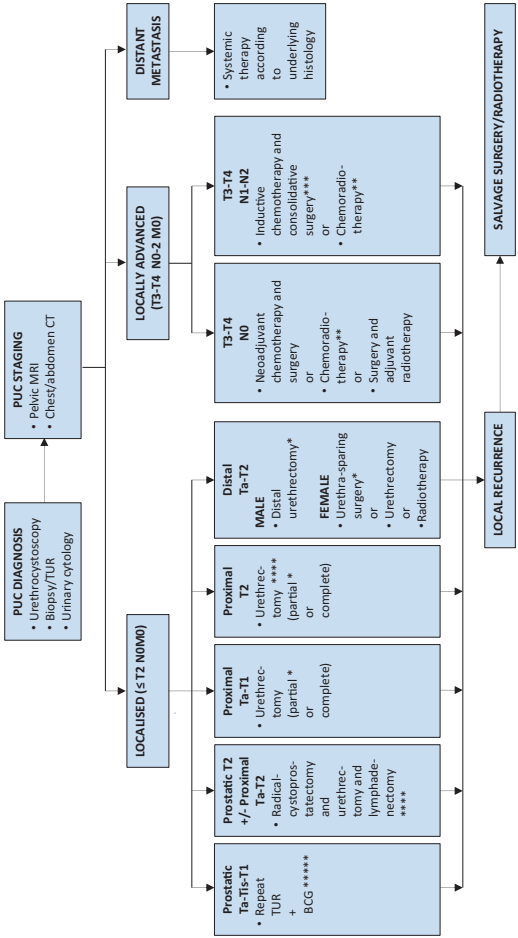
Recommendations	Strength rating
Discuss treatment of patients with locally advanced urethral carcinoma within a multidisciplinary team of urologists, radio-oncologists, and oncologists.	Strong
In locally advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	Weak
In locally advanced squamous cell carcinoma (SCC) of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	Weak
Offer inguinal lymph node (LN) dissection to patients with limited LN-positive urethral SCC.	Weak

Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive transurethral resection (TUR) and subsequent bacillus Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic urethral carcinoma. Patients undergoing TUR of the prostate for prostatic urethral carcinoma prior to BCG treatment show superior complete response rates compared to those who do not.

Recommendations	Strength rating
Offer a urethra-sparing approach with transurethral resection (TUR) and bacillus Calmette-Guérin (BCG) to patients with non-invasive urethral carcinoma or carcinoma *in situ* of the prostatic urethra and prostatic ducts.	Strong
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	Weak

Figure 1: Management of primary urethral carcinoma



* Ensure complete circumferential assessment if penis-preserving/urethra-sparing surgery or partial urethrectomy is intended.
** Squamous cell carcinoma.
*** Regional lymphadenectomy should be considered in clinically enlarged lymph nodes.
**** Consider neoadjuvant chemotherapy.
***** In extensive or BCG-unresponsive disease: consider (primary) cystoprostatectomy +/- urethrectomy + lymphadenectomy.

BCG = bacillus Calmette-Guérin; CT = computed tomography; MRI = magnetic resonance imaging; PUC = primary urethral carcinoma; TUR = transurethral resection.

Follow-up

Given the low incidence of primary urethral carcinoma, follow-up has not been systematically investigated. Therefore, it seems reasonable to tailor surveillance regimens according to patients' individual risk factors. In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocystoscopy and cross-sectional imaging despite the lack of specific data.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU-EANM-ESTRO-ESUR-ISUP-SIOG GUIDELINES ON PROSTATE CANCER

(Limited text update March 2021)

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Introduction

Prostate cancer (PCa) is a complex disease, in which disease characteristics, age, comorbidities and individual patient preference will impact treatment choice. All available management options need to be discussed, in full, with the patient.

Epidemiology and Risk Prevention

Prostate cancer is the second most common cancer in males. It is a major health concern, especially in developed countries due to the greater proportion of elderly men in the general population, and the potential risk of over-treatment following early diagnosis. There are three well-established risk factors for PCa: increasing age, ethnic origin, and genetic predisposition. There is currently no high-level evidence that preventative measures may reduce the risk of PCa.

Classification and Staging Systems

The 2017 Tumour Node Metastasis (TNM) classification is used for staging (Table 1).

Table 1: 2017 TNM classification

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	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 PSA)
T2	Tumour that is **palpable** and confined within prostate	
	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	
	T3a	Extracapsular extension (unilateral or bilateral)
	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 (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	

M - Distant Metastasis[2]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*
[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCas after radical prostatectomy (RP) are pathological stage T2 and the current UICC no longer recognises pT2 substages.

Table 2: EAU risk groups for biochemical recurrence of localised and locally-advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

The International Society of Urological Pathology (ISUP) World Health Organization (WHO) 2014 grade groups have been adopted which allow patients to better understand the behaviour of their diagnosed prostate carcinoma, while separating GS 7 adenocarcinoma into two prognostically very distinct categories; grade group 2 for GS 7(3+4) and grade group 3 for GS 7(4+3) (see Table 3).

Table 3: ISUP 2014 grade

Gleason score	ISUP grade
2-6	1
7(3+4)	2
7(4+3)	3
8(4+4 or 3+5 or 5+3)	4
9-10	5

Early detection

An individualised risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis. It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

Recommendations for germline testing*	Strength rating
Consider germline testing in men with metastatic PCa.	Weak
Consider germline testing in men with high-risk PCa who have a family member diagnosed with PCa at age < 60 years.	Weak

Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.	Weak
Consider germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Weak

**Genetic counseling is required prior to germline testing.*

Recommendations for screening and early detection	**Strength rating**
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *BRCA2* mutations from 40 years of age.	Strong

Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

Diagnostic Evaluation

Clinical diagnosis

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores, specimens from transurethral resection of the prostate (TURP), or prostatectomy for benign prostatic enlargement.

The decision whether to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking the patient's life expectancy into consideration. Diagnostic procedures that will not affect the treatment decision can usually be avoided.

Guidelines for diagnostic imaging	**Strength rating**
Recommendations for all patients	
Do not use multi-parametric magnetic resonance imaging (mpMRI) as an initial screening tool.	Strong

Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	Strong
Recommendations in biopsy-naïve patients	
Perform mpMRI before prostate biopsy.	Strong
When mpMRI is positive (i.e., PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low, omit biopsy based on shared decision-making with the patient.	Weak
Recommendations in patients with prior negative biopsy	
Perform mpMRI before prostate biopsy.	Strong
When mpMRI is positive (i.e., PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared decision-making with the patient.	Strong

Recommendations for prostate biopsy	**Strength rating***
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong

Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g., fosfomycin trometamol, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak
Use a single oral dose of either cefuroxime or cephalexin or cephazolin as antibiotic prophylaxis for transperineal biopsy. Patients with severe penicillin allergy may be given sulphamethoxazole.	Weak
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong

**Note on strength ratings:*
The above strength ratings are explained here due to the major clinical implications of these new recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its Strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy as, although quality of data is low, the clinical benefit is high and practical application simple. A Strong rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.

Pathology of prostate biopsies

A biopsy pathology report includes the type of carcinoma and parameters describing its extent (e.g., proportion of positive cores, percentage or mm of carcinoma involvement per core) as well as Gleason score (GS) per biopsy site and global GS. Reporting of a RP specimen includes type of carcinoma, global

ISUP grade, pathological stage and surgical margin status.

Guidelines for staging of PCa

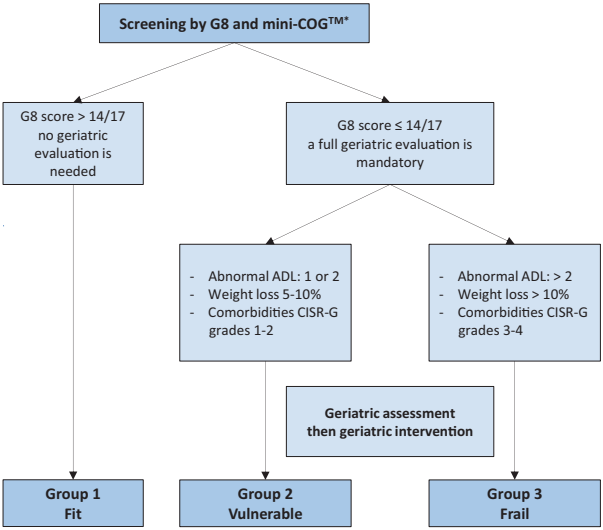
Any risk group staging	Strength rating
Use pre-biopsy mpMRI for staging information.	Weak
Low-risk localised PCa	
Do not use additional imaging for staging purposes.	Strong
Intermediate-risk PCa	
In ISUP grade ≥ 3, include at least a cross-sectional abdominopelvic imaging and bone-scan for metastatic screening.	Weak
High-risk localised PCa/locally-advanced PCa	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

Evaluating life expectancy and health status

Recommendations	Strength rating
Use individual life expectancy, health status, and comorbidity in PCa management.	Strong
Use the Geriatric-8, mini-COG and Clinical Frailty Scale tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak

Offer adapted treatment to patients with irreversible impairment.	Weak
Offer symptom-directed therapy alone to frail patients.	Strong

Figure 1: Decision tree for health status screening (men > 70 years)*



Mini-COG™ = Mini-COG™ cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.
**For Mini-COG™, a cut-off point of < 3/5 indicates a need to refer the patient for full evaluation of potential dementia.*
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Disease Management

Deferred treatment

Many men with localised PCa will not benefit from definitive treatment and 45% of men with PSA-detected PCa may be candidates for deferred management.

In men with comorbidity and a limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life (QoL).

General guidelines for active treatment of PCa

Recommendations	Strength rating
Inform patients that based on robust current data with up to 12 years of follow-up, no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Inform patients that all active treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.	Strong

Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, multiparametric magnetic resonance imaging).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT including IGRT to the prostate, to selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or good prognosis intermediate-risk localised disease.	Strong
Offer LDR or high-dose rate brachytherapy boost combined with IMRT including IGRT to patients with good urinary function and intermediate-risk disease with adverse features or high-risk disease.	Strong

Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

Guidelines for first-line treatment of various disease stages

Recommendations		Strength rating
Low-risk disease		
Active surveillance (AS)	*Selection of patients*	
	Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
	If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
	Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong

	Perform a mpMRI before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
	Follow-up strategy	
	Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
	Perform digital rectal examination (DRE) every 12 months.	Strong
	Counsel patients about the possibility of needing further treatment in the future.	Strong
Active treatment	Offer surgery and radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND.	Strong

Radiotherapy	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa, without a recent transurethral resection of the prostate (TURP) and a good International Prostatic Symptom Score (IPSS).	Strong
	Use intensity-modulated radiation therapy (IMRT) plus image-guided radiation therapy (IGRT) with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
Other options	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Strong
	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong
Intermediate-risk disease		
Active surveillance	Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and biopsy) accepting the potential increased risk of metastatic progression.	Weak

Radical prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
Extended pelvic lymph node dissection (ePLND)	Perform an ePLND in intermediate-risk disease based on predicted risk of lymph node invasion (validated nomogram).	Strong
Radiotherapy	Offer LDR brachytherapy to intermediate-risk patients with ISUP grade 2 with ≤ 33% of biopsy cores involved, without a recent transurethral resection of the prostate and with a good IPSS.	Strong
	For IMRT plus IGRT use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) in combination with short-term ADT (4 to 6 months).	Strong
	In patients not willing to undergo ADT, use a total dose of IMRT plus IGRT (76-78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with brachytherapy.	Weak

Other therapeutic options	Only offer whole-gland ablative therapy (such as cryotherapy, HIFU, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men unable to receive any local treatment.	Weak
High-risk localised disease		
Radical prostatectomy (RP)	Offer RP to selected patients with high-risk localised PCa as part of a potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapy	In patients with high-risk localised disease, use IMRT plus IGRT with 76-78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease, use IMRT plus IGRT with brachytherapy boost (either HDR or LDR) in combination with long-term ADT (2 to 3 years).	Weak

Other options	Do not offer either whole gland or focal therapy to patients with high-risk localised disease.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong
Locally-advanced disease		
Radical prostatectomy	Offer RP to selected patients with locally-advanced PCa as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND prior to RP in locally-advanced PCa.	Strong
Radiotherapy	In patients with locally-advanced disease offer IMRT plus IGRT in combination with long-term ADT.	Strong
	Offer long-term ADT for at least 2 years.	Weak

Other options	Do not offer whole gland treatment or focal treatment to patients with locally-advanced disease.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-DT < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
	Offer patients with cN1 disease a local treatment (either RP or IMRT plus IGRT) plus long-term ADT.	Weak
Adjuvant treatment after radical prostatectomy		
Do not prescribe adjuvant ADT in pN0 patients.		Strong
Only offer adjuvant intensity-modulated radiation therapy (IMRT) plus image-guided radiation therapy (IGRT) to high-risk patients (pN0) with at least two out of three high-risk features (ISUP grade group 4–5, pT3 ± positive margins).		Strong
Discuss three management options with patients with pN1 disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.		Weak

Non-curative or palliative treatments in a first-line setting		
Localised disease		
Watchful waiting (WW)	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
Localised-advanced disease		
Watchful waiting	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA-DT > 12 months, a PSA < 50 ng/mL and well-differentiated tumour, who are unwilling or unable to receive any form of local treatment.	Weak
Persistent PSA after RP		
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scan to men with a persistent PSA > 0.2 ng/mL if the results will influence subsequent treatment decisions.		Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.		Weak

Follow-up after treatment with curative intent

- After RP, PSA should be undetectable (< 0.1 ng/mL). A PSA of > 0.1 ng/mL after RP is a signal of residual prostate tumour tissue.
- After an undetectable PSA is obtained following RP, a PSA > 0.4 ng/mL and rising, best predicts further metastases.
- After RT, an increase in PSA > nadir + 2 ng/mL best predicts further metastases.

- Palpable nodules and increasing serum PSA are often signs of local recurrence.

In case of relapse, the decision for subsequent salvage therapy should not be based on the PSA thresholds listed above.

Recommendations for follow-up	Strength rating
Routinely follow up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

Guidelines for metastatic disease, second-line and palliative treatments

Recommendations	Strength rating
Metastatic disease in a first-line setting	
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak

Offer surgery and/or local radiotherapy (RT) to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong

Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate RT (using the doses from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

Recommendations for imaging in biochemical recurrence	**Strength rating**
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen positron emission tomography/ computed tomography (PSMA PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	Weak

In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate mpMRI to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

Recommendations for second-line therapy after treatment with curative intent		**Strength rating**
Biochemical recurrence after treatment with curative intent		
Biochemical recurrence (BCR) after radical prostatectomy (RP)	Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
	Offer early salvage intensity-modulated radiotherapy plus image-guided radiotherapy to men with two consecutive PSA rises.	Strong
	A negative PET/CT scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong

	Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak
Biochemical recurrence after RT	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Only offer salvage RP, brachytherapy, high intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
	Salvage RP should only be performed in experienced centres.	Weak
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > 12 months.	Strong
Life-prolonging treatments of castrate-resistant disease		
Ensure that testosterone levels are confirmed to be < 50 ng/dL before diagnosing castration-resistant PCa (CRPC).		Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.		Strong

Treat patients with mCRPC with life-prolonging agents.	Strong
Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong
Systemic treatments of castrate-resistant disease	
Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naïve docetaxel with 75 mg/m^2 every 3 weeks.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak

Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Supportive care of castrate-resistant disease	
Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as IMRT plus IGRT and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong
Non-metastatic castrate-resistant disease	
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

Follow-up after treatment with life-prolonging treatments

Recommendations for follow-up during hormonal treatment	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3 to 6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong

When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In M1 patients perform regular imaging (CT and bone scan) even without PSA progression.	Weak
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nM/L).	Strong

Quality of Life

Treating PCa can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of 'quality of life (QoL)'. Prostate cancer care should not be reduced to focusing on the organ in isolation.

Taking QoL into consideration relies on understanding the patient's wishes and preferences so that optimal treatment can be discussed. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON RENAL CELL CARCINOMA

(Limited update March 2021)

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Epidemiology

The widespread use of imaging techniques such as ultrasound (US) and computed tomography (CT) has increased the detection of asymptomatic renal cell carcinoma (RCC). The peak incidence of RCC occurs between 60 and 70 years of age, with a 3 : 2 ratio of men to women. Aetiological factors include lifestyle factors, such as smoking, obesity and hypertension. Having a first-degree relative with RCC is associated with a significantly increased risk of RCC.

Staging system

The current UICC 2017 TNM (Tumour Node Metastasis) classification is recommended for the staging of RCC (Table 1).

Table 1: The 2017 TNM staging classification system

T - Primary Tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney	
	T1a	Tumour ≤ 4 cm or less
	T1b	Tumour > 4 cm but ≤ 7 cm
T2	Tumour > 7 cm in greatest dimension, limited to the kidney	
	T2a	Tumour > 7 cm but ≤ 10 cm
	T2b	Tumours > 10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	
	T3a	Tumour extends into the renal vein or its segmental branches, or invades the pelvicalyceal system or invades perirenal and/or renal sinus fat, but not beyond Gerota's fascia*
	T3b	Tumour grossly extends into the vena cava below diaphragm
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota 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 regional lymph node(s)	

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	Any N	M1

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.
**Adapted based on the American Joint Committee on Cancer (AJCC), 8th Edn. 2017.*

Clinical Diagnosis

Many renal masses remain asymptomatic until late disease stages. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare and correlates with aggressive histology and advanced disease.

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs. A few symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough.

Imaging

Computed tomography imaging, unenhanced, and during the nephrographic phase after intravenous contrast, can verify the diagnosis and provide information on the function and morphology of the contralateral kidney and assess tumour extension, including extra-renal spread, venous involvement, and enlargement of lymph nodes (LNs) and adrenals.

Abdominal US and magnetic resonance imaging (MRI) are supplements to CT. Contrast-enhanced US can be helpful

in specific cases (e.g., chronic renal failure with a relative contraindication for iodinated or gadolinium-based contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis).

Magnetic resonance imaging can be used in patients with possible venous involvement, or allergy to intravenous contrast. Chest CT is the most accurate for chest staging and is recommended in the primary work-up of patients with suspected RCC.

In younger patients who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative for follow-up imaging.

Biopsy

Percutaneous renal tumour biopsies are used:

- to obtain histology of radiologically indeterminate renal masses;
- to select patients with small renal masses for active surveillance;
- to obtain histology before (advantageous), or simultaneously with ablative treatments;
- to select the most suitable form of medical and surgical strategy in the setting of metastatic disease.

In patients with any sign of impaired renal function, a renal scan and total renal function evaluation using estimated glomerular filtration rate should always be undertaken to optimise the treatment decision.

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results.

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use magnetic resonance imaging (MRI) to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, if the results of contrast-enhanced CT are indeterminate.	Strong
Do not routinely use bone scan and/or positron-emission tomography CT for staging of renal cell carcinoma.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

Histological diagnosis

A variety of renal tumours exist, and about 15% are benign. All kidney lesions require examination for malignant behaviour.

Histopathological classification

The new WHO/ISUP classification will replace the Fuhrman nuclear grade system but will need validation.

The three most common RCC subtypes, with genetic and histological differences, are: clear-cell RCC (70-85%), papillary RCC (10-15%), and chromophobe RCC (4-5%). The various RCC types have different clinical courses and responses to therapy.

Prognostic factors

In all RCC types, prognosis worsens with stage and histopathological grade. Histological factors include tumour grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the peri-renal fat and collecting system. Clinical factors include performance status, local symptoms, cachexia, anaemia, platelet count, neutrophil/lymphocyte ratio, C-reactive protein and albumin (see Tables 6.3 and 6.4 in the 2021 RCC Guidelines publication).

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use the WHO/ISUP grading system and classify renal cell carcinoma type.	Strong
Use prognostic models in localised and metastatic disease.	Strong
Do not routinely use molecular markers to assess prognosis.	Strong

Disease Management

Treatment of localised RCC

Localised RCCs are best managed with partial nephrectomy (PN) rather than radical nephrectomy (RN), irrespective of the surgical approach. Partial nephrectomy is unsuitable in some patients with localised RCC due to:

- locally advanced tumour growth;
- unfavourable tumour location;
- significant health deterioration.

If pre-operative imaging and intra-operative findings are normal, routine adrenalectomy is not indicated.

Lymphadenectomy should be restricted to staging because the survival benefit of extended LN dissection is unclear in patients with localised disease. In patients who have RCCs with tumour thrombus and no metastatic spread, prognosis is improved after nephrectomy and complete thrombectomy.

Nephron-sparing surgery versus radical nephrectomy

Based on current available oncological and quality of life outcomes, localised RCC is best managed by nephron-sparing surgery (NSS) rather than RN, irrespective of the surgical approach. Before routine nephrectomy, tumour embolisation has no benefit. In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy (PN) to patients with T1 tumours.	Strong
Offer PN to patients with T2 tumours and a solitary kidney or chronic kidney disease, if technically feasible.	Weak
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Do not offer an extended lymph node dissection to patients with organ-confined disease.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

Radical- and partial nephrectomy techniques

Summary of evidence	LE
Laparoscopic RN has lower morbidity than open nephrectomy.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic- and open RN.	2a
Partial nephrectomy can be performed, either by open-, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b
Robotic-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared to RN.	3

Hospital volume in PN might impact on surgical complications, warm ischaemia and surgical margins.	3
Radical nephrectomy after positive surgical margins can result in over-treatment in many cases.	3

LE = level of evidence

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological-, functional- and peri-operative outcomes.	Strong
Intensify follow-up in patients with a positive surgical margin.	Weak

Alternatives to surgery

Surveillance

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality. In selected patients with advanced age and/or comorbidities, active surveillance (AS) is appropriate to initially monitor small renal masses, followed, if required, by treatment for progression. The concept of AS differs from the concept of watchful waiting. Watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and who do not require follow-up imaging, unless clinically indicated.

Cryoablation and radiofrequency ablation

Currently there are no data showing oncological benefit of cryoablation or radiofrequency ablation (RFA) techniques over PN.

Recommendation	Strength rating
Offer active surveillance (AS), or thermal ablation (TA) to frail and/or comorbid patients with small renal masses.	Weak
Perform a percutaneous renal mass biopsy prior to, and not concomitantly with TA.	Strong
When TA or AS are offered, discuss with patients about the harms/benefits with regards to oncological outcomes and complications.	Strong
Do not routinely offer TA for tumours > 3 cm and cryoablation for tumours > 4 cm.	Weak

Treatment of locally advanced RCC

Management of clinically positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), LND is always justified but the extent of LND is still controversial.

Low level data suggest that tumour thrombus in the setting of non-metastatic disease should be excised. Adjunctive procedures such as tumour embolisation or inferior vena cava filter do not appear to offer any benefits in the treatment of tumour thrombus.

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain. At present there is no evidence for the use of adjuvant therapy following surgery.

Treatment of advanced/metastatic RCC

Management of RCC with venous tumour thrombus

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection to guide staging, prognosis and follow-up.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong
In case of metastatic disease, discuss surgery within the context of a multidisciplinary team.	Weak

Management of RCC with neoadjuvant and adjuvant therapy

Summary of evidence	LE
Adjuvant therapy does not improve survival after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved disease-free survival (DFS) but not overall survival (OS).	1b
Adjuvant sorafenib, pazopanib, everolimus, girentuximab or axitinib does not improve DFS or OS after nephrectomy.	1b
Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma.	Weak

Cytoreductive nephrectomy

Tumour nephrectomy is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary.

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-metastatic RCC (mRCC) shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	1a
Cytoreductive nephrectomy in patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a

Patients with their primary tumour in place treated with ICI-based combination therapy have better PFS and OS in exploratory subgroup analyses compared to treatment with sunitinib.	2b

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Discuss delayed CN with patients who derive clinical benefit from systemic therapy.	Weak
Perform immediate CN in patients with a good performance status who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

IMDC = International Metastatic RCC Database Consortium; MSKCC = Memorial Sloan-Kettering Cancer Center.

Local therapy of metastases in metastatic RCC

A systematic review of the local treatment of metastases from RCC in any organ was undertaken. The heterogeneity of the data will only allow for cautious recommendations.

Summary of evidence	LE
All studies included in a Panel systematic review were retrospective, non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, CSS and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3
Tyrosine kinase inhibitors treatment after metastasectomy in patients with no evidence of disease did not improve RFS when compared to placebo or observation.	1b

Recommendations	Strength rating
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone- or brain metastases for local control and symptom relief.	Weak
Do not offer tyrosine kinase inhibitor treatment to mRCC patients after metastasectomy and no evidence of disease.	Strong

Systemic therapy for advanced/metastatic RCC

Chemotherapy

Recommendation	Strength rating
Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong

Immunotherapy

Interferon-α monotherapy and combined with bevacizumab, has been superseded as standard treatment by targeted therapy of advanced cc-mRCC.

Immune checkpoint inhibition of programmed death receptor (PD-1) and ligand (PD-L1) inhibition have been investigated in mRCC. Randomised data support the use of nivolumab (a PD-1 inhibitor) in VEGF-refractory disease. The combination of two immune checkpoint inhibitors: ipilimumab and nivolumab showed superior survival in intermediate- and poor-risk patients while the combination of pembrolizumab and axitinib showed survival advantage for patients in all risk groups.

Summary of evidence	LE
Interferon-α monotherapy is inferior to VEGF-targeted therapy or mammalian target of rapamycin (mTOR) inhibition in mRCC.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b
The combination of nivolumab and ipilimumab in treatment-naive patients with cc-mRCC of IMDC intermediate and poor risk demonstrated OS and ORR benefits compared to sunitinib.	1b

The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naive patients with cc-mRCC across all IMDC risk groups demonstrated PFS, OS and ORR benefits compared to sunitinib.	1b
Currently, PD-L1 expression is not used for patient selection.	2b
Axitinib, cabozantinib or lenvatinib can be continued if immune-related adverse events results in cessation of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab. Re-challenge with immunotherapy requires expert support.	4
Patients who do not receive the full 4 doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4
The combination of nivolumab plus ipilimumab in the IMDC intermediate- and poor-risk population of treatment-naive patients with cc-mRCC leads to superior survival compared to sunitinib while OS was higher in IMDC good-risk patients with sunitinib.	2b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths.	1b

Recommendations	Strength rating
Offer pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to treatment-naive patients with any IMDC-risk clear-cell metastatic renal cell carcinoma (cc-mRCC).	Strong
Offer ipilimumab plus nivolumab to treatment-naive patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Administer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab and cabozantinib in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Patients who do not receive the full 4 doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Offer axitinib, cabozantinib or lenvatinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multidisciplinary team.	Strong

Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong*

* *While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.*

IMDC = International Metastatic RCC Database Consortium.

Targeted therapies

At present, several targeting drugs have been approved for the treatment of mRCC.

Summary of evidence	LE
Single agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naïve cc-RCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3

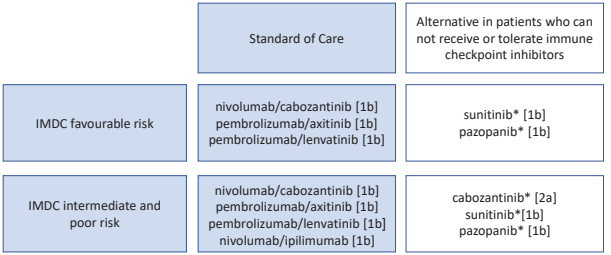
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo. This is no longer widely recommended before third-line therapy.	1b
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	**Strength rating**
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naïve vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak

Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong

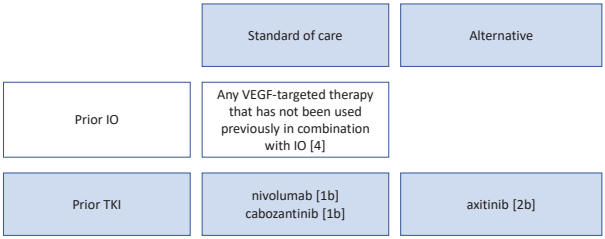
IMDC = International Metastatic RCC Database Consortium.

Figure 1: Updated EAU Guidelines recommendations for the first-line treatment of mRCC



IMDC = International Metastatic RCC Database Consortium.
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on one randomised controlled phase II trial.

Figure 2: EAU Guidelines recommendations for later-line therapy



IO = immunotherapy; TKI = tyrosine kinase inhibitors;
VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

Recurrent RCC

Locally recurrent disease in the treated kidney can occur either after PN, or ablative therapy. After RN or nephron-sparing treatment approaches, recurrence may occur in the renal fossa or regional, e.g. venous tumour thrombi or retroperitoneal LN metastases. Isolated local recurrence in the true renal fossa after RN is rare.

Patients can benefit from a complete surgical resection of local recurrent disease. In cases where complete surgical removal is not feasible due to advanced tumour growth and pain, palliative treatments including radiation treatment can be considered as well as systemic therapy.

Surveillance following surgery for RCC

The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable. Surveillance after treatment for RCC allows the urologist to assess:

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- development of metastases.

Depending on the availability of new effective treatments, more intensive follow-up schedules may be required, particularly as there is a higher local recurrence rate after cryotherapy and RFA. At present there is no evidence-based standard for the follow-up of patients with RCC, or for the optimal duration of follow-up. An example of a surveillance algorithm monitoring patients after treatment for RCC that recognises not only the patient's risk profile but also treatment efficacy is provided in Table 2. For patients with metastatic disease, individualised follow-up is indicated.

Table 2: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy (expert opinion [LE: 4])

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	> 3 yr	> 5 yr (optional)
Low risk of recurrence	-	CT	-	CT	-	CT	-	CT every two yrs	-
Intermediate risk of recurrence	-	CT	CT	-	CT	-	CT	CT once yr	CT every two yrs
High risk of recurrence	CT	CT	CT	CT	CT	-	CT	CT once yr	CT every two yrs

**Leibovich Score 0-2 / 3-5 / ≥ 6; for non-ccRCC: pT1NX-0, grade 1-2 / pT1b, grade 3-4 / vs. high risk: pT2-4, grade 1-4, or pT any, N1, grade 1-4.*

CT = computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen; US = ultrasound of abdomen, kidneys and renal bed.

Summary of evidence and recommendations for surveillance following RN or PN or ablative therapies in RCC

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4
Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be surgically curable.	4

After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3
Patients undergoing follow-up have a better OS than patients not undergoing surveillance.	3
Prognostic models provide stratification of RCC risk of recurrence based on TNM and histological features.	3
In competing risk models, risk of non-RCC-related death exceeds that of RCC recurrence or related death in low-risk patients.	3
Life expectancy estimation is feasible and may help in counselling patients on duration of follow-up.	4

Recommendations	Strength rating
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Perform functional follow-up (renal function assessment and prevention of cardiovascular events) both in nephron-sparing and radical nephrectomy patients.	Weak
Intensify follow-up in patients after nephron-sparing surgery for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Consider curtailing follow-up when the risk of dying from other causes is double that of recurrence risk.	Weak
Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for ccRCC or the University of California Los Angeles integrated staging system or the SSIGN score.	Strong

SSIGN = (Mayo Clinic) stage, size, grade, and necrosis score.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON TESTICULAR CANCER

(Limited text update March 2021)

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Epidemiology, aetiology and pathology

Testicular cancer (TC) is relatively rare accounting for approximately 1-1.5% of all cancers in men. At diagnosis 1-2% are bilateral and the predominant histology is germ cell tumour (GCT).

Most malignant post-pubertal testicular GCTs or type II GCT, originate from the Germ Cell Neoplasia "*in situ*" (GCNIS). They are clinically and histologically sub-divided into seminomas and non-seminomas. Non-seminomas include elements of embryonal carcinoma, yolk sac, choriocarcinoma and teratoma. Most of the non-related GCNIS tumours present at paediatric age with the exception of spermatocytic tumours (Type III GCT) which are diagnosed in the elderly. Type II TGCT have a low mutational burden and few somatic changes, but i12p is over-represented in most of the invasive GCNIS-related TGCT.

Peak incidence is in the third decade of life for non-seminoma and mixed GCTs, and fourth decade for pure seminoma. Epidemiological risk factors for the development of TC are components of testicular dysgenesis syndrome, which

encompasses cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility, familial history of testicular tumours among first-grade relatives, and the presence of a contralateral tumour, or GCNIS.

Histological classification

The recommended pathological classification is the 2016 update of the World Health Organization (WHO).

Staging and Classification systems

Staging systems

The 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC) is recommended to assess the anatomical extent of the disease (Table 1).

Table 1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.)

T - Primary Tumour[1]	
pTX	Primary tumour cannot be assessed[1]
pT0	No evidence of primary tumour (e.g., histological scar in testis)
pTIS	Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1	Tumour limited to testis and epididymis[2] 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 more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn - Regional Lymph Nodes - 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 of 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 metastasis
	M1b Distant metastasis other than non-regional lymph nodes and lung

S - Serum tumour markers (Pre-chemotherapy)			
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.

** AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension.*

*** AJCC eight edition considers the hilar soft tissue invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1.*

[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.

[2] The current "carcinoma in situ" nomenclature is replaced by GCNIS

The International Germ Cell Cancer Collaborative Group (IGCCCG) defined a prognostic factor-based staging system for metastatic germ cell cancer that includes 'good' and 'intermediate' prognosis seminoma and 'good', 'intermediate', and 'poor' prognosis non-seminomatous germ cell tumour (NSGCT) (Table 2).

The IGCCG for metastatic Testicular Cancer

A prognostic factor-based staging system is widely used for metastatic TC based on identification of clinically independent adverse factors.

Table 2: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG)*

Good-prognosis group	
Non-seminoma 5-year PFS 90% 5-year survival 96%	*All of the following criteria:* • Testis/retro-peritoneal 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 5-year PFS 89% 5-year survival 95%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma 5-year PFS 78% 5-year survival 89%	*Any of the following criteria:* • Testis/retro-peritoneal 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 5-year PFS 79% 5-year survival 88%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma 5-year PFS 54% 5-year survival 67%	*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.

Diagnostic evaluation

The diagnosis of TC is based on:

1. ***Physical examination***
   Testicular cancer usually presents as a unilateral testicular scrotal mass detected by the patient, or as an incidental ultrasound (US) finding. Around 1% of patients presenting with gynecomastia have a germ cell or sex cord/gonadal tumour of the testes and 11% present with back and flank

pain. When there is suspicion of TC, physical exploration must include abdominal and supraclavicular exploration.

2. *Imaging*

a. *Ultrasound*
High frequency (> 10 MHz) testicular US should be used to confirm a testicular tumour even in the presence of clinically evident testicular lesion. Testicular US is also recommended for all men with retroperitoneal or visceral masses and/or without elevated serum human chorionic gonadotropin (hCG) or alpha-fetoprotein (AFP) in the absence of a palpable testicular mass.

b. *Computerised tomography*
Contrast enhanced computerised tomography (CECT) is the most sensitive means to evaluate the thorax, abdomen and pelvis for TC staging. Contrast enhanced computerised tomography is recommended in all patients for staging before orchidectomy but may be postponed until histopathological confirmation of malignancy. Cerebral imaging by CECT is recommended in patients with NSGCT, multiple lung metastases and poor-prognosis IGCCCG risk group (for patients with hCG values > 5,000 UI/L), or if clinical symptoms are present.

c. *Magnetic resonance imaging*
Magnetic resonance imaging (MRI) has similar accuracy to CECT in the detection of retroperitoneal nodal enlargement. However, there are no indications for routine use of MRI for TC staging unless CT is contraindicated because of allergy to iodine contrast media. Magnetic resonance imaging has a primary

role in the detection of brain metastasis because it is more sensitive than CECT.

d. *Fluorodeoxyglucose-positron emission tomography*
There is no evidence to support the use of fluorodeoxy-glucose-positron emission tomography (FDG-PET) for initial staging and routine follow-up of TC.

e. *Bone scan*
There is no evidence to support the use of bone scan for staging of TC.

3. Serum tumour markers

Serum tumour markers (AFP, β-hCG and LDH,) should be determined before, and after orchidectomy until normalisation. Normal serum markers levels do not exclude the presence of TC, whilst persistence or increase of elevated serum tumour markers following orchidectomy indicates the likely presence of metastatic disease. Tumour markers should be routinely used for follow-up.

4. Inguinal exploration and initial management

- Orchidectomy including division of the spermatic cord at the internal inguinal ring represents the standard of care in patients with TC.
- Testis sparing surgery (TSS) may be offered in cases with synchronous bilateral tumours, metachronous contralateral tumours or in patients with a solitary testis to attempt to preserve fertility and hormonal function*.
- Testis sparing surgery should only be offered when accompanied with frozen section examination.
- Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy.
- Routine contralateral biopsy for diagnosis of GCNIS should be discussed with the patient and is

recommended in 'high-risk' patients (testicular volume < 12 mL, a history of cryptorchidism and age < 40 years).

**Limited data exists on oncological safety of TSS. Local recurrence rates (up to 8% when TC in specimen) necessitate close surveillance of the testis, possible use of adjuvant radiotherapy when GCNIS is present, as well as potential infertility and need for hormonal supplementation.*

5. Pathological examination of the testis

Following orchidectomy, the pathological examination of the testis should include a number of investigations:

1. macroscopic features: side, testis size, maximum tumour size, and macroscopic features of the epididymis, spermatic cord, and tunica vaginalis;
2. sampling: a 1 cm^2 section for every cm^2 of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspicious areas;
3. at least one proximal and one distal section of spermatic cord plus any suspected area;
4. microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2016;
   - 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 GCNIS in non-tumour parenchyma;
   - in cases of rete testis invasion, attention should be paid to distinguishing between the pagetoid involvement and stromal invasion;
5. pT category according to TNM 2016;
6. immunohistochemical studies: in seminoma and mixed GCT, AFP and hCG.

6. Screening

There are no high-level evidence studies supporting screening programs. In the presence of clinical risk factors, and a family history of TC, family members and the patient should be informed about the importance of physical self-examination.

7. Impact on fertility and fertility-associated issues

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchidectomy. Furthermore, treatment for TC, including orchidectomy, may have a negative impact on reproductive function. As such, all patients should be offered semen preservation.

Recommendations for diagnosis and staging of testicular cancer	Strength rating
Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).	Strong
Perform bilateral testicular ultrasound in all patients with suspicion of TC.	Strong
Perform physical examination including supraclavicular, cervical, axillary and inguinal lymph nodes, breast and testicles.	Strong
Measure serum tumour markers both before and after orchidectomy taking into account half-life kinetics.	Strong
Perform orchidectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, commence chemotherapy prior to orchidectomy.	Strong

Perform contrast enhanced computerised tomography (CECT) scan (chest, abdomen and pelvis) in patients with diagnosis of TC. If iodine allergy or other limiting factors, perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong
Perform MRI of the brain (or brain CECT if not available) in patients with multiple lung metastases or high beta subunit of human Chorionic Gonadotropin (β-hCG), values or those in the poor-prognosis International Germ Cell Cancer Collaborative Group (IGCCCG) risk group.	Strong
Do not use positron-emission tomography computed tomography or bone scan for staging.	Strong
Encourage patients with TC to perform self-examination and to inform first-degree male relatives of the need for self-examination.	Weak
Discuss testis-sparing surgery with frozen section examination in patients with a high likelihood of having a benign testicular tumour which is suitable for enucleation.	Strong
Discuss biopsy of the contralateral testis to patients with TC and high-risk for contralateral germ cell neoplasia "*in situ*" (GCNIS).	Weak

Prognosis

Table 3: Pathological risk-factors for occult metastatic disease in Stage I TC

Histological type	Seminoma	Non seminoma
Pathological risk factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoural tissue

Disease management

1. Stage I Germ cell Tumours

Germ cell neoplasia "*in situ*", when diagnosed, can be treated by local radiotherapy (18-20 Gy in fractions of 2 Gy) or orchidectomy.

Recommendations for the treatment of stage I seminoma	Strength rating
Fully inform the patient about all available management options, including surveillance or adjuvant chemotherapy after orchidectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as a management option if facilities are available and the patient is compliant.	Strong
Offer one course at area under curve (AUC) 7 if carboplatin chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low risk of recurrence (no risk factors).	Strong

Do not routinely perform adjuvant radiotherapy.	Strong
Adjuvant radiotherapy should be reserved only for highly selected patients not suitable for surveillance and with contraindication for chemotherapy.	Strong

Recommendations for the treatment of stage I non-seminomatous germ cell tumour	**Strength rating**
Inform patients with stage I non-seminomatous germ cell tumour (NSGCT) about all management options after orchidectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
Offer surveillance or risk-adapted treatment based on lymphovascular invasion in patients with stage I NSGCT.	Strong
Discuss one course of cisplatin, etoposide, bleomycin (BEP) as an adjuvant treatment alternative if patients are not willing to undergo or comply with surveillance.	Strong

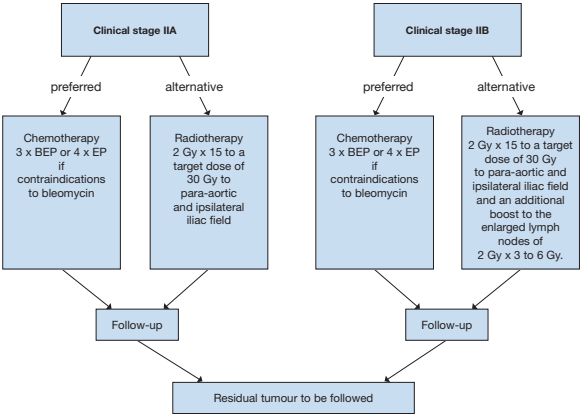
Recommendations for risk-adapted treatment for clinical stage I based on vascular invasion	**Strength rating**
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong

Offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin BEP in low-risk patients not willing (or unsuitable) to undergo surveillance.	Strong
Stage IB (pT2-pT4): high risk	
Offer primary chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection (RPLND) to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong
Primary RPLND should be advised in men with teratoma with somatic-type malignancy.	Weak

2. Metastatic Germ cell Tumours

Clinical Stage I (CS I) patients with persistently elevated serum tumours markers require repeated imaging including US examination of contralateral testis and abdominal and extra-abdominal sites. They should be treated according to IGCCCG prognostic groups.

Figure 1: Treatment options in patients with seminoma clinical stage IIA and IIB*



BEP = cisplatin, etoposide, bleomycin; EP = etopside and cisplatin.
** When enlarged retroperitoneal lymph nodes are < 2 cm and with normal markers, treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise.*

Recommendations for prevention of thromboembolism events during chemotherapy	**Strength rating**
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.	Weak
Avoid use of central venous-access devices during first-line chemotherapy whenever possible.	Weak

Recommendations for the treatment of metastatic germ cell tumours	Strength rating
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like good- or intermediate-prognosis risk group IGCCCG, with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
Nerve-sparing RPLND when performed by an experienced surgeon in a specialised centre is the recommended initial treatment in clinical stage (CS) IIA NSGCT disease without elevated tumour markers.	Weak
Repeat staging should be considered after six weeks before making a final decision on further management in patients with small volume (CS IIA < 2 cm) marker negative NSGCT.	Weak
Treat metastatic NSGCT (stage ≥ IIC) with an intermediate prognosis with four cycles of standard BEP.	Strong
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, (or cisplatin, etoposide and ifosfamide [PEI] in case of poor lung function), followed by tumour marker assessment after three weeks. In case of a favourable marker decline, continue BEP (or PEI) up to a total of four cycles. In case of an unfavourable decline, initiate chemotherapy intensification.	Weak
Perform surgical resection of visible (> 1 cm) residual masses after chemotherapy in NSGCT when serum levels of tumour markers are normal or normalising.	Strong

Initially offer cisplatin-based chemotherapy according to IGCCCG prognosis groups, or alternatively radiotherapy to seminoma patients with stage II A/B and, inform the patient of potential long-term side effects of both treatment options.	Weak
Treat seminoma stage IIC and higher, with primary chemotherapy according to IGCCCG classification (BEP x 3 in good prognosis and BEP x 4 in intermediate prognosis).	Strong

Relapse after chemotherapy

The treatment of relapsed GCT after chemotherapy is typically salvage chemotherapy. For patients at first relapse with good prognostic features (initial achievement of complete response/partial remission negative markers [CR/PRm-] and gonadal primary tumour) four cycles of standard-dose salvage chemotherapy is proposed. For patients with poor prognostic factors (extra-gonadal primary and/or incomplete response to first-line chemotherapy) and for all patients with subsequent (second or more) relapse, high-dose chemotherapy with autologous stem cell support is recommended.

Follow-up

The primary aim of follow-up in the first five years is the timely diagnosis of recurrent disease in order to be able to treat the patient with curative intent with the least aggressive therapy.

The following factors should be taken into account:

a) Follow-up must be tailored to the individual patient with a schedule acceptable to the patient, the clinician, and the health care system.

b) The interval of follow-up visits and the clinical investigations to be performed at each visit should depend on the risk of relapse, in general, as well as the likely sites of relapse in an individual patient.
c) When possible, an effort should be made to minimise any risks associated with ionising radiation exposure.
d) The increased risk of second malignancy (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 selection of tests.

Table 4: Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)[1]

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography (CT)/ magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

[1] *Recommendations based upon ESMO Testicular seminoma and non-seminoma consensus meeting outcomes.*

Table 5: Recommended minimal follow-up for non-seminoma clinical stage I on active surveillance[1]

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times**	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography (CT)/ magnetic resonance imaging	2 times	At 24 months***	Once at 36 months*	Once at 60 months*	

LVI+ = lymphovascular invasion

[1] Recommendations based upon ESMO Testicular seminoma and non-seminoma consensus meeting outcomes.

** Recommended by 50% of the consensus group members.*

*** In case of high risk (LVI+) a minority of the consensus group members recommended six times.*

**** In case of high risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*

Table 6: Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)[1]

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography (CT)/ magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	1-2 times*	At 24 months*	Once at 36 months*	Once at 60 months*	

[1] *Recommendations based upon ESMO Testicular seminoma and non-seminoma consensus meeting outcomes.*

* *Same time points as abdomino-pelvic CT/MRI in case of pulmonary metastases at diagnosis.*

** *In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

Quality of life and long-term toxicities after cure

Patients diagnosed with TC are usually between 18 and 40 years of age at diagnosis, and life expectancy after cure extends over several decades. Patients should be informed before treatment of common long-term toxicities before any treatment is planned.

During follow-up, patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidaemia and testosterone deficiency. When follow-up by the clinical expert is discontinued, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up might be helpful.

Included among the long-term toxicity and secondary effects of TC treatment are: second malignant neoplasms, leukaemia, infections, pulmonary and cardiovascular complications, Raynaud-like phenomena, neuro- nephro- and ototoxiciy, impaired cognitive function, hypogonadism and fatigue as well as quality of life issues.

Rare adult testicular tumours

Rare testicular tumours have similar clinical presentation as GCTs and are identified by histopathological examination. Available literature is based on case reports and retrospective series. Classification is according to the 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs.

1. Spermatocytic Tumours

Spermatocytic tumours are GCTs unrelated to GCNIS and extremely rare. Normally they do not show elevated markers and cannot be differentiated from seminomatous GCT by frozen section analysis. Radical orchiectomy is the standard treatment option. Metastatic disease is very rare and, if occurring, it presents early after initial diagnosis with limited survival.

2. Sex cord-stromal tumours

Sex cord–stromal tumours are the second largest group of primary testicular tumours. They are relatively uncommon and only a small minority malignant. Morphological features

associated with malignant potential in both types include two or more of the following features:

- size > 5 cm
- infiltrative borders
- cytological atypia
- 3 or more mitotic figures per 10 high-power fields
- vascular invasion
- necrosis

Leydig cell tumours

Leydig cell tumours comprise about 4% of adult testicular tumours. They may present with hormonal manifestations, including gynecomastia and rarely accompanied by Cushing's Syndrome. Local recurrence of 7% has been reported after testis sparing surgery. Survival of men with metastatic disease is poor but response to surgical and systemic treatment has been reported in several cases.

Sertoli cell tumours

Sertoli represent approximately 1% of all testicular neoplasms. The risk of metastatic potential remains unclear. After testis sparing surgery a local recurrence rate of < 1% has been reported. Survival of men with metastatic disease is poor but response to surgery has been reported in a few cases.

Granulosa cell tumour

Granulosa cell tumours include adult and juvenile variants and are very infrequent. After testis sparing surgery a local recurrence rate of 5% has been reported. Metastatic disease has only been described, albeit extremely rare, in men with adult type. Survival of men with metastatic disease is poor but response to surgical or systemic treatment has been reported in a few cases.

Thecoma/fibroma group of tumours

These tumours derive from the testicular parenchymal stroma or from the tunica albuginea. They seem to be uniformly benign.

Conclusions

Most testis tumours are diagnosed at an early stage. Staging is the cornerstone of treatment. Following orchidectomy, excellent cure rates are achieved for those early stages irrespective of the treatment policy adopted, although pattern and relapse rates are closely linked to the treatment modality chosen. In metastatic disease a multidisciplinary therapeutic approach offers an acceptable survival. Follow-up schedules should be tailored to initial staging and treatment.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON PENILE CANCER

(Text update March 2018)

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Introduction and epidemiology

The incidence of penile cancer increases with age, peaking during the sixth decade of life. However, the disease does occur in younger men. There are significant geographical variations within Europe as well as worldwide. Penile cancer is common in regions with a high prevalence of human Papilloma virus (HPV), which may account for the global incidence variation, as the worldwide HPV prevalence varies considerably. There is at present no recommendation for the use of HPV vaccination in boys.

Risk factors

Recognised aetiological and epidemiological risk factors for penile cancer are:

Risk factors	Relevance
Phimosis	Odds ratio 11-16 vs. no phimosis
Chronic penile inflammation (balanoposthitis related to phimosis), lichen sclerosus	Risk
Sporalene and ultraviolet A phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments
Smoking	Five-fold increased risk (95% Confidence interval: 2.0-10.1) vs. non-smokers
HPV infection, condylomata acuminata	22.4% in verrucous squamous cell carcinoma 36-66.3% in basaloid-warty
Rural areas, low socio-economic status, unmarried	
Multiple sexual partners, early age of first intercourse	Three to five-fold increased risk of penile cancer

Pathology

Different variants of squamous cell carcinoma (SCC) accounts for more than 95% of cases of malignant penile disease. Table 1 lists premalignant lesions and Table 2 lists the pathological subtypes of penile carcinomas.

Table 1: Premalignant penile lesions (precursor lesions)

Lesions sporadically associated with squamous cell carcinoma (SCC) of the penis: • Bowenoid papulosis of the penis (HPV related) • Lichen sclerosus
Premalignant lesions (up to one-third transform to invasive SCC): • Penile intraepithelial lesions • Giant condylomata (Buschke-Löwenstein) • Bowen's disease • Paget's disease (intradermal ADK)

Table 2: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common squamous cell carcinoma (SCC)	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group

Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosis, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential (higher than in warty, lower than in basaloid SCC)
Adenosquamous carcinoma	< 1	Central and peri-meatal glans, high-grade carcinoma, high metastatic potential but low mortality
Mucoepidermoid carcinoma	< 1	Highly aggressive, poor prognosis
Clear cell variant of penile carcinoma	1-2	Exceedingly rare, associated with human papilloma virus, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis

Biopsy

Doubtful penile lesions should be biopsied and histological verification obtained before local treatment. Histological confirmation is necessary to guide management when:

- there is doubt about the exact nature of the lesion (e.g. carcinoma *in situ*, metastasis or melanoma);
- treatment with topical agents, radiotherapy or laser surgery is planned.

Recommendations for the pathological assessment of tumour specimens	Strength rating
The pathological evaluation of penile carcinoma specimens must include an assessment of the HPV status.	Strong
The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype.	Strong
The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin.	Strong

Staging and classification systems

The 2016 UICC, Tumour Node Metastasis (TNM) classification should be used for staging and classification (Table 3). The T1 category is stratified into two prognostically different risk groups. The classification T2 denotes invasion of the corpus spongiosum and T3 invasion of the corpora cavernosa, recognising that these two invasion patterns differ prognostically. The current pN1 group consists of one or two inguinal lymph node metastases, pN2 is more than two uni- or bilateral metastatic nodes, and pN3 any pelvic nodes, uni- or bilateral and any extranodal extension.

Table 3: 2016 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*
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated
T2	Tumour invades corpus spongiosum with or without invasion of the urethra
T3	Tumour invades corpus cavernosum with or without invasion of the 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 nodes
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 clinical 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	Metastasis in one or two inguinal lymph nodes
pN2	Metastasis in more than two unilateral inguinal nodes 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	
pM1	Distant metastasis microscopically confirmed
G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

**Verrucous carcinoma not associated with destructive invasion.*

Diagnostic evaluation and staging

Penile cancer can be cured in over 80% of all cases if diagnosed early. Once metastatic spread has occurred, it is a life-threatening disease with poor prognosis. Local treatment, although potentially life-saving, can be mutilating and devastating for the patient's psychological well-being.

Physical Examination

Careful palpation of both groins for enlarged inguinal lymph nodes must be part of the initial physical examination of patients with penile cancer.

Imaging

- Ultrasound (US) can give information about infiltration of the corpora.
- Magnetic resonance imaging (MRI) with an artificially induced erection can help to exclude tumour invasion of the corpora cavernosa if preservation of the penis is planned.
- In case of non-palpable inguinal nodes, current imaging techniques are not reliable in detecting micrometastases.
- A pelvic computed tomography (CT) scan can be used to assess pelvic lymph nodeIn case of positive inguinal nodes, CT of the abdomen and pelvis and a chest X-ray are recommended; a thoracic CT will be more sensitive than an X-ray.

Recommendations for the diagnosis and staging of penile cancer	Strength rating
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	Strong
Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery.	Weak
Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients; • If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT.	Strong
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan.	Strong
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

Disease management

Treatment of the primary penile cancer lesion aims to remove the tumour completely while preserving as much of the penis as possible without compromising radicality.

Recommendations for stage-dependent local treatment of penile carcinoma		
Primary tumour	**Use organ-preserving treatment whenever possible**	**Strength rating**
Tis	Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control.	Strong
	Laser ablation with carbon dioxide (CO_2) or neodymium: yttrium-aluminium-garnet (Nd:YAG) laser.	
	Glans resurfacing.	
Ta, T1a (G1, G2)	Wide local excision with circumcision, CO_2 or Nd:YAG laser with circumcision.	Strong
	Laser ablation with CO_2 or Nd:YAG laser.	
	Glans resurfacing.	
	Glansectomy with reconstruction.	
	Radiotherapy for lesions < 4 cm.	
T1b (G3) and T2	Wide local excision plus reconstruction.	Strong
	Glansectomy with circumcision and reconstruction.	
	Radiotherapy for lesions < 4 cm in diameter.	
T3	Partial amputation with reconstruction or radiotherapy for lesions < 4 cm in diameter.	Strong

T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	Strong
T4	Neoadjuvant chemotherapy followed by surgery in responders or palliative radiotherapy.	Weak
Local recurrence	Salvage surgery with penis-sparing in small recurrences or partial amputation.	Weak
	Large or high-stage recurrence: partial or total amputation.	

Management of inguinal lymph nodes

The treatment of regional lymph nodes is crucial for the survival of the patient. A surveillance strategy carries considerable risk as regional lymph node recurrence dramatically reduces the chance of long-term survival. Invasive staging by modified inguinal lymphadenectomy or dynamic sentinel node biopsy is recommended for penile cancers pT1G1 and higher.

Recommendations for treatment strategies for nodal metastases		
Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**Strength rating**
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	Strong
	> T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	Strong
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.	Strong
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.	Weak
Pelvic lymph nodes	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported.	Strong
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	Strong
Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong

Recommendations for chemotherapy in penile cancer patients	Strength rating
Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide).	Strong
Offer patients with non-resectable or recurrent lymph node metastases neoadjuvant chemotherapy (four cycles of a cisplatin- and taxane-based regimen) followed by radical surgery.	Weak
Offer palliative chemotherapy to patients with systemic disease.	Weak

Follow-up

Follow-up after curative treatment in penile carcinoma, as in any malignant disease, is important for two reasons:

- early detection of recurrence allows for potentially curative treatment;
- the detection and management of treatment-related complications.

Local recurrence does not significantly reduce long-term survival if successfully treated, while inguinal nodal recurrence leads to a drastic reduction in the probability of long-term disease-specific survival.

Recommendations for follow-up in penile cancer					
	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	Strength rating
	Years one to two	Years three to five			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	Three months	Six months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for penile intraepithelial neoplasia.	Five years	Strong
Amputation	Three months	One year	Regular physician or self-examination.	Five years	Strong
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	Three months	Six months	Regular physician or self-examination.	Five years	Strong
pN0 at initial treatment	Three months	One year	Regular physician or self-examination. Ultrasound with fine-needle aspiration biopsy optional.	Five years	Strong
pN+ at initial treatment	Three months	Six months	Regular physician or self-examination. Ultrasound with fine-needle aspiration cytology optional, computed tomography/magnetic resonance imaging optional.	Five years	Strong

Quality of life

Overall, nearly 80% of penile cancer patients of all stages can be cured. Partial penectomy has negative consequences for the patients' self-esteem and sexual function. Organ preserving treatment allows for better quality of life and sexual function and should be offered to all patients whenever feasible. Referral to centres with experience is recommended and psychological support is very important for penile cancer patients.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON NON-NEUROGENIC MALE LUTS INCLUDING BENIGN PROSTATIC OBSTRUCTION

(Limited text update March 2021)

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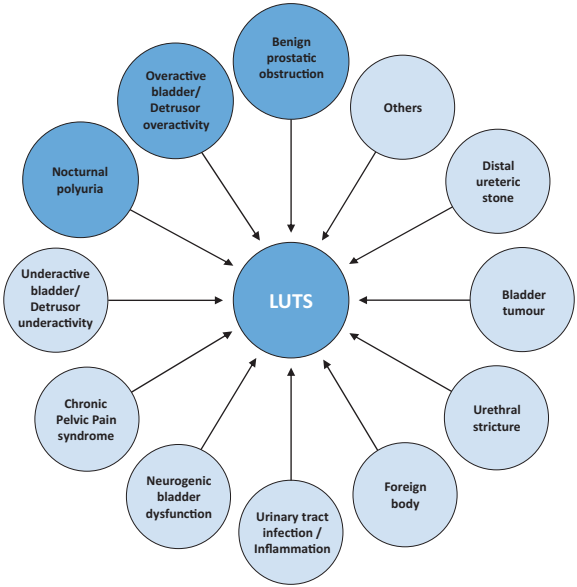
Introduction

The EAU Guidelines on Male Lower Urinary Tract Symptoms (LUTS) is a symptom-orientated guideline that mainly reviews LUTS secondary to benign prostatic obstruction (BPO), detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria in men ≥ 40 years. The multifactorial aetiology of LUTS is illustrated in Figure 1.

Figure 1: Causes of male lower urinary tract symptoms (LUTS)



Diagnostic Evaluation

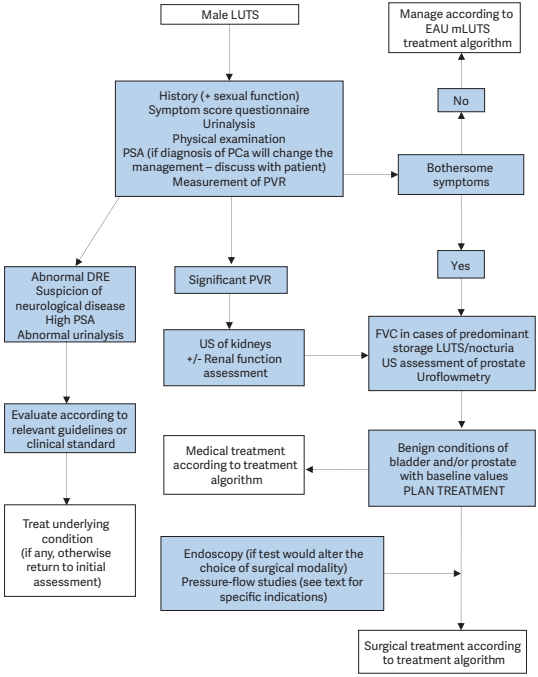
The high prevalence and the underlying multifactorial pathophysiology of male LUTS mean that an accurate assessment of LUTS is critical to provide best evidence-based care. Clinical assessment of LUTS aims to differentially diagnose and to define the clinical profile. A practical algorithm has been developed (Figure 2).

Recommendations for the diagnostic evaluation of male LUTS	Strength rating
Take a complete medical history from men with LUTS.	Strong
Use a validated symptom score questionnaire including bother and quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment.	Strong
Use a bladder diary to assess male LUTS with a prominent storage component or nocturia.	Strong
Tell the patient to complete a bladder diary for at least three days.	Strong
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	Strong
Urinalysis and prostate-specific antigen (PSA)	
Use urinalysis (by dipstick or urinary sediment) in the assessment of male LUTS.	Strong
Measure PSA if a diagnosis of prostate cancer will change management.	Strong
Measure PSA if it assists in the treatment and/or decision making process.	Strong
Renal function, post-void residual and uroflowmetry	
Assess renal function if renal impairment is suspected based on history and clinical examination, or in the presence of hydronephrosis, or when considering surgical treatment for male LUTS.	Strong
Measure post-void residual in the assessment of male LUTS.	Weak

Perform uroflowmetry in the initial assessment of male LUTS.	Weak
Perform uroflowmetry prior to medical or invasive treatment.	Strong
Imaging and urethrocystoscopy	
Perform ultrasound of the upper urinary tract in men with LUTS.	Weak
Perform imaging of the prostate when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	Weak
Perform imaging of the prostate when considering surgical treatment.	Strong
Perform urethrocystoscopy in men with LUTS prior to minimally invasive/surgical therapies if the findings may change treatment.	Weak
Pressure-flow studies (PFS)	
Perform PFS only in individual patients for specific indications prior to invasive treatment or when evaluation of the underlying pathophysiology of LUTS is warranted.	Weak
Perform PFS in men who have had previous unsuccessful (invasive) treatment for LUTS.	Weak
Perform PFS in men considering invasive treatment who cannot void > 150 mL.	Weak
Perform PFS when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s.	Weak

Perform PFS when considering invasive therapy in men with bothersome, predominantly voiding LUTS with a post-void residual > 300 mL.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged > 80 years.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged < 50 years.	Weak
Non-invasive tests in diagnosing bladder outlet obstruction	
Do not offer non-invasive tests, as an alternative to PFS, for diagnosing bladder outlet obstruction in men.	Strong

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older



DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

Note: Readers are strongly recommended to read the full text that highlights the current position of each test in detail.

Disease Management

Conservative and pharmacological treatment

Watchful waiting is suitable for mild-to-moderate uncomplicated LUTS. It includes education, re-assurance, lifestyle advice, and periodic monitoring.

Recommendations for the conservative and pharmacological management of male LUTS	Strength rating
Conservative management	
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	Strong
Offer men with LUTS lifestyle advice prior to, or concurrent with, treatment.	Strong
Pharmacological management	
Offer α1-blockers to men with moderate-to-severe LUTS.	Strong
Use 5α-reductase inhibitors (5-ARIs) in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong
Counsel patients about the slow onset of action (three to six months) of 5-ARIs.	Strong
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Strong
Do not use antimuscarinic overactive bladder medications in men with a post-void residual (PVR) volume > 150 mL.	Weak
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Weak

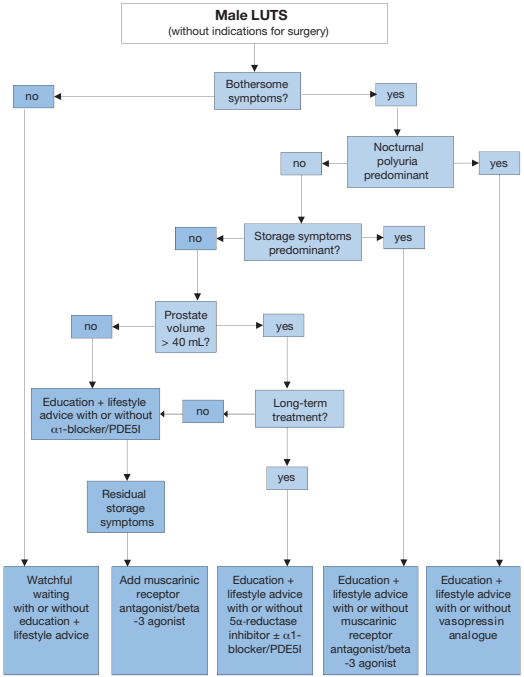
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	Strong
Offer hexane extracted *Serenoa repens* to men with LUTS who want to avoid any potential adverse events especially related to sexual function.	Weak
Inform the patient that the magnitude of *S. repens* efficacy may be modest.	Strong
Offer combination treatment with an α1-blocker and a 5-ARIs to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong
Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	Strong
Do not prescribe combination treatment in men with a PVR volume > 150 mL.	Weak

Summary conservative and/or medical treatment

First choice of therapy is behavioural modification, with or without pharmacological treatment. A flowchart illustrating conservative and pharmacological treatment choices according to evidence-based medicine and patients' profiles is provided in Figure 3.

Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options.

Treatment decisions depend on results assessed during initial evaluation. Note that patients' preferences may result in different treatment decisions.



PDE5I = phosphodiesterase type 5 inhibitor.
Note: Readers are strongly recommended to read the full text that highlights the current position of each treatment in detail.

Surgical treatment

Prostate surgery is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent urinary tract infections, bladder stones or diverticula, treatment-resistant visible haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery). Surgery is usually needed when patients have had insufficient relief of LUTS or post-void residual after conservative or pharmacological treatments (relative operation indications). Surgical management is divided by surgical approach into: resection; enucleation; vaporisation; alternative ablative techniques; and non-ablative techniques.

Recommendations for surgical treatment of male LUTS

Recommendations for resection of the prostate	Strength rating
Offer bipolar- or monopolar-transurethral resection of the prostate (TURP) to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Strong
Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to TURP.	Weak
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	Strong

Recommendations for enucleation of the prostate	
Offer open prostatectomy in the absence of bipolar transurethral enucleation of the prostate and holmium laser enucleation of the prostate to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	Strong
Offer bipolar transurethral (plasmakinetic) enucleation of the prostate to men with moderate-to-severe LUTS as an alternative to TURP.	Weak
Offer laser enucleation of the prostate using Ho:YAG laser (HoLEP) to men with moderate-to-severe LUTS as an alternative to TURP or open prostatectomy.	Strong
Offer enucleation of the prostate using the Tm:YAG laser (ThuLEP, ThuVEP) to men with moderate-to-severe LUTS as an alternative to TURP, holmium laser enucleation or bipolar transurethral (plasmakinetic) enucleation.	Weak
Offer Tm:YAG laser enucleation of the prostate to patients receiving anticoagulant or antiplatelet therapy.	Weak
Offer 120-W 980 nm, 1,318 nm or 1,470 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to bipolar transurethral (plasmakinetic) enucleation or bipolar-TURP.	Weak

Recommendations for vaporisation of the prostate	
Offer bipolar transurethral vaporisation of the prostate as an alternative to monopolar TURP to surgically treat moderate-to-severe LUTS in men with a prostate volume of 30-80 mL.	Weak
Offer 80-W 532-nm Potassium-Titanyl-Phosphate (KTP) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer 120-W 532-nm Lithium Borat (LBO) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer 180-W 532-nm LBO laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer laser vaporisation of the prostate using 80-W KTP, 120- or 180-W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80 mL.	Weak
Recommendations for alternative ablative techniques	
Offer Aquablation* to patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL as an alternative to TURP.	Weak
Inform patients about the risk of bleeding with aquablation and the lack of long-term follow up data.	Strong

Offer prostatic artery embolisation (PAE)* to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal outcomes compared with TURP.	Weak
Perform PAE only in units where the work up and follow up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients.	Strong
Recommendations for non-ablative techniques	
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe.	Strong
Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS.	Strong

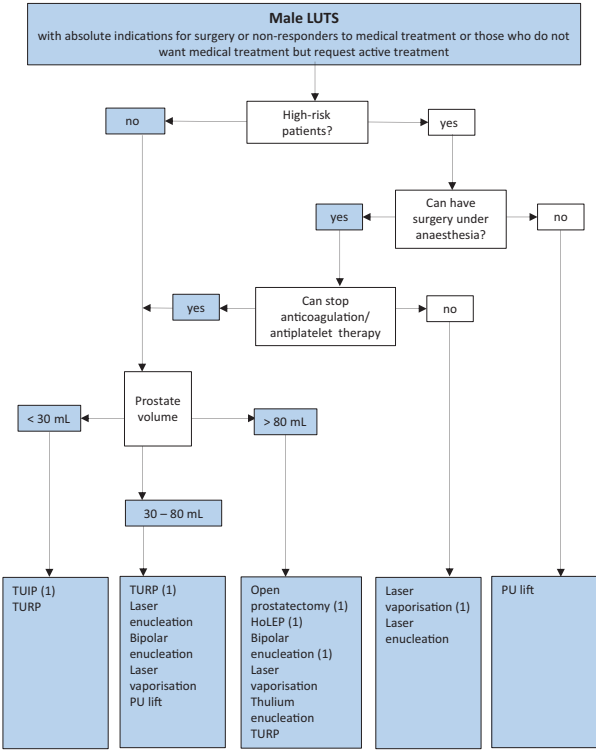
**Technique remains under investigation*

Summary surgical treatment

The choice of the surgical technique depends on prostate size, co-morbidities, ability to undergo anaesthesia, patient's preference/willingness to accept surgery-associated side effects, availability of the surgical armamentarium, and experience of the surgeon. Figure 4 illustrates surgical treatment choices according to the patient's profile.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications.

The flowchart is stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size.



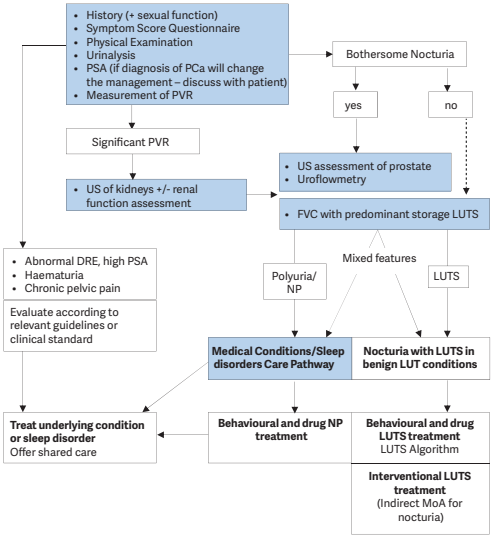
Laser vaporisation includes GreenLight, thulium, and diode laser vaporisation; Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate; PU = prostatic urethral.
(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.

Management of Nocturia in Men with LUTS

Diagnostic assessment

Evaluation is outlined in Figure 5.

Figure 5: Evaluation of nocturia in non-neurogenic male LUTS



Assessment must establish whether the patient has polyuria, LUTS, sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment with a frequency volume chart, (indicated by the dotted line), depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.
DRE = digital rectal examination; NP = nocturnal polyuria; MoA = mechanism of action; PVR = post-void residual; PSA = prostate-specific antigen; US = ultrasound; FVC = frequency volume chart.

Medical conditions and sleep disorders shared care pathway

Table 1: Shared care pathway for nocturia, highlighting the need to manage potentially complex patients using relevant expertise for the causative factors.

UROLOGICAL CONTRIBUTION	*SHARED CARE*	*MEDICAL CONTRIBUTION*
Diagnosis of LUTD • Urological/ LUTS evaluation • Nocturia symptom scores • Bladder diary		**Diagnosis of conditions causing NP** • Evaluate patient's known conditions • Screening for sleep disorders • Screening for potential causes of polyuria*

Conservative management Behavioural therapy • Fluid/sleep habits advice • Drugs for storage LUTS • Drugs for voiding LUTS • ISC/ catherisation • Leg elevation • Weight loss **Interventional therapy** • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS	**Conservative management** • Antidiuretic • Diuretics • Drugs to aid sleep	**Management** • Initiation of therapy for new diagnosis • Optimised therapy of known conditions * Potential causes of polyuria NEPHROLOGICAL DISEASE • Tubular dysfunction • Global renal dysfunction CARDIOVASCULAR DISEASE • Cardiac disease • Vascular disease ENDOCRINE DISEASE • Diabetes insipidus/mellitus • Hormones affecting diuresis/natriuresis NEUROLOGICAL DISEASE • Pituitary and renal innervation • Autonomic dysfunction RESPIRATORY DISEASE • Obstructive sleep apnoea BIOCHEMICAL • Altered blood oncotic pressure

Recommendations for treatment of nocturia	Strength rating
Treat underlying causes of nocturia, including behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	Weak
Discuss behavioural changes with the patient to reduce nocturnal urine volume and episodes of nocturia, and improve sleep quality.	Weak
Offer desmopressin to decrease nocturia due to nocturnal polyuria in men < 65 years of age.	Weak
Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria.	Weak
Screen for hyponatremia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatremia.	Strong
Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age.	Strong
Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS.	Weak
Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder.	Weak

Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL).	Weak
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	Weak

Follow-up

Recommended follow-up strategy:

- Patients managed with watchful waiting should be reviewed at six months and then annually, provided symptoms do not deteriorate or absolute indications develop for surgical treatment.
- Patients receiving α1-blockers, muscarinic receptor antagonists, beta-3 agonists, phospodiesterase 5 inhibitors, or a combination should be reviewed four to six weeks after drug initiation. If patients gain symptomatic relief, without troublesome side effects, drug therapy may be continued. Patients should be reviewed at six months and then annually, provided symptoms do not deteriorate or absolute indications develop for surgical treatment.
- Patients receiving 5α-reductase inhibitors should be reviewed after twelve weeks and six months to determine their response and adverse events.
- Patients receiving desmopressin: serum sodium concentration should be measured at day three and seven and after one month and, if serum sodium concentration has remained normal, every three months subsequently; the follow-up sequence should be restarted after dose escalation.
- Patients after prostate surgery should be reviewed four to six weeks after catheter removal to evaluate treatment response and side effects. If patients have symptomatic relief and there are no side effects, further assessment is not necessary.

Recommendations for follow-up	Strength rating
Follow-up all patients who receive conservative, medical or surgical management.	Weak
Define follow-up intervals and examinations according to the specific treatment.	Weak

Readers are strongly recommended to read the full version of the Guidelines where the efficacy, safety and considerations for each treatment are presented.

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EAU GUIDELINES ON NON-NEUROGENIC FEMALE LUTS

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Introduction

The latest edition of the guidelines has seen a significant expansion of scope from 'urinary incontinence (UI)' to 'non-neurogenic female lower urinary tract symptoms (LUTS)'. The primary consideration here was to include the significant population of women with functional urological conditions not necessarily associated with UI that were hitherto not accounted for in previous guidelines. This reconfiguration has also seen some additional sections added to this guideline (including non-obstetric fistulae, female bladder outlet obstruction [BOO], underactive bladder [UAB] and nocturia) and over the course of the next two or three iterations the scope is likely to widen further.

DIAGNOSIS - GENERAL

History and physical examination

Taking a thorough clinical history is fundamental to the process of clinical evaluation. Despite the lack of high-level evidence to support it, there is universal agreement that taking a history should be the first step in the assessment of anyone with LUTS.

The history should include a full evaluation of LUT symptoms (storage, voiding and post-micturition symptoms), sexual, gastrointestinal and neurological symptoms. Details of urgency episodes, the type, timing and severity of UI, and some attempt to quantify symptoms should also be made. The history should help to categorise LUTS as storage, voiding and post-void symptoms, and classify UI as stress urinary incontinence (SUI), urgency UI (UUI), mixed UI (MUI) or overflow incontinence, the latter being defined as *'the complaint of UI in the symptomatic presence of an excessively (over-) full bladder (no cause identified)'*.

Recommendation	Strength rating
Take a complete medical history including symptoms and comorbidities and a focused physical examination in the evaluation of women with LUTS.	Strong

Patient questionnaires

Summary of evidence	LE
Validated condition-specific symptom scores assist in the screening for, and categorisation of LUTS.	3
Patient questionnaires cannot replace a detailed patient consultation and should only be used as part of a complete medical history.	4

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised assessment of female LUTS.	Strong

Bladder diaries

Recommendations	Strength rating
Ask patients with lower urinary tract symptoms to complete a bladder diary as part of the standardised assessment of female LUTS.	Strong
Use a bladder diary with a duration of at least three days.	Strong

Urinalysis

Recommendations	Strength rating
Perform urinalysis as a part of the initial assessment of a patient LUTS.	Strong
If a UTI is present with LUTS, reassess the patient after treatment.	Strong
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve UI.	Strong

Post-void residual volume

Recommendations	Strength rating
Measure post-void residual volume (PVR) in patients with LUTS during initial assessment.	Strong
Use ultrasound to measure PVR.	Strong
Monitor PVR in patients receiving treatments that may cause or worsen voiding dysfunction.	Strong
Provide Bladder Voiding Efficiency as an additional parameter when measuring PVR.	Weak

Urodynamics

Summary of evidence	LE
Most urodynamic parameters show variability within the same session and over time, and this may limit their clinical interpretation.	3
There may be inconsistency between history and urodynamic results.	3
Urodynamic diagnosis of detrusor overactivity (DO) does not influence treatment outcomes in patients with OAB.	1a
Pre-operative urodynamics in women with uncomplicated, clinically demonstrable, SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that pre-operative DO is associated with surgical failure of MUS in women.	3
The presence of pre-operative DO may be associated with persistence of urgency post-operatively.	3

Recommendations	Strength rating
Adhere to 'Good Urodynamic Practice' standards as described by the International Continence Society when performing urodynamics in patients with LUTS.	Strong
Do not routinely carry out urodynamics when offering treatment for uncomplicated SUI.	Strong

Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated overactive bladder (OAB) symptoms.	Strong
Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of UI as they are primarily tests of urethral function.	Strong

Pad testing

Recommendations	Strength rating
Use a pad test of standardised duration and activity protocol.	Strong
Use a pad test when quantification of UI is required, especially to assess response to treatment.	Weak

Imaging

Recommendation	Strength rating
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of LUTS.	Strong

DISEASE MANAGEMENT

Overactive bladder

Overactive bladder is defined by the International Continence Society as '*urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of urinary tract infection (UTI) or other obvious pathology*'.

Diagnostic evaluation

Recommendations	Strength rating
Request that patients complete at least a three-day bladder diary at initial evaluation and before each therapeutic intervention for OAB.	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated OAB symptoms.	Strong

Conservative management

Addressing underlying disease/cognitive impairment

Lower urinary tract symptoms, especially in the elderly, have been associated with multiple comorbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease;
- general cognitive impairment;
- sleep disturbances, e.g. sleep apnoea;
- depression;
- metabolic syndrome.

Management of associated conditions

Recommendation	Strength rating
Review any new medication associated with the development or worsening of UI.	Weak

Adjustment of non-LUTS medication

Recommendations	Strength rating
Take a history of current medication use from all patients with OAB.	Strong
Review any new medication associated with the development or worsening of OAB symptoms.	Weak

Urinary containment

Recommendations	Strength rating
Ensure that women with OAB and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of OAB-wet, either for temporary symptom control or where other treatments are not feasible.	Strong
Offer prophylactic antibiotics to patients with recurrent UTIs who perform clean intermittent self-catheterisation, or have an indwelling catheter, after discussion regarding the risk of increasing antimicrobial resistance.	Strong

Lifestyle interventions

Summary of evidence	LE
Obesity is a risk factor for UI in women, but the relationship to other OAB symptoms remains unclear.	1b
There is weak evidence that smoking cessation will improve the symptoms of OAB.	3

Recommendations	Strength rating
Encourage overweight and obese adults with OAB/UI to lose weight and maintain weight loss.	Strong
Advise adults with OAB that reducing caffeine intake may improve symptoms of urgency and frequency, but not incontinence.	Strong
Review type and amount of fluid intake in patients with OAB.	Weak
Provide smoking cessation strategies to patients with OAB who smoke.	Strong

Behavioural and physical therapies

Summary of evidence	LE
Pelvic floor muscle training (PFMT) may improve symptoms of frequency and incontinence in women.	1b
Electrical stimulation may improve symptoms of OAB in some women, but the type and mode of delivery of ES remains variable and poorly standardised.	1a

Recommendations	Strength rating
Offer prompted voiding to adults with OAB who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with OAB/UUI.	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for improvement of OAB/UUI in women who have not benefited from anticholinergic medication.	Strong

Pharmacological management

Anticholinergic drugs

Summary of evidence	LE
No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI.	1a
Higher doses of anticholinergic drugs are more effective to improve OAB symptoms, but exhibit a higher risk of side effects.	1a
Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2a
Most patients will stop anticholinergic agents within the first three months.	2a

Recommendations	Strength rating
Offer anticholineric drugs to adults with OAB who fail conservative treatment.	Strong
Consider extended release formulations of anticholinergic drugs, whenever possible.	Strong
If an anticholinergic treatment proves ineffective, consider dose escalation or offering an alternative anticholinergic formulation, or mirabegron, or a combination.	Strong
Encourage early review (of efficacy and side effects) of patients on anticholinergic medication for OAB.	Strong

Beta-3 agonists

Mirabegron

Summary of evidence	LE
Mirabegron is better than placebo and as efficacious as anticholinergics for improvement of OAB/UUI symptoms.	1a
Adverse event rates with mirabegron are similar to placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin.	1b

Recommendation	Strength rating
Offer mirabegron as an alternative to anticholinergics to women with OAB who fail conservative treatment.	Strong

Anticholinergics and beta-3 agonists: the elderly and cognition

Recommendations	Strength rating
Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction.	Strong
Assess anticholinergic burden and associated co-morbidities in patients being considered for anticholinergic therapy for OAB syndrome.	Weak

Oestrogens

Recommendation	Strength rating
Offer vaginal oestrogen therapy to women with LUTS and associated symptoms of genito-urinary syndrome of menopause.	Weak

Surgical management

Bladder wall injection of botulinum toxin A

Summary of evidence	LE
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy but discontinuation rates are high.	2a
There is a risk of increased PVR and UTI with onabotulinum toxin A injections.	2
Onabotulinum toxin A (100 U) is superior to anticholinergics and mirabegron for cure of UUI and improvement of symptoms of OAB at twelve weeks.	1a

Recommendations	Strength rating
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with OAB/UUI refractory to conservative therapy (such as PFMT and/or drug treatment).	Strong

Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to self-catheterise (ensure that they are willing and able to do so).	Strong

Sacral nerve stimulation

Summary of evidence	LE
Sacral nerve stimulation is more effective than continuation of failed conservative treatment for OAB/UUI, but no sham controls have been used.	1b
Sacral nerve stimulation is not more effective than onabotulinum A toxin 200 U injection at 24 months.	1b
In patients who have been implanted, 50% improvement of UUI is maintained in at least 50% of patients and 15% may remain cured at four years.	3

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have OAB/UUI refractory to anticholinergic therapy.	Strong

Cystoplasty/urinary diversion

Recommendations	Strength rating
Offer augmentation cystoplasty to patients with OAB/UUI who have failed all other treatment options and have been warned about the possible small risk of malignancy.	Weak

Inform 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) and that they need life-long surveillance.	Strong
Do not offer detrusor myectomy as a treatment for UUI.	Weak
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of OAB/UUI, who will accept a stoma and have been warned about the possible small risk of malignancy.	Weak

Follow-up

Follow-up for women with OAB is guided by the type of treatment instituted and local service capacity. Standardisation of follow-up pathways can therefore be difficult. The Panel provide recommendations based on best practice and standards from clinical trials.

Recommendations	Strength rating
Offer early follow up to women who have been commenced on anti-anticholinergic or beta-3 agonist therapy.	Strong
Offer repeat injections of onabotulinum toxin, as required, to women in whom it has been effective (refer to the manufacturers' guidance regarding the minimum timeframe for repeat injections).	Strong

Offer life-long surveillance to women who have a sacral nerve stimulation implant to monitor for lead displacement, malfunction and battery wear.	Strong
Offer cystoscopic surveillance to women with an augmentation cystoplasty due to the small risk of malignancy.	Weak

Stress Urinary Incontinence

Classification

Patients with SUI can be classified as '*uncomplicated*' and '*complicated*'. The Panel reached consensus on the definition to be used throughout this Guideline document:

- Women with uncomplicated SUI: no history of prior surgery for SUI, no prior extensive pelvic surgery, no prior pelvic radiation treatment, no neurogenic LUT dysfunction, no bothersome genitourinary prolapse, absence of voiding symptoms, and no medical conditions that affect the LUT. In cases where additional significant storage symptoms, especially OAB, are present, consider a possible diagnosis of MUI.
- Women with complicated SUI: women with previous surgery for incontinence or previous extensive pelvic surgery, women with a history of pelvic irradiation, the presence of anterior or apical pelvic-organ prolapse, the presence of voiding symptoms or the presence of neurogenic LUT dysfunction, and women with significant OAB/UUI.

Diagnostic evaluation

History taking and physical examination

Recommendation	Strength rating
Take a full clinical history and perform a thorough physical examination in all women presenting with SUI.	Strong

Patient questionnaires

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised assessment of patients with SUI.	Strong

Post-void residual volume

Recommendations	Strength rating
Measure PVR volume, particularly when assessing patients with voiding symptoms or complicated SUI.	Strong
When measuring PVR, use ultrasound in preference to catheterisation.	Strong
Monitor PVR in patients scheduled for treatment which may cause or worsen voiding dysfunction, including surgery for SUI.	Strong

Urodynamics

Summary of evidence	LE
Pre-operative urodynamics in women with uncomplicated, clinically demonstrable, SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent evidence that pre-operative DO is associated with surgical failure of MUS in women.	3

Recommendations	Strength rating
Do not routinely carry out urodynamics when offering treatment for uncomplicated SUI.	Strong
Perform pre-operative urodynamics in cases of SUI with associated storage symptoms, cases in which the type of incontinence is unclear, cases where voiding dysfunction is suspected, cases with associated pelvic organ prolapse or those with a previous history of SUI surgery.	Weak
Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence as they are primarily tests of urethral function.	Strong

Pad testing

Recommendations	Strength rating
Use a pad test of standardised duration and activity protocol.	Strong

Use a standardised pad test when quantification of UI is required, especially to assess response to treatment.	Weak

Imaging

Recommendation	Strength rating
Do not carry out imaging of the upper or lower urinary tract as part of the routine assessment of SUI.	Strong

Disease management

Conservative management

Obesity and weight loss

Recommendation	Strength rating
Encourage overweight and obese women with LUTS/SUI to lose weight and maintain weight loss.	Strong

Urinary containment

Recommendations	Strength rating
Ensure that women with SUI and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of SUI, either for temporary symptom control or where other treatments are not feasible.	Strong

Pelvic floor muscle training

Recommendations	Strength rating
Offer supervised intensive PFMT, lasting at least three months, as first-line therapy to all women with SUI or MUI (including the elderly and pre- and post-natal).	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Balance the efficacy and lack of adverse events from PFMT against the expected effect and complications from invasive surgery for SUI.	Strong
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of SUI.	Strong

Pharmacological management

Oestrogens

Recommendations	Strength rating
Offer vaginal oestrogen therapy to post-menopausal women with SUI and symptoms of vulvo-vaginal atrophy.	Strong
In women taking oral conjugated equine oestrogen as hormone replacement therapy who develop or experience worsening SUI discuss alternative hormone replacement therapies.	Strong

Duloxetine

Summary of evidence	LE
Duloxetine improves SUI in women, but the chances of cure are low.	1a
Duloxetine may cause significant gastrointestinal and central nervous system side effects leading to a high rate of treatment discontinuation, although these symptoms may be limited to the first weeks of treatment.	1a

Recommendations	Strength rating
Offer duloxetine (where licensed) to selected patients with SUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Strong
Duloxetine should be initiated and withdrawn using dose titration because of the high risk of adverse events.	Strong

Surgical management

General considerations

The use of polypropylene mesh, synthetic mid-urethral sling (MUS) for the treatment of SUI has recently come under scrutiny following concerns raised regarding long-term complications. In some European countries such as the United Kingdom the use of synthetic MUS has been paused. A 2020 UK parliamentary review concluded that "*For many women mesh surgery is trouble-free and leads to improvements in their condition. However, this is not the case for all. There is no reliable information on the true number of women who have suffered complications. While they may be in*

the minority, that does not diminish the catastrophic nature of their suffering or the importance of providing support to them and learning from what has happened to them".

Surgical management of uncomplicated SUI

Recommendations	Strength rating
Offer patients who have explored/failed conservative treatment options a choice of different surgical procedures, where appropriate, and discuss the advantages and disadvantages of each approach.	Strong
Use new devices for the treatment of SUI only as part of a structured research programme. Their outcomes must be monitored in a registry or as part of a well-regulated research trial.	Strong

Open and laparoscopic colposuspension surgery

Recommendation	Strength rating
Offer colposuspension (open or laparoscopic) to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

Autologous sling

Summary of evidence	LE
Autologous sling is more effective in terms of cure rate than colposuspension.	1a

Autologous sling has a similar rate of adverse events compared to open colposuspension, with higher rates of voiding dysfunction and post-operative UTI, but a lower rate of bladder- or urethral perforation.	1a

Recommendation	Strength rating
Offer autologous sling placement to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

Urethral bulking agents

Summary of evidence	LE
Urethral bulking agents may provide short-term improvement and cure, in women with SUI.	1b
Bulking agents are less effective than MUS, colposuspension or autologous sling for cure of SUI and repeat injections may be required in order to achieve sustained benefits.	1b
There is no evidence that one type of bulking agent is better than another type.	1b

Recommendations	Strength rating
Offer urethral bulking agents to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

Offer urethral bulking agents to women with SUI who request a low-risk procedure with the understanding that efficacy is lower than other surgical procedures, repeat injections are likely and long-term durability and safety are not established.	Strong
Do not offer autologous fat and hyaluronic acid as urethral bulking agents due to the higher risk of adverse events.	Strong

Mid-urethral slings

Summary of evidence	**LE**
The retropubic MUS appears to provide better patient-reported subjective and objective cure of SUI, compared with colposuspension.	1a
Mid-urethral synthetic slings inserted by the retropubic routes have higher patient-reported cure rates in the longer term.	1b
Long-term analyses of MUS cohorts showed a sustained response beyond ten years.	2b
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 groin pain than the retropubic route.	1a
The comparative efficacy of single-incision slings against conventional MUS is uncertain.	1a

Recommendations	Strength rating
Offer a mid-urethral sling (MUS) to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Inform women that long-term outcomes from MUS inserted by the retropubic route are superior to those inserted via the transobturator route.	Strong
Inform women of the complications associated with MUS procedures and discuss all alternative treatments in the light of recent publicity surrounding surgical mesh.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong

Other treatments of uncomplicated SUI

Recommendations	Strength rating
Offer Vesair® intravesical balloon to women with mild-to-moderate SUI who failed conservative treatments only as part of a well-conducted research trial.	Weak
Offer mechanical devices to women with mild-to-moderate SUI who failed conservative treatments only as part of a well-conducted research trial.	Strong

Inform women receiving artificial urinary sphincter or adjustable compression device (ACT©) that although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Strong

Management of complicated SUI

Recommendations	**Strength rating**
Management of complicated SUI should only be offered in centres with appropriate experience.	Strong
Base the choice of surgery for recurrent SUI on careful evaluation, including individual patient factors and considering further investigations such as cystoscopy, multichannel urodynamics, as appropriate.	Strong
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Only offer adjustable mid-urethral sling as a primary surgical treatment for SUI as part of a structured research programme.	Strong
Consider secondary synthetic sling, bulking agents, colposuspension, autologous sling or artificial urinary sphincter (AUS) as options for women with complicated SUI.	Weak

Inform women receiving AUS or adjustable compression device (ACT®) that although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Strong

Surgery of SUI in special patient groups

Recommendations	Strength rating
Inform obese women with SUI about the increased risks associated with surgery, together with the lower probability of benefit.	Weak
Inform older women with SUI about the increased risks associated with surgery, together with the likelihood of lower probability of benefit.	Weak

Follow-up

The follow-up of patients with SUI will be dependent on the treatment given. For conservative and physical therapies sufficient time should be allowed for the demonstration of treatment effect. For pharmacological treatment early follow-up is recommended. For most surgical interventions short term follow-up should be arranged to assess efficacy and identify any surgical complications in the early post-operative phase.

Mixed Urinary Incontinence

The term 'mixed urinary incontinence' is extremely broad because it may refer to equal stress and urgency symptoms, stress-predominant symptoms, urgency-predominant symptoms, urodynamic SUI (USUI or USI) with detrusor

overactivity (DO), or USUI with clinical urgency symptoms, but no DO.

Diagnosis

Summary of evidence	LE
There is no evidence that urodynamics affects outcomes of treatment for MUI.	3

Recommendations	Strength rating
Complete a thorough history and examination as part of the assessment of MUI.	Strong
Characterise MUI as either stress-predominant or urgency-predominant where possible.	Weak
Use bladder diaries and urodynamics as part of the multi-modal assessment of patients with MUI to help inform the most appropriate management strategy.	Strong

Disease Management

Conservative management in MUI

Summary of evidence	LE
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with MUI.	Weak
Offer bladder training as a first-line therapy to adults with MUI.	Strong

Offer supervised intensive PFMT, lasting at least three months, as a first-line therapy to all women with MUI (including elderly and postnatal women).	Strong

Pharmacological management of MUI

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with MUI.	Weak
Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI.	Strong
Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Weak

Surgical management of MUI

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with MUI.	Weak
Warn women that surgery for MUI is less likely to be successful than surgery for SUI alone.	Strong
Inform women with MUI that one single treatment may not cure UI; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	Strong

Underactive Bladder

Underactive bladder is defined by the ICS as *'a symptom complex characterised by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms'.*

Management of underactive bladder

Recommendations	Strength rating
Encourage double voiding in those women who are unable to completely empty their bladder.	Weak
Warn women with underactive bladder (UAB) who use abdominal straining to improve emptying about pelvic organ prolapse risk.	Weak
Use clean intermittent self-catheterisation (CISC) as a standard treatment in patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of CISC.	Strong
Offer indwelling transurethral catheterisation and suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak
Do not routinely recommend intravesical electrical stimulation in women with UAB.	Weak
Do not routinely recommend parasympathomimetics in the treatment of women with UAB.	Strong
Offer alpha-blockers before more invasive techniques.	Weak

Offer intravesical prostaglandins to women with urinary retention after surgery only in the context of well-regulated clinical trials.	Weak
Offer onabotulinumtoxin A external sphincter injections before more invasive techniques as long as the patient is informed that the evidence to support this treatment is of low quality.	Weak
Offer sacral nerve stimulation to women with UAB refractory to conservative measures.	Strong
Do not routinely offer detrusor myoplasty as a treatment for detrusor underactivity.	Weak

Follow-up

Natural history and clinical evolution at long-term follow-up of women with DU is not well known. The interval between follow-up visits will depend on patient characteristics, treatments given and the frequency of urinary complications.

Bladder Outlet Obstruction

Bladder outlet obstruction is defined by the ICS as '*obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate*'.

Classification of BOO

Recommendation	Strength rating
Use standardised classification of BOO in women (anatomical or functional) and research populations should be fully characterised using such classification.	Strong

Diagnosis of BOO

Recommendations	Strength rating
Take a full clinical history and perform a thorough clinical examination in women with suspected BOO.	Strong
Do not rely on measurements from urine flow studies alone to diagnose female BOO.	Strong
Perform cystourethroscopy in women with suspected BOO.	Strong
Perform urodynamic evaluation in women with suspected BOO.	Strong

Conservative treatment of BOO

Recommendations	Strength rating
Offer PFMT aimed at pelvic floor muscle relaxation to women with functional BOO.	Weak
Prioritise research that will investigate and advance the understanding of the mechanisms and impact of PFMT on the co-ordinated relaxation of the pelvic floor during voiding.	Strong
Offer the use of a vaginal pessary to women with grade 3 to 4 cystocoeles and BOO who are not eligible/inclined towards other treatment options.	Weak
Offer urinary containment devices to women with BOO to address urinary leakage as a result of BOO, but not as a treatment to correct the condition.	Weak

Offer intermittent self-catheterisation to women with urethral strictures or post-UI surgery for BOO.	Weak
Do not offer an intraurethral device to women with BOO.	Strong

Pharmacologic treatment of BOO

Recommendations	Strength rating
Offer uroselective alpha-blockers, as an off-label option, to women with functional BOO following discussion of the potential benefits and adverse events.	Weak
Offer oral baclofen to women with BOO particularly those with increased electromyography activity and a sustained detrusor contraction during voiding.	Weak
Only offer sildenafil to women with BOO as part of a well-regulated clinical trial.	Strong
Do not offer thyrotropin-releasing hormone to women with BOO.	Strong

Surgical treatment of BOO

Recommendations	Strength rating
Offer intrasphincteric injection of botulinum toxin to women with functional BOO.	Weak
Offer sacral nerve stimulation to women with functional BOO.	Weak
Advise women with voiding symptoms associated with pelvic organ prolapse (POP) that symptoms may improve after POP surgery.	Weak

Offer urethral dilatation to women with urethral stenosis causing BOO, but advise on the likely need for repeated intervention.	Weak
Offer internal urethrotomy with post-operative urethral self-dilatation to women with BOO due to urethral stricture disease but advise on its limited long-term improvement and the risk of post-operative UI.	Weak
Do not offer urethral dilatation or urethrotomy as a treatment for BOO to women who have previously undergone mid-urethral synthetic tape insertion due to the theoretical risk of causing urethral mesh extrusion.	Weak
Inform women of limited long-term improvement (only in terms of PVR and QoL) after internal urethrotomy.	Weak
Offer bladder neck incision to women with BOO secondary to primary bladder neck obstruction.	Weak
Advise women who will undergo bladder neck incision on the small risk of developing SUI, vesico-vaginal fistula or urethral stricture post-operatively.	Strong
Offer urethroplasty to women with BOO due to recurrent urethral stricture after failed primary treatment.	Weak
Caution women on the possible recurrence of strictures on long-term follow-up after urethroplasty.	Weak
Offer urethrolysis to women who have voiding difficulties after anti-UI surgery.	Weak

Offer sling revision (release, incision, partial excision, excision) to women who develop urinary retention or significant voiding difficulty post tape surgery for UI.	Strong
Caution women about the risk for recurrent SUI and the need for a repeat/concurrent anti-UI surgery after sling revision.	Strong

Follow up

Women with BOO should be followed up and monitored regularly due to the risk of further deterioration of voiding or renal function in case of persistence and progression of the obstruction. For those who received treatment, monitoring must be undertaken for the recurrence of the BOO. In particular, women who underwent urethral dilation, urethrotomy or urethroplasty for urethral stricture need to be monitored for the recurrence of the stricture.

Nocturia

Nocturia was defined by the ICS in 2002 as 'the complaint that the individual has to wake at night one or more times to void' and quantified in an updated document in 2019 as '*the number of times an individual passes urine during their main sleep period, from the time they have fallen asleep up to the intention to rise from that period*'.

Diagnosis of nocturia

Recommendations	Strength rating
Take a complete medical history from women with nocturia.	Strong
Use a validated questionnaire during the assessment of women with nocturia and for re-evaluation during and/or after treatment.	Weak

Use a three-day bladder diary to assess nocturia in women.	Strong
Do not use nocturnal-only bladder diaries to evaluate nocturia in women.	Weak

Conservative management of nocturia

Recommendations	Strength rating
Offer women with LUTS lifestyle advice prior to, or concurrent with, treatment.	Strong
Offer PFMT for nocturia (either individually or in the group setting) to women with UI or other storage LUTS.	Strong
Offer women with nocturia and a history suggestive of obstructive sleep apnoea a referral to a sleep clinic for an assessment of suitability for continuous positive airway pressure treatment.	Strong

Pharmacological management of nocturia

Recommendations	Strength rating
Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women following appropriate counselling regarding the potential benefits and associated risks (including hyponatraemia).	Strong
Desmopressin treatment in elderly patients should include careful monitoring of the serum sodium concentration and should be avoided in patients with a baseline serum sodium concentration below normal range.	Strong

Offer an anticholinergic treatment for nocturia to women with UUI or other storage LUTS following appropriate counselling regarding the potential benefits and associated risks.	Strong
Inform women with nocturia that the combination treatment with behavioural therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone.	Weak
Offer combination treatment with anticholinergics and desmopressin to women with OAB and nocturia secondary to nocturnal polyuria following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer vaginal oestrogen treatment to women with nocturia following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer timed diuretic treatment to women with nocturia secondary to polyuria following appropriate counselling regarding the potential benefits and associated risks.	Weak

Follow-up

The follow-up of patients with nocturia will be dependent on both the underlying aetiology of this symptom and the treatment given.

Pelvic organ prolapse and LUTS

Detection of SUI in women with pelvic organ prolapse

Recommendation	Strength rating
Perform a pelvic organ prolapse (POP) reduction test in continent women to identify those with occult SUI and counsel them about the pros and cons of additional anti-incontinence surgery at the time of POP surgery.	Strong

Conservative treatment of POP and LUTS

Recommendations	Strength rating
Inform women with pelvic organ prolapse (POP), who do not need a vaginal pessary or surgical intervention, about the potential relief from LUTS from PFMT.	Strong
Do not offer pre-operative PFMT in order to improve outcome of LUTS if pessary therapy or surgical intervention is indicated for POP.	Strong

Surgery for bothersome POP

Recommendations for women requiring surgery for bothersome POP who have symptomatic or occult SUI	Strength rating
Offer simultaneous surgery for POP and SUI only after a full discussion of the potential risks and benefits of combined surgery vs. POP surgery alone.	Strong

Inform women of the increased risk of adverse events with combined prolapse and anti-UI surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome POP who do not have symptomatic or occult SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Warn women that the benefit of combined surgery for POP and SUI may be outweighed by the increased risk of adverse events compared to prolapse surgery alone.	Strong

Urinary Fistula

Epidemiology, aetiology and pathophysiology of urinary fistula

Summary of evidence	LE
The risk of injury to the urinary tract and subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures.	2
The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment.	4

Adapted WHO Classification of fistulae*

Simple fistula with good prognosis	Complex fistula with uncertain prognosis
• Single fistula < 4 cm • Vesico-vaginal fistula • Closing mechanism not involved • No circumferential defect • Minimal tissue loss • Ureters not involved • First attempt to repair	• Fistula > 4 cm • Multiple fistula • Recto-vaginal mixed fistula, cervical fistula • Closing mechanism involved • Scarring • Circumferential defect • Extensive tissue loss • Intravaginal ureters • Failed previous repair • Radiation fistula

**Although this classification was developed for obstetric fistula initially, it could be relevant for iatrogenic fistula as well.*

Classification of urinary fistula

Recommendation	Strength rating
Use a classification system for urinary tract fistulae to try to standardise terminology in this subject area.	Strong

Management of urinary fistula

Recommendations	Strength rating
General	
When reporting on outcomes after fistula repair, authors should make a clear distinction between fistula closure rates and post-operative UI rates and the time at which the follow-up was organised.	Strong
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	Strong
Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs post-operatively, or if drainage fluid contains high levels of creatinine.	Strong
Use three-dimensional imaging techniques to diagnose and localise urinary fistulae particularly in cases with negative direct visual inspection or cystoscopy.	Weak
Manage upper urinary tract fistulae initially by conservative or endoluminal techniques where such expertise and facilities exist.	Weak
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient.	Weak
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to, and following, fistula repair.	Weak

Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	Weak
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: 10–14 days for simple and/or post-surgical fistulae; 14–21 days for complex and/or post-radiation fistulae).	Weak
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	Weak
Use interposition graft when repair of radiation-associated fistulae is undertaken.	Weak
Repair persistent uretero-vaginal fistulae by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence.	Weak
Urethro-vaginal fistulae should preferably be repaired by a vaginal approach.	Weak

Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion composed of the entire urethral wall or only by the urethral mucosa, situated between the peri-urethral tissues and the anterior vaginal wall.

Classification*

Localisation	Mid-urethral Distal Proximal Full length
Configuration	Single Multiloculated Saddle shaped
Communication	Mid-urethral No communication visualised Distal Proximal
Continence	Stress urinary incontinence Continent Post-void dribble Mixed incontinence

**Limited LNS C3 classification of urethral diverticula.*

Management of urethral diverticulum

Recommendations	Strength rating
Offer surgical removal of symptomatic urethral diverticula.	Weak
If conservative treatment is adopted, warn patients of the small (1–6%) risk of cancer developing within the diverticulum.	Weak
Carefully question and investigate patients for co-existing voiding dysfunction and UI.	Strong

Following appropriate counselling, address bothersome SUI at the time of urethral diverticulectomy with concomitant non-synthetic sling.	Weak
Counsel patients regarding the possibility of *de novo* or persistent LUTS including UI despite technically successful urethral diverticulectomy.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON NEURO-UROLOGY

(Limited text update March 2020)

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Introduction

Neuro-urological disorders can cause a variety of long-term complications; the most dangerous being damage of renal function. Treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

Terminology

The terminology used and the diagnostic procedures outlined in this document follow those published by the International Continence Society.

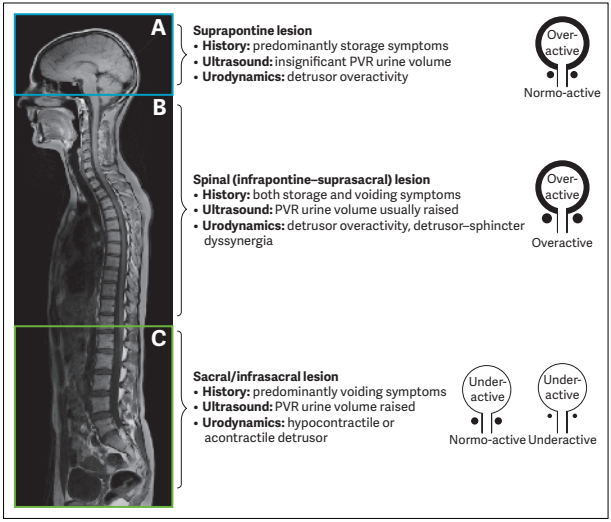
Risk factors and epidemiology

All central and peripheral neurological disorders carry a high risk of causing functional disturbances of the urinary tract.

Classification

The pattern of lower urinary tract (LUT) dysfunction following neurological disease is determined by the site and nature of the lesion. A very simple classification system, for use in daily clinical practice, to decide on the appropriate therapeutic approach is provided in Figure 1.

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease



The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. Panel A denotes the region above the pons, panel B the region between the pons and sacral cord and panel C the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. Figure adapted from Panicker et al. with permission from Elsevier. PVR = post-void residual.

Diagnostic evaluation

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders, even in the presence of normal neurological reflexes. Neuro-urological disorders

can be the presenting feature of neurological pathology and early intervention can prevent irreversible deterioration of the lower and upper urinary tract.

Patient assessment

Diagnosis of neuro-urological disorders should be based on a comprehensive assessment of neurological and non-neurological conditions. Initial assessment should include a detailed history, physical examination, and urinalysis.

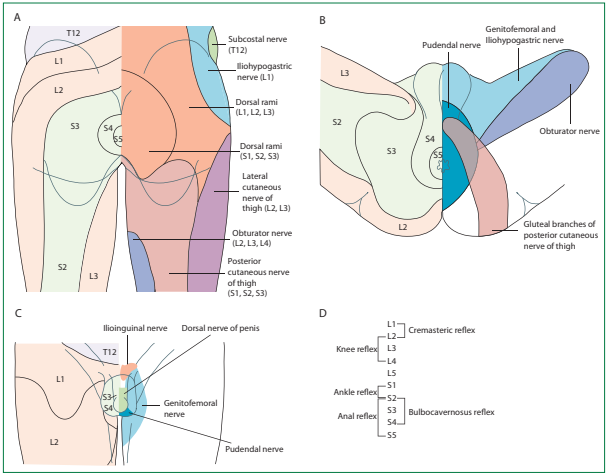
History

An extensive general and specific history is mandatory and should concentrate on past and present symptoms, disorders of the urinary tract as well as bowel, sexual and neurological function. Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria, fever) that warrant further investigation.

Physical examination

The neurological status should be described as completely as possible. All sensations and reflexes in the urogenital area must be tested, including detailed testing of the anal sphincter and pelvic floor functions (Figure 2). Availability of this clinical information is essential for the reliable interpretation of subsequent diagnostic investigations.

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes



The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum (B), male external genitalia (C) and root values of lower spinal cord reflexes (D). Figure adapted from Panicker et al., with parts A-C adapted from Standring, both with permission from Elsevier.

Recommendations for history taking and physical examination

Recommendations	Strength rating
History taking	
Take an extensive general history, concentrating on past and present symptoms.	Strong
Take a specific history for each of the four mentioned functions - urinary, bowel, sexual and neurological.	Strong
Pay special attention to the possible existence of alarm signs (e.g. pain, infection, haematuria, fever) that warrant further specific diagnosis.	Strong
Assess quality of life when evaluating and treating the neuro-urological patient.	Strong
Use available validated tools including the Qualiveen and I-QoL for urinary symptoms and the QoL-BM for bowel dysfunction in multiple sclerosis and spinal cord injury patients. In addition, generic (SF-36 or KHQ) questionnaires can be used.	Strong
Use MSISQ-15 and MSISQ-19 to evaluate sexual function in multiple sclerosis patients.	Strong
Physical examination	
Acknowledge individual patient disabilities when planning further investigations.	Strong
Describe the neurological status as completely as possible, sensations and reflexes in the urogenital area must all be tested.	Strong

Test the anal sphincter and pelvic floor functions.	Strong
Perform urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging.	Strong

I-QoL = Incontinence Quality of Life Instrument; OoL-BM = Quality of Life Bowel Management scoring tool; KHQ = King's Health Questionnaire; SF-36 = Short Form 36-item Health Survey Questionnaires; MSISQ 15/19 = Multiple Sclerosis Intimacy and Sexuality Questionnaire 15/19 question version.

Urodynamic tests

Bladder diaries are considered a valuable diagnostic tool in patients with neuro-urological disorders. A bladder diary should be recorded for at least two to three days. Uroflowmetry and ultrasound assessment of post-void residual should be repeated at least two or three times in patients able to void. Invasive urodynamic studies comprise mandatory assessment tools to determine the exact type of neuro-urological disorder. Video-urodynamics combines filling cystometry and pressure flow studies with radiological imaging. Currently, video-urodynamics is considered to provide the most comprehensive information for evaluating neuro-urological disorders.

Recommendations for urodynamics and uro-neurophysiology

Recommendations	Strength rating
Perform a urodynamic investigation to detect and specify lower urinary tract (dys-)function, use same session repeat measurement as it is crucial in clinical decision making.	Strong
Non-invasive testing is mandatory before invasive urodynamics is planned.	Strong
Use video-urodynamics for invasive urodynamics in neuro-urological patients. If this is not available, then perform a filling cystometry continuing into a pressure flow study.	Strong
Use a physiological filling rate and body-warm saline.	Strong

Treatment

The primary aims and their prioritisation when treating neuro-urological disorders are:

1. protection of the upper urinary tract;
2. improvement of urinary continence;
3. restoration of (parts of) LUT function;
4. improvement of the patient's quality of life (QoL).

Further considerations are the patient's disability, cost-effectiveness, technical complexity, and possible complications.

Conservative treatment

Assisted bladder emptying

Triggered reflex voiding is not recommended as there is a risk

of pathologically elevated bladder pressures. Only in the case of absence, or surgically reduced outlet obstruction, may it be an option.

Caution: bladder compression techniques to expel urine (Credé) and voiding by abdominal straining (Valsalva manoeuvre) create high pressures and are potentially hazardous; therefore, their use should be discouraged.

Rehabilitation

In selected patients, pelvic floor muscle exercises, pelvic floor electro-stimulation, and biofeedback might be beneficial.

External appliances

Social continence for the incontinent patient can be achieved using an appropriate method of urine collection.

Medical therapy

A single, optimal, medical therapy for patients with neuro-urological symptoms is not yet available. Muscarinic receptor antagonists are the first-line choice for treating neuro-urological disorders.

Recommendations for drug treatment

Recommendations	Strength rating
Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity.	Strong
Prescribe α-blockers to decrease bladder outlet resistance.	Strong
Do not prescribe parasympathomimetics for underactive detrusor.	Strong

Recommendations for minimal invasive treatment

Recommendations	Strength rating
Catheterisation	
Use intermittent catheterisation, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of intermittent catheterisation.	Strong
Avoid indwelling transurethral and suprapubic catheterisation whenever possible.	Strong
Intravesical drug treatment	
Offer intravesical oxybutynin to neurogenic patients with detrusor overactivity and poor tolerance to the oral route.	Strong
Botulinum toxin	
Use botulinum toxin injection in the detrusor to reduce neurogenic detrusor overactivity in multiple sclerosis or spinal cord injury patients if antimuscarinic therapy is ineffective.	Strong
Bladder neck incision is effective in a fibrotic bladder neck.	Strong

Surgical treatment

Recommendations for surgical treatment

Recommendations	Strength rating
Perform bladder augmentation in order to treat refractory neurogenic detrusor overactivity.	Strong
Place an autologous urethral sling in female patients with neurogenic stress urinary incontinence who are able to self-catheterise.	Strong
Insert an artificial urinary sphincter in male patients with neurogenic stress urinary incontinence.	Strong

Urinary tract infections (UTI)

Patients with neuro-urological disorders, especially those with spinal cord injury, may have other signs and symptoms in addition to, or instead of, traditional signs and symptoms of a UTI in able-bodied individuals.

Recommendations for the treatment of UTI

Recommendations	Strength rating
Do not screen for or treat asymptomatic bacteriuria in patients with neuro-urological disorders.	Strong
Avoid the use of long-term antibiotics for recurrent urinary tract infections (UTIs).	Strong

In patients with recurrent UTI, optimise treatment of neuro-urological symptoms and remove foreign bodies (e.g. stones, indwelling catheters) from the urinary tract.	Strong
Individualise UTI prophylaxis in patients with neuro-urological disorders as there is no optimal prophylactic measure available.	Strong

Sexual function and fertility

Patients with neurological disease often suffer from sexual dysfunction, which frequently impairs QoL.

Recommendations for erectile dysfunction and male fertility

Recommendations	Strength rating
Prescribe oral phosphodiesterase type 5 inhibitors as first-line medical treatment in neurogenic erectile dysfunction (ED).	Strong
Give intracavernous injections of vaso-active drugs (alone or in combination) as second-line medical treatment in neurogenic ED.	Strong
Offer mechanical devices such as vacuum devices and rings to patients with neurogenic ED.	Strong
Perform vibrostimulation and transrectal electroejaculation for sperm retrieval in men with spinal cord injury.	Strong

Perform microsurgical epididymal sperm aspiration, testicular sperm extraction and intracytoplasmic sperm injection after failed vibrostimulation and/or transrectal electroejaculation in men with spinal cord injury.	Strong
Counsel men with spinal cord injury at or above Th 6 and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	Strong

Recommendations on female sexuality and fertility

Recommendations	Strength rating
Do not offer medical therapy for the treatment of neurogenic sexual dysfunction in women.	Strong
Take a multidisciplinary approach, tailored to individual patient's needs and preferences, in the management of fertility, pregnancy and delivery in women with neurological diseases.	Strong

Follow-up

Neuro-urological disorders are often unstable and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary.

Recommendations for follow-up

Recommendations	Strength rating
Assess the upper urinary tract at regular intervals in high-risk patients.	Strong
Perform a physical examination and urine laboratory every year in high-risk patients.	Strong
Any significant clinical changes should instigate further, specialised, investigation.	Strong
Perform urodynamic investigation as a mandatory baseline diagnostic intervention in high-risk patients at regular intervals.	Strong

Summary

Neuro-urological disorders present a multifaceted pathology. Extensive investigation and a precise diagnosis are required before the clinician can initiate individualised therapy. Treatment must take into account the patient's medical and physical condition and expectations with regard to his/her future social, physical, and medical situation.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.

EAU GUIDELINES ON SEXUAL AND REPRODUCTIVE HEALTH

(Limited text update March 2021)

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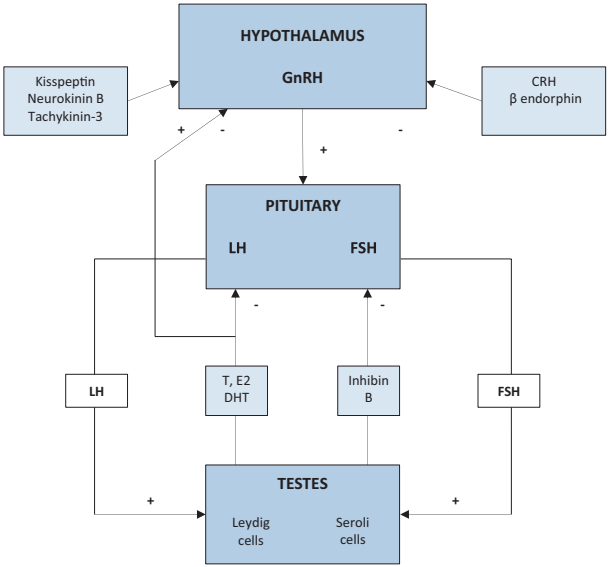
Introduction

The EAU Working Group has published guidelines on Male Sexual and Reproductive Health, further updating the 2020 guideline which combined the former guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

Male Hypogonadism

Male Hypogonadism, also known as Testosterone Deficiency, is a disorder associated with decreased functional activity of the testes, with decreased production of androgens and/or impaired sperm production. It may adversely affect multiple organ functions and quality of life (QoL). The prevalence increases with age.

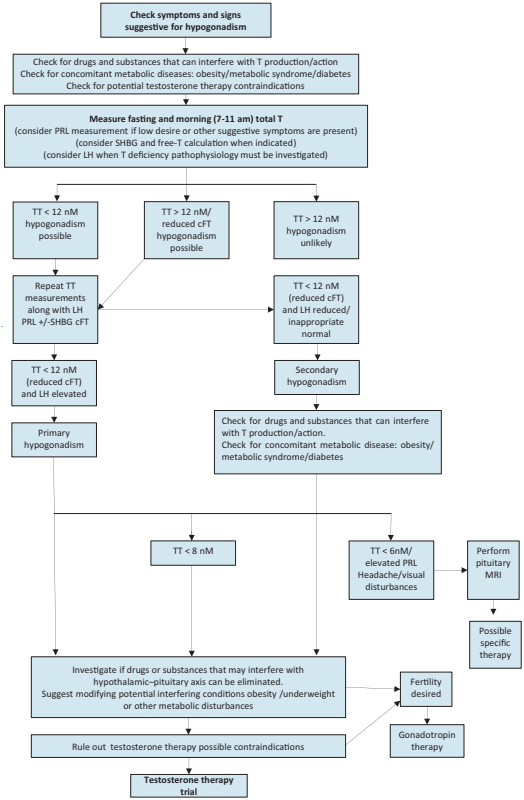
Figure 1: Physiology of testosterone production



GnRH = gonadotropin releasing hormone; LH = luteinising hormone; FSH = follicular stimulating hormone; T = testosterone; E2 = 7-β-estradiol; DHT = dehydroepiandrosterone; CRH = corticotrophin releasing hormone.

Diagnostic evaluation of Late-Onset Hypogonadism

Figure 2: Diagnostic evaluation of late-onset hypogonadism



TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = magnetic resonance imaging.

Recommendations for the diagnostic evaluation of late-onset hypogonadism

Recommendations	Strength rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Total testosterone must be measured in the morning (07.00 and 11.00 hours) and in the fasting state, with a reliable method.	Strong
Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy.	Strong
12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Consider sex hormone-binding globulin and free-testosterone calculation when indicated.	Strong
Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut-off to diagnose LOH.	Weak
Analyse luteinising hormone (LH) and follicle-stimulating hormone (FSH) serum levels to differentiate between primary and secondary hypogonadism.	Strong
Consider prolactin (PRL) measurement if low sexual desire (or other suggestive signs/symptoms) and low or low-normal testosterone is present.	Strong

Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak

Recommendations for screening men for late-onset hypogonadism

Recommendations	Strength rating
Screen for late-onset hypogonadism (LOH) (including in T2DM) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

Recommendations for disease management

Recommendations for testosterone therapy outcome	Strength rating
The use of testosterone therapy in eugonadal men is not indicated.	Strong
Use testosterone therapy as first-line treatment in patients with symptomatic hypogonadism and mild erectile dysfunction (ED).	Strong
Use combination of phosphodiesterase type 5 inhibitors (PDE5Is) and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak

Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong

Recommendations for LOH choice of treatment	**Strength rating**
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat co-morbidity before starting testosterone therapy.	Weak
Fully inform patients about expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, only with fully informed patients.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse effects.	Weak

Recommendations on risks factors in testosterone treatment	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., pre-operative PSA < 10 ng/mL; Gleason score < 7 (International Society for Urological Pathology grade 1); cT1-2a)* and treatment should start after at least 1 year follow-up with PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess for cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak

Exclude a family history of venous-thromboembolism before starting testosterone therapy.	Strong
Monitor testosterone, haematocrit at 3, 6 and 12 months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

**As for EAU risk groups for biochemical recurrence of localised or locally advanced prostate cancer (see EAU guidelines 2021 on prostate cancer).*

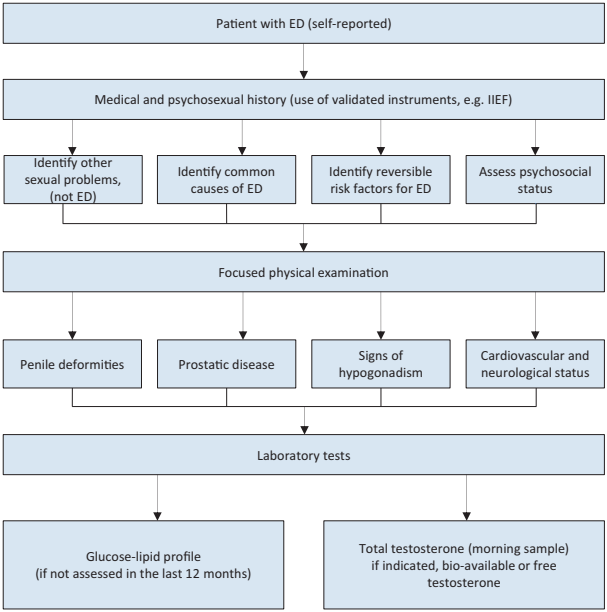
Erectile dysfunction

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Erectile dysfunction may affect physical and psychosocial health and may have a significant impact on the QoL of sufferers and their partners. There is increasing evidence that ED can also be an early manifestation of coronary artery and peripheral vascular disease; therefore, ED should not be regarded only as a QoL issue, but also as a potential warning sign of CVD.

Diagnostic evaluation

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with erectile dysfunction



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

Table 1: Cardiac risk stratification (based on 2nd Princeton Consensus)

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	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 or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardio-myopathies
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.

Table 2: Indications for specific diagnostic tests

Primary ED (not caused by acquired organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation surgery or angioplasty.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital penile 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 their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

Table 3: Specific diagnostic tests

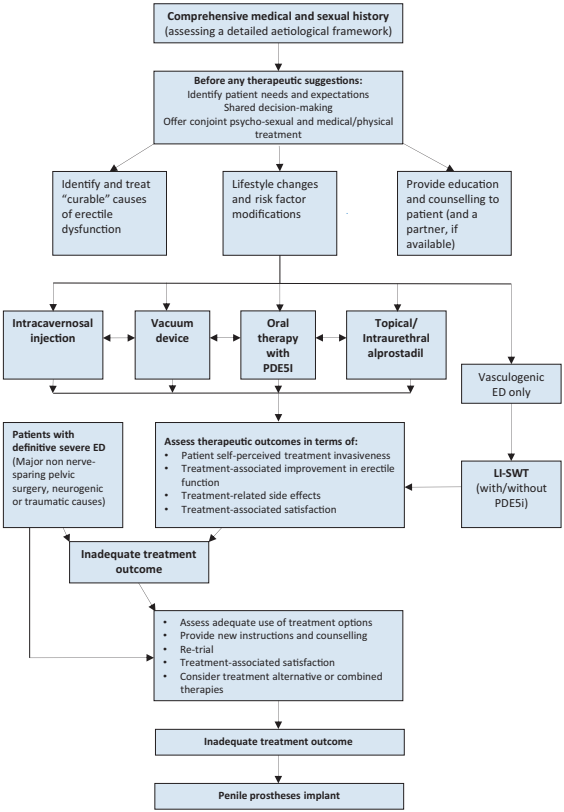
Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies: - Intracavernous vasoactive drug injection - Penile dynamic duplex ultrasonography - Penile dynamic infusion cavernosometry and cavernosography - Internal pudendal arteriography
Specialised endocrinological studies
Specialised psycho-diagnostic evaluation

Recommendations for the diagnosis of erectile dysfunction

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/ thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 2.	Strong

Disease management

Figure 4: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors ; LI-SWT = low-intensity shockwave treatment.

Table 4: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat erectile dysfunction*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200 mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bio-availability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.*

C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination halftime; AUC = area under curve or serum concentration time curve.

Table 5: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat erectile dysfunction*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon

Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Table 6: Penile prostheses models available on the market

Semi-rigid prostheses	**Inflatable prostheses**	
	Two-piece	**Three-piece**
AMS Tactra™ [Boston Scientific]	AMS Ambicor™ [Boston Scientific]	Titan™ [Coloplast]
Genesis™ [Coloplast]		Titan OTR NB™ (Narrow base) [Coloplast]
		Titan Zero Degree™
Tube™ [Promedon]		AMS 700 CX™ [Boston Scientific]
ZSI 100™ [Zephyr]		AMS 700 LGX™ [Boston Scientific]
Virilis II™ [Subrini]		AMS 700 CXR™ [Boston Scientific]
		ZSI 475™ [Zephyr]

Recommendations for the treatment of erectile dysfunction

Recommendations	Strength rating
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to phosphodiesterase type 5 inhibitors (PDE5Is).	Weak
Use Cognitive Behaviour Therapy as a psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than erectile dysfunction (ED), including libido reduction, changes in orgasm, anejaculation, Peyronie's-like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to, or at the same time, as initiating ED treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use PDE5Is as first-line therapeutic option.	Strong
Use topical/intraurethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy.	Weak

Use topical/intraurethral alprostadil as an alternative first-line therapy, in well-informed patients, who do not wish to have intracavernous injections or in patients who prefer a less-invasive therapy.	Weak
Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices (VEDs) as first-line therapy in well-informed patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use implantation of a penile prosthesis if other treatments fail or based upon patient preference.	Strong
Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/pelvic surgery and other curative treatments for prostate cancer.	Weak

Disorders of ejaculation

Introduction

Ejaculation is a complex physiological process, which is composed of emission and expulsion and is mediated by interwoven neurological and hormonal pathways. Any condition that interferes with these pathways may cause a wide range of ejaculatory disorders.

Table 7: Spectrum of ejaculatory disorders

Premature ejaculation
Retarded or delayed ejaculation
Anejaculation
Painful ejaculation
Retrograde ejaculation
Anorgasmia
Haemospermia

Diagnostic evaluation

Recommendations for the diagnostic evaluation of premature ejaculation

Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong

Use of stopwatch-measured IELT is not compulsory in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

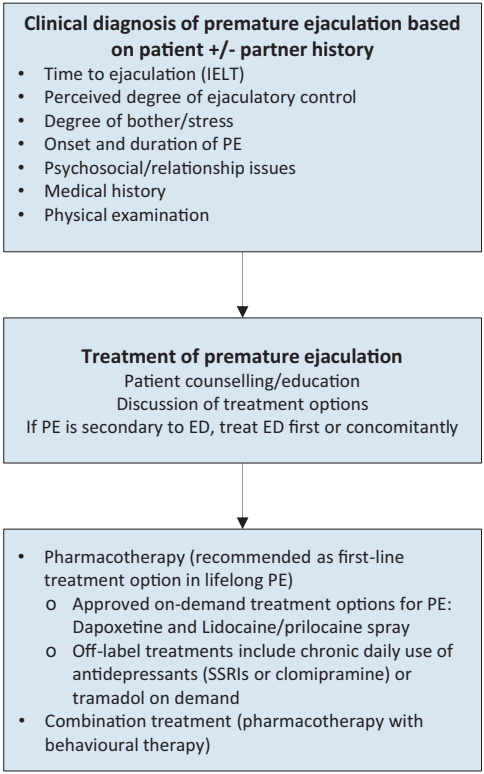
Disease management

Recommendations for the treatment of premature ejaculation

Recommendations	Strength rating
Treat erectile dysfunction (ED), and other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on-demand as a weak alternative to SSRIs.	Weak

Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

Figure 5: Management of premature ejaculation*



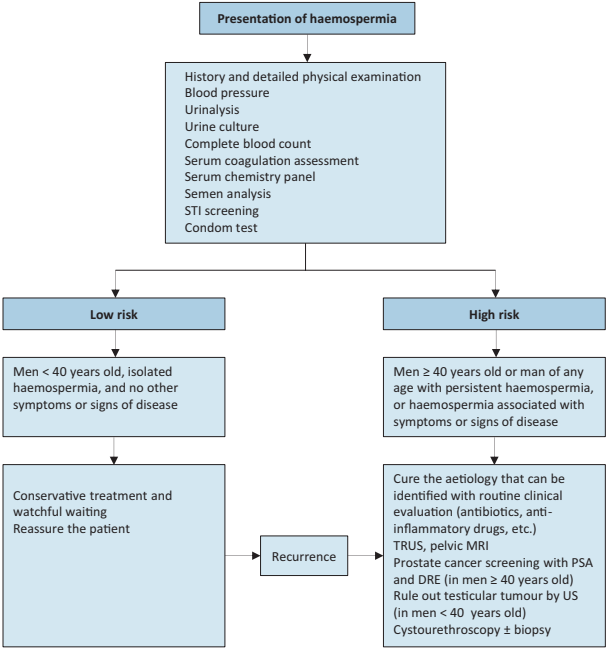
*Adapted from Lue *et al*. 2004.

ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

Recommendations for the management of recurrent haemospermia

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Men aged ≥ 40 years with persistent haemospermia should be screened for prostate cancer.	Weak
Consider non-invasive imaging modalities (TRUS and MRI) in men aged ≥ 40 years or men of any age with persistent or refractory haemospermia.	Weak
Consider invasive methods such as cystoscopy and vesiculoscopy when the non-invasive methods are inconclusive.	Weak

Figure 6: Management algorithm for haemospermia



STI = sexually transmitted infections; PSA = prostate-specific antigen; DRE = digital rectal examination; US = ultrasonography; TRUS = transrectal ultrasonography; MRI = magnetic resonance imaging.

Low Sexual Desire

Introduction

It has been always a challenge to define sexual desire because of its complex nature and it can be conceptualised in many different ways. According to the ICD-10, lack or loss of sexual desire should be the principal problem and no other sexual problems accompanying it such as erectile dysfunction (ED). In the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), male hypoactive sexual desire disorder was defined as *"the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity"*. The judgment of deficiency is made by the clinician, taking into account other factors that may affect sexual function, such as age and socio-cultural factors in an individual's life. According to fourth International Consultation on Sexual Medicine (ICSM-IV), the definition of male hypoactive sexual desire disorder was proposed as a *"persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)"*.

Table 8: The list of common causes of low sexual desire in men

Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome
Renal failure
Coronary disease and heart failure

Ageing
HIV infection
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

Psychological intervention

Findings on treatment efficacy for psychological intervention are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for low sexual desire (LSD) in men. Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the aging couple (thus including LSD) as a whole rather than treating the individual patient.

Disease management

Recommendations for the treatment of low sexual desire

Recommendations	Strength rating
Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires.	Weak
Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction.	Weak
Perform laboratory tests to rule out endocrine disorders.	Strong

Modulate chronic therapies which can negatively impact toward sexual desire.	Weak
Provide testosterone therapy if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

Penile curvature

Introduction

Congenital penile curvature (CPC) results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of the cases curvature is ventral but can be lateral and rarely dorsal.

Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish the diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and a severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernosal injection of vasoactive drugs) is useful to document curvature and exclude other pathologies.

Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Surgical treatments for CPC generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit's procedure with excision of an ellipse of the tunica albuginea is the optimum surgical treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies. Most of the time, dissection and mobilisation of the penile

dorsal neurovascular bundle are required in order to avoid loss of sensation and ischaemia to the glans penis.

Recommendation for the treatment of congenital penile curvature	Strength rating
Use plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction, although there is currently no optimum surgical technique.	Strong

Peyronie's disease

An insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease. Abnormal wound healing leads to the remodelling of connective tissue into a fibrotic plaque. Penile plaque formation can result in curvature which, if severe, may impair penetrative sexual intercourse. The most commonly associated comorbidity and risk factors are diabetes, hypertension, dyslipidemia, ischaemic cardiopathy, autoimmune diseases, ED, smoking, excessive consumption of alcohol, low testosterone and pelvic surgery (e.g., radical prostatectomy).

Two phases of the disease can be distinguished. The first is the active inflammatory phase, which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and development of the penile deformity.

Diagnostic evaluation

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD.

Recommendations for the diagnostic evaluation of Peyronie's disease

Recommendations	Strength rating
Take a medical and sexual history of patients with Peyronie's disease (PD), include duration of the disease, pain on erection, penile deformity, difficulty in vaginal/anal intromission due to disabling deformity and erectile dysfunction (ED).	Strong
Take a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g., Dupuytren's contracture, Ledderhose disease) in patients with PD.	Strong
Use the intracavernous injection (IC) method in the diagnostic work-up of PD to provide an objective assessment of penile curvature with an erection.	Weak
Use the PD specific questionnaire especially in clinical trials, but mainstream usage in daily clinical practice is not mandatory.	Weak

Do not use ultrasound (US), computed tomography or magnetic resonance imaging to assess plaque size and deformity in everyday clinical practice.	Weak
Use penile Doppler US in the case of diagnostic evaluation of ED, to evaluate penile haemodynamic and vascular anatomy, and to assess location and calcification of plaques, especially prior to surgery.	Weak

Disease management

Non-operative treatment

Table 9: Conservative treatments for Peyronie's disease

Oral treatments
Non-steroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase
Interferon α2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Extracorporeal shockwave treatment

Other
Traction devices
Multimodal treatment

Recommendations for the non-operative treatment of Peyronie's disease

Recommendations	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Discuss with patients all the available treatment options and expected results before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifylline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Nonsteroidal anti-inflammatory drugs can be used to treat penile pain in the acute phase of PD.	Strong
Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD.	Weak
Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30º seeking a minimal invasive procedure.	Strong

Intralesional therapy with collagenase *clostridium histolyticum* (CCH) may be offered in patients with stable PD and dorsal or lateral curvature > 30º, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

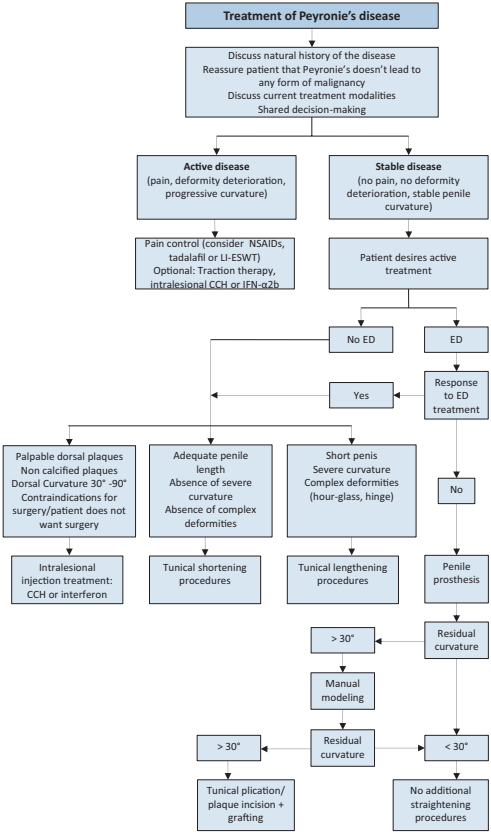
Surgical treatment

Recommendations for the surgical treatment of Peyronie's disease

Recommendations	Strength rating
Perform surgery only when Peyronie's disease (PD) has been 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.	Strong

Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, non-severe curvature and absence of complex deformities (hourglass or hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hourglass or hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.	Weak
Use the sliding techniques with caution, as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional procedure (modelling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

Figure 7 : Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT= low-intensity extracorporeal shockwave treatment; US = ultrasound; CCH = collagenase clostridium histolyticum.

Priapism

Introduction

Priapism is a persistent erection in the absence of sexual stimulation that fails to subside. It can be divided into ischaemic, non-ischaemic and stuttering priapism.

Ischaemic (low-flow or veno-occlusive) priapism

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow. Ischaemic priapism is the most common subtype of priapism, accounting for > 95% of all episodes.

Diagnostic evaluation

Table 10: Key points when taking the history of priapism

Duration of erection
Presence and severity of pain
Previous episodes of priapism and methods of treatment
Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements
Medications and recreational drug use
Sickle cell disease, haemoglobinopathies, hypercoagulable states, vessel vasculitis
Trauma to the pelvis, perineum or penis

Table 11: Key findings in priapism

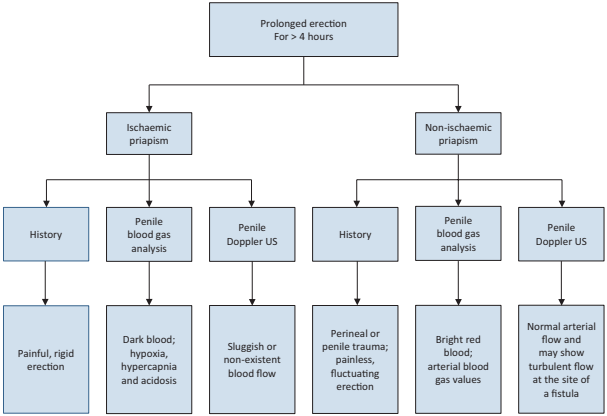
	Ischaemic priapism	Non-ischaemic priapism
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Haematological abnormalities	Sometimes	Seldom
Recent intracavernosal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Typically

Table 12: Typical blood gas values

Source	pO_2 (mmHg)	pCO_2 (mmHg)	pH
Normal arterial blood (room air) (similar values are found in arterial priapism)	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen

Figure 8: Differential diagnosis of priapism



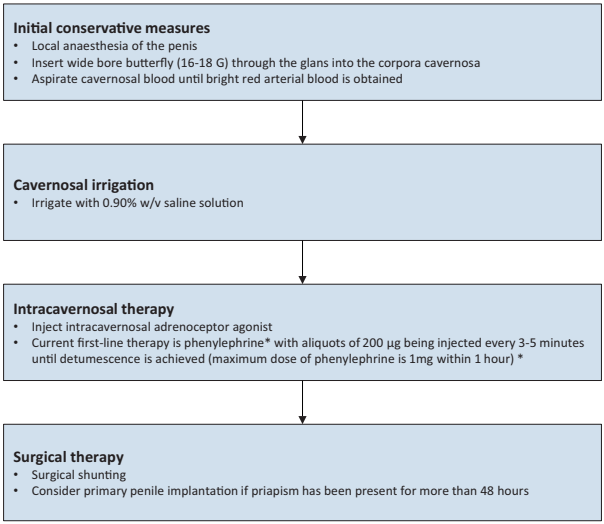
Recommendations for the diagnosis of ischaemic priapism	Strength rating
Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong

For laboratory testing, include complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile. Direct further laboratory testing should be performed depending upon history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex US of the penis and perineum before aspiration to differentiate between ischaemic and non-ischaemic priapism.	Strong
In cases of prolonged ischaemic priapism or refractory priapism, magnetic resonance imaging of the penis may be used as an adjunct to predict smooth muscle viability.	Weak
Perform selected pudendal arteriogram when embolisation is planned for the management of non-ischaemic priapism.	Strong

Disease management of ischaemic priapism

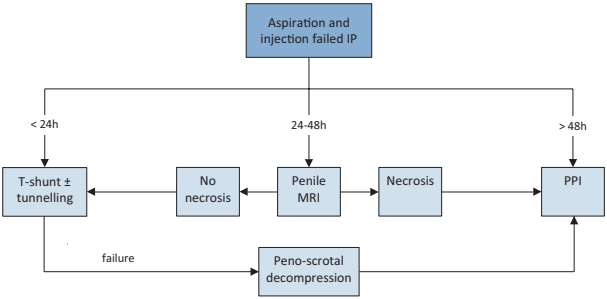
The treatment is sequential and physicians should move on to the next stage if treatment fails.

Figure 9: Medical and surgical management of ischaemic priapism



(*) Dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease. Monitoring of pulse and blood pressure is advisable in all patients during administration and for 1 hour afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

Figure 10: Algorithm on surgical management of priapism



Recommendations for the treatment of ischaemic priapism	Strength rating
Start management of ischaemic priapism as early as possible (within 4 to 6 hours) and follow a stepwise approach.	Strong
First, decompress the corpus cavernosum by penile aspiration and washout until fresh red blood is obtained.	Strong
In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step.	Strong
In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug.	Strong

In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps before considering surgical intervention.	Strong
Treat ischaemic priapism associated with sickle cell disease in the same fashion as idiopathic ischaemic priapism. Provide other supportive measures (intravenous hydration, oxygen administration with alkalisation with bicarbonate, blood exchange transfusions), but do not delay initial treatment to the penis.	Strong
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed.	Strong
Perform distal shunt surgical procedures first and combine them with tunnelling if necessary.	Weak
Proximal procedures may be used in cases of distal shunt failure (< 48 hours) or in patients who do not wish to proceed with immediate penile implant insertion.	Weak
Peri- and post-operative anticoagulation may decrease priapism recurrence.	Weak
A penile prosthesis may be preferred over proximal shunting particularly in delayed > 48 hours) or refractory priapism	Weak
Implantation of a prosthesis may be considered in delayed presentation (> 48 hours) and in those cases refractory to injection therapy and distal shunting.	Weak

If a shunt has been performed, then implantation of a penile prosthesis should be delayed to minimise the risk of infection and erosion of the implant.	Strong
The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience and availability and cost of the equipment. If malleable penile prosthesis is implanted it can be later exchanged to an inflatable penile implant.	Strong
Patients must be fully counselled regarding the risks and benefits of implant insertion in every case of delayed presentation of refractory priapism.	Weak

Priapism in special situations

Stuttering (recurrent or intermittent) priapism

Stuttering priapism is similar to ischaemic priapism in that it is low-flow and ischaemic and, if left untreated, can result in significant penile fibrosis, with SCD being the most common cause.

Recommendations for treatment of stuttering priapism	Strength rating
Manage each acute episode similar to that for ischaemic priapism.	Strong
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or antiandrogens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	Weak

Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state.	Weak
Use digoxin, α-adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with frequent and uncontrolled relapses.	Weak
Use intracavernous self-injections of sympathomimetic drugs at home for treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	Weak

Non-ischaemic (high-flow or arterial) priapism

Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases.

Diagnosis evaluation

A comprehensive history is also mandatory in the diagnosis of non-ischaemic priapism and follows the same principles as described in Table 10.

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis, which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a neurological examination if neurogenic non-ischaemic priapism is suspected.	Strong

For laboratory testing, include complete blood count, with white blood cell differential, and coagulation profile.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum for differentiation between ischaemic and non-ischaemic priapism.	Strong
Perform selected pudendal arteriography when embolisation is planned for non-ischaemic priapism.	Strong

Disease management

Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases.

Recommendations for the treatment of non-ischaemic priapism	**Strength rating**
Because non-ischaemic priapism is not an emergency, perform definitive management at the discretion of the treating physician.	Weak
Manage conservatively with the use of site-specific perineal compression as the first step. Consider androgen deprivation therapy only in adults.	Weak
Perform selective arterial embolisation when conservative management has failed.	Strong
Perform first selective arterial embolisation using temporary material.	Weak

Repeat the procedure with temporary or permanent material for recurrent non-ischaemic priapism following selective arterial embolisation.	Weak
Reserve selective surgical ligation of a fistula as a final treatment option when repeated arterial embolisations have failed.	Weak

Male infertility

Introduction

'Infertility is the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy in one year' (World Health Organization 2000).

Diagnostic evaluation

A focused evaluation of the male patient must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to World Health Organization (WHO) reference values for human semen characteristics, and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and findings on semen analysis.

Semen analysis

A comprehensive andrological examination is always indicated if the semen analysis shows abnormalities when compared to reference values (Table 13).

Table 13: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6/ejaculate)	39 (33-46)
Sperm concentration (10^6/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/mL)	< 1.0
Optional investigations	
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

CIs = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

Recommendations for the diagnostic work-up of male infertility

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention).	Strong
A complete medical history, physical examination and semen analysis are the essential components of male infertility evaluation.	Strong
Prader's orchidometer-derived testicular volume is a reliable surrogate of ultrasound (US)-measured testicular volume in everyday clinical practice.	Weak
Perform semen analyses according to the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) indications and reference criteria.	Strong
Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
Include counselling for infertile men or men with abnormal semen parameters of the associated health risks.	Weak

In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle Stimulating Hormone/Luteinising Hormone.	Weak
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Do not test for Y-chromosome micro-deletions in men with pure obstructive azoospermia as spermatogenesis will be normal.	Strong
Y-chromosome microdeletion testing may be offered in men with sperm concentrations of < 5 million sperm/mL, but must be mandatory in men with sperm concentrations of ≤ 1 million sperm/mL.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intra-cytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters.	Strong
Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery.	Strong

In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for cystic fibrosis transmembrane conductance regulator gene mutations, which should include common point mutations and the 5T allele.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For men with Klinefelter syndrome, offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility.	Strong
Perform scrotal ultrasound in patients with infertility, as there is a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testicular biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak

Perform transrectal ultrasound if a partial or complete distal obstruction is suspected.	Strong
Consider imaging for renal abnormalities in men with structural abnormalities of the vas deferens and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.	Strong

Special Conditions and Relevant Clinical Entities

Crytorchidism

Cryptorchidism is the most common congenital abnormality of the male genitalia; at one year of age nearly 1% of all full-term male infants have cryptorchidism. Approximately 30% of undescended testes are non-palpable and may be located within the abdominal cavity.

Recommendations	Strength rating
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*).	Strong
Men with unilateral undescended testis and normal hormonal function/spermato-genesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible.	Weak

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 sub-fertile men. Overall, sperm, cryopreservation is considered standard practice in all patients with cancer and not only those with testicular cancer. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery which may impair spermatogenesis or ejaculation (i.e., chemotherapy; radiation therapy; retroperitoneal surgery). Men with TGCT have decreased semen quality, even before cancer treatment.

Recommendations	Strength rating
Men with testicular microcalcification (TM) should learn to perform self-examination even without additional risk factors, as this may result in early detection of testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound (US), measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (< 12 mL), history of undescended testes and TGCT.	Weak

If there are suspicious findings on physical examination or US in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multidisciplinary meeting and discussion with the patient.	Strong
Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular risk. Men should be managed in a multi-disciplinary team setting with a dedicated late-effects clinic.	Weak
Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak
Men with testicular cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction (onco-TESE) at the time of radical orchidectomy.	Weak

Varicocele

Varicocele is a common genital abnormality, which may be associated with the following andrological conditions:

- male subfertility;
- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- hypogonadism.

Recommendations	Strength rating
Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele.	Weak
Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation.	Weak

Male accessory gland infections and infertility

Infections of the male urogenital tract are potentially curable causes of male infertility. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs). Semen analysis clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome.

Recommendations	Strength rating
Treating male accessory gland infections may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	Weak
Data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocyto-spermia improve fertility outcomes.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

Non-Invasive Male Infertility Management

Idiopathic male infertility and OATS

Oligo-astheno-teratozoospermia (OAT) is a clinical condition, with a reduced number of spermatozoa in the ejaculate, which is also characterised by a reduced motility and morphology; often referred to as OAT syndrome (OATS).

Recommendations	Strength rating
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction can improve sperm quality and the chances of conception.	Weak

No clear recommendation can be made for treatment of patients with idiopathic infertility using antioxidants, although antioxidant use may improve semen parameters.	Weak
No conclusive recommendations on the use of selective oestrogen receptor modulators in men with idiopathic infertility can be drawn.	Weak
No conclusive recommendations on the use of either steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility can be drawn, even before testis surgery.	Weak

Hormonal therapy

Recommendations	Strength rating
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH) (recombinant FSH; highly purified FSH) or pulsed Gonadotropin-releasing hormone (GnRH) via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong

The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given on the use of high-dose FSH in men with idiopathic infertility and prior (m)TESE and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong
Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
In the presence of hyperprolactinaemia, dopamine agonist therapy may improve spermatogenesis.	Weak

Invasive Male Infertility Management

Obstructive azoospermia

Obstructive azoospermia (OA) is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction. Obstructive azoospermia is less common than Non-obstructive azoospermia (NOA) and occurs in 20-40% of men with azoospermia. Men with OA usually have a normal FSH, testes of normal size and epididymal enlargement or distension. Of clinical relevance, men with late maturation

arrest may present with normal gonadotrophins and testis size and may be only be distinguished from OA at the time of surgical exploration. The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

Recommendations	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA and TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong

Non-obstructive azoospermia

Non-obstructive azoospermia (NOA) is defined as the absence of sperm in semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed on at least two consecutives semen analyses. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

Recommendations	Strength rating
Patients with non-obstructive azoospermia (NOA) should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated co-morbidity. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.	Strong
Surgery for sperm retrieval can be performed in men who are candidates for assisted reproductive technology (i.e., ICSI). In patients with complete AZFa and AZFb microdeletions, surgery is contraindicated since the chance of sperm retrieval is zero.	Strong
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to cTESE and mTESE.	Weak
Fine needle aspiration as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Conventional TESE (cTESE) and microdissection TESE (mTESE) are the techniques of choice for retrieving sperm in patients with NOA.	Weak

No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.	Weak
No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone (FSH); highly purified FSH; human chorionic gonadotrophin (hCG); aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE.	Weak

This short booklet is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON UROLOGICAL INFECTIONS

(Limited text update March 2021)

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Introduction

The European Association of Urology (EAU) Urological Infections Guidelines Panel has compiled these clinical guidelines to provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urological tract infections (UTIs). These guidelines also aim to address the important public health aspects of infection control and antimicrobial stewardship.

Important notice:
On March 11, 2019 the European Commission implemented stringent regulatory conditions regarding the use of fluoroquinolones due to their disabling and potentially long-lasting side effects. This legally binding decision is applicable in all EU countries. National authorities have been urged to enforce this ruling and to take all appropriate measures to promote the correct use of this class of antibiotics.

Antimicrobial Stewardship

Stewardship programs have two main sets of actions. The first set mandates use of recommended care at the patient level conforming to guidelines. The second set describes strategies to achieve adherence to the mandated guidance.

These include persuasive actions such as education and feedback together with restricting availability linked to local formularies. The important components of antimicrobial stewardship programs are:

- regular training of staff in best use of antimicrobial agents;
- adherence to local, national or international guidelines;
- regular ward visits and consultation with infectious diseases physicians and clinical microbiologists;
- audit of adherence and treatment outcomes;
- regular monitoring and feedback to prescribers of their performance and local pathogen resistance profiles.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria in an individual without urinary tract symptoms is defined by a mid-stream sample of urine showing bacterial growth ≥ 10^5 cfu/mL in two consecutive samples in women and in one single sample in men.

Recommendations	Strength rating
Do not screen or treat asymptomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with renal transplants; • patients prior to arthoplasty surgeries; • patients with recurrent urinary tract infections.	Strong

Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	Strong
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.	Weak

Uncomplicated Cystitis

Uncomplicated cystitis is defined as acute, sporadic or recurrent cystitis limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.

Recommendations for the diagnostic evaluation of uncomplicated cystitis	**Strength rating**
Diagnose uncomplicated cystitis in women who have no other risk factors for complicated urinary tract infections based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge or irritation.	Strong
Use urine dipstick testing for diagnosis of acute uncomplicated cystitis.	Weak
Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within four weeks after the completion of treatment; • women who present with atypical symptoms; • pregnant women.	Strong

In uncomplicated cystitis a fluoroquinolone should only be used when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Recommendations for antimicrobial therapy for uncomplicated cystitis	Strength rating
Prescribe fosfomycin trometamol, pivmecillinam or nitrofurantoin as first-line treatment for uncomplicated cystitis in women.	Strong
Do not use aminopenicillins or fluoroquinolones to treat uncomplicated cystitis.	Strong

Table 1: Suggested regimens for antimicrobial therapy in uncomplicated cystitis

Antimicrobial	Daily dose	Duration of therapy	Comments
First-line women			
Fosfomycin trometamol	3 g SD	1 day	Recommended only in women with uncomplicated cystitis
Nitrofurantoin macrocrystal	50-100 mg four times a day	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg b.i.d	5 days	
Nitrofurantoin macrocrystal prolonged release	100 mg b.i.d	5 days	
Pivmecillinam	400 mg t.i.d	3-5 days	

Alternatives			
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable
If the local resistance pattern for E. coli is < 20%			
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy
Treatment in men			
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.

SD = single dose; b.i.d = twice daily; t.i.d = three times daily.

Recurrent UTIs

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.

Recommendations for the diagnostic evaluation and treatment of rUTIs	Strength rating
Diagnose recurrent UTI by urine culture.	Strong
Do not perform an extensive routine workup (e.g cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors.	Weak
Advise patients on behavioural modifications which might reduce the risk of recurrent UTI.	Weak
Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.	Weak
Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	Strong
Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects.	Strong
For patients with good compliance self-administered short term antimicrobial therapy should be considered.	Strong

Uncomplicated Pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known relevant urological abnormalities or comorbidities.

Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis	Strength rating
Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	Strong
Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong

Recommendations for the treatment of uncomplicated pyelonephritis	Strength rating
Treat patients with uncomplicated pyelonephritis not requiring hospitalisation with short course fluoroquinolones as first-line treatment.	Strong
Treat patients with uncomplicated pyelonephritis requiring hospitalisation with an intravenous antimicrobial regimen initially.	Strong
Switch patients initially treated with parenteral therapy, who improve clinically and can tolerate oral fluids, to oral antimicrobial therapy.	Strong
Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis.	Strong

Table 2: Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis			
Antimicrobial	**Daily dose**	**Duration of therapy**	**Comments**
Ciprofloxacin	500-750 mg b.i.d	7 days	Fluoroquinolone resistance should be less than 10%.
Levofloxacin	750 mg q.d	5 days	
Trimethoprim sulphamethoxazol	160/800 mg b.i.d	14 days	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	
Ceftibuten	400 mg q.d	10 days	

b.i.d = twice daily; q.d = every day.

Table 3: Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis		
Antimicrobials	**Daily dose**	**Comments**
First-line treatment		
Ciprofloxacin	400 mg b.i.d	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1-2 g q.d	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1-2 g b.i.d	Lower dose studied, but higher dose recommended.
Piperacillin/ tazobactam	2.5-4.5 g t.i.d	
Gentamicin	5 mg/kg q.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	

Last-line alternatives		
Imipenem/ cilastatin	0.5 g t.i.d	Consider only in patients with early culture results indicating the presence of multi-drug resistant organisms.
Meropenem	1 g t.i.d	
Ceftolozane/ tazobactam	1.5 g t.i.d	
Ceftazidime/ avibactam	2.5 g t.i.d	
Cefiderocol	2 g t.i.d	
Meropenem-vaborbactam	2 g t.i.d	
Plazomicin	15 mg/kg o.d	

b.i.d = twice daily; t.i.d = three times daily; q.d = every day; o.d = once daily.

Complicated UTIs

A complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection.

Recommendations for the treatment of complicated UTIs	Strength rating
Use the combination of; • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms.	Strong
Only use ciprofloxacin provided that the local resistance percentages are < 10% when; • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials.	Strong
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months.	Strong
Manage any urological abnormality and/or underlying complicating factors.	Strong

Catheter-associated UTIs

Catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours.

Recommendations for diagnostic evaluation of CA-UTI	Strength rating
Do not carry out routine urine culture in asymptomatic catheterised patients.	Strong
Do not use pyuria as sole indicator for catheter-associated UTI.	Strong
Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	Strong

Recommendations disease management and prevention of CA-UTI	Strength rating
Treat symptomatic catheter-associated-UTI according to the recommendations for complicated UTI.	Strong
Take a urine culture prior to initiating anti-microbial therapy in catheterised patients in whom the catheter has been removed.	Strong
Do not treat catheter-associated asymptomatic bacteriuria in general.	Strong
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	Strong
Replace or remove the indwelling catheter before starting antimicrobial therapy.	Strong
Do not apply topical antiseptics or anti-microbials to the catheter, urethra or meatus.	Strong
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	Strong

Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal.	Weak
The duration of catheterisation should be minimal.	Strong
Use hydrophilic coated catheters to reduce CA-UTI.	Strong
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal or in patients performing intermittent self-catheterisation	Weak

Urosepsis

Urosepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs.

Recommendations for the diagnosis and treatment of urosepsis	**Strength rating**
Perform the quickSOFA score to identify patients with potential sepsis.	Strong
Take a urine culture and two sets of blood cultures before starting antimicrobial treatment.	Strong
Administer parenteral high dose broad spectrum antimicrobials within the first hour after clinical assumption of sepsis.	Strong
Adapt initial empiric antimicrobial therapy on the basis of culture results.	Strong
Initiate source control including removal of foreign bodies, decompression of obstruction and drainage of abscesses in the urinary tract.	Strong

Provide immediate adequate life-support measures.	Strong

Table 4: Suggested regimens for antimicrobial therapy for urosepsis

Antimicrobials	Daily dose	Duration of therapy
Cefotaxime	2 g t.i.d	7-10 days Longer courses are appropriate in patients who have a slow clinical response
Ceftazidime	1-2 g t.i.d	
Ceftriaxone	1-2 g q.d	
Cefepime	2 g b.i.d	
Piperacillin/tazobactam	4.5 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Gentamicin*	5 mg/kg q.d	
Amikacin*	15 mg/kg q.d	
Ertapenem	1 g q.d	
Imipenem/cilastatin	0.5 g t.i.d	
Meropenem	1 g t.i.d	

** Not studied as monotherapy in urosepsis*
b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

Urethritis

Inflammation of the urethra presents usually with lower urinary tract symptoms and must be distinguished from other infections of the lower urinary tract. The following recommendations are based on a review of several European national guidelines and are aligned with the CDC's guidelines on sexual transmitted diseases.

Recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis	Strength rating
Perform a Gram stain of urethral discharge or a urethral smear to preliminarily diagnose gonococcal urethritis.	Strong
Perform a validated nucleic acid amplification test (NAAT) on a first-void urine sample or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections.	Strong
Delay treatment until the results of the NAATs are available to guide treatment choice in patients with mild symptoms.	Strong
Perform a urethral swab culture, prior to initiation of treatment, in patients with a positive NAAT for gonorrhoea to assess the antimicrobial resistance profile of the infective strain.	Strong
Use a pathogen directed treatment based on local resistance data.	Strong
Sexual partners should be treated maintaining patient confidentiality.	Strong

Table 5: Suggested regimens for antimicrobial therapy for urethritis

Pathogen	Antimicrobial	Alternative regimens
Gonococcal Infection:	Ceftriaxone: 1 g i.m. or i.v., SD Azithromycin: 1-1 g p.o., SD	• Cefixime 400 mg p.o., SD plus Azithromycin 1 g p.o., SD In case of cephalosporin allergy: • Gentamicin 240 mg i.m SD plus Azithromycin 2 g p.o., SD • Gemifloxacin 320 mg p.o., SD plus Azithromycin 2 g p.o., SD • Spectinomycin 2 g i.m., SD • Fosfomycin trometamol 3 g p.o., on days 1, 3 and 5 In case of azithromycin allergy, in combination with ceftriaxone or cefixime: • Doxycycline 100 mg b.i.d, p.o., 7 days
Non-Gonococcal infection (non-identified pathogen)	Doxycycline: 100 mg b.i.d, p.o., 7-10 days	Azithromycin 500 mg p.o., day 1, 250 mg p.o., 4 days

Chlamydia trachomatis	Azithromycin: 1.0-1.5 g p.o., SD OR Doxycycline: 100 mg b.i.d, p.o., for 7 days	• Levofloxacin 500 mg p.o., q.d., 7 days • Ofloxacin 200 mg p.o., b.i.d., 7 days
Mycoplasma genitalium	Azithromycin: 500 mg p.o., day 1, 250 mg p.o., 4 days	In case of macrolide resistance: • Moxifloxacin 400 mg q.d., 7-14 days
Ureaplasma urealyticum	Doxycycline: 100 mg b.i.d, p.o., 7 days	Azithromycin 1.0-1.5 g p.o., SD
Trichomonas vaginalis	Metronidazole: 2 g p.o., SD Tinidazole: 2 g p.o., SD	Metronidazole 500 mg p.o., b.i.d., 7 days
Persistent non-gonococcal urethritis		
After first-line doxycycline	Azithromycin: 500 mg p.o., day 1, 250 mg p.o., 4 days plus Metronidazole: 400 mg b.i.d. p.o., 5 days	If macrolide resistant *M. genitalium* is detected moxifloxacin should be substituted for azithromycin
After first-line azithromycin	Moxifloxacin: 400 mg p.o. q.d., 7–14 days plus Metronidazole: 400 mg b.i.d. p.o., 5 days	

SD = single dose; b.i.d = twice daily; q.d = everyday; p.o. = orally; i.m. = intramuscular; i.v. = intravenous.

Bacterial Prostatitis

Bacterial prostatitis is a clinical condition caused by bacterial pathogens. It is recommended that urologists use the classification suggested by the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health, in which bacterial prostatitis, with confirmed or suspected infection, is distinguished from chronic pelvic pain syndrome.

Recommendations for the diagnosis of bacterial prostatitis	Strength rating
Do not perform prostatic massage in acute bacterial prostatitis (ABP).	Strong
Take a mid-stream urine dipstick to check nitrite and leukocytes in patients with clinical suspicion of ABP.	Weak
Take a mid-stream urine culture in patients with ABP symptoms to guide diagnosis and tailor antibiotic treatment.	Weak
Take a blood culture and a total blood count in patients presenting with ABP.	Weak
Perform accurate microbiological evaluation for atypical pathogens such as *Chlamydia trachomatis* or Mycoplasmata in patients with chronic bacterial prostatitis (CBP).	Weak
Perform the Meares and Stamey 2- or 4-glass test in patients with CBP.	Strong
Perform transrectal ultrasound in selected cases to rule out the presence of prostatic abscess.	Weak
Do not routinely perform microbiological analysis of the ejaculate alone to diagnose CBP.	Weak

Recommendations for the disease management of bacterial prostatitis	Strength rating
Acute bacterial prostatitis	
Treat acute bacterial prostatitis according to the recommendations for complicated UTI.	Strong
Chronic bacterial prostatitis (CBP)	
Prescribe a fluoroquinolone (e.g. ciprofloxacin, levofloxacin) as first-line treatment for CBP.	Strong
Prescribe a macrolide (e.g. azithromycin) or a tetracycline (e.g. doxycycline) if intracellular bacteria have been identified as the causative agent of CBP.	Strong
Prescribe metronidazole in patients with *T. vaginalis* CBP.	Strong

Table 6: Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis

Antimicrobial	Daily dose	Duration of therapy	Comments
Floroquinolone	Optimal oral daily dose	4-6 weeks	
Doxycycline	100 mg b.i.d	10 days	Only for *C. trachomatis* or mycoplasma infections
Azithromycin	500 mg once daily	3 weeks	Only for *C. trachomatis* infections
Metronidazole	500 mg t.i.d.	14 days	Only for *T. vaginalis* infections

b.i.d = twice daily; t.i.d = three times daily.

Acute Infective Epididymitis

Acute epididymitis is clinically characterised by pain, swelling and increased temperature of the epididymis, which may involve the testis and scrotal skin. It is generally caused by migration of pathogens from the urethra or bladder. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

Recommendations for the diagnosis and treatment of acute infective epididymitis	Strength rating
Obtain a mid-stream urine and a first voided urine for pathogen identification by culture and nucleic acid amplification test.	Strong
Initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.	Strong
If gonorrhoeal infection is likely give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against *Chlamydia trachomatis*.	Strong
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	Weak
Follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.	Strong

Fournier's Gangrene

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal

region, and external genitalia. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway.

Recommendations for the disease management of Fournier's Gangrene	Strength rating
Start treatment for Fournier's gangrene with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.	Strong
Commence repeated surgical debridement for Fournier's gangrene within 24 hours of presentation.	Strong
Do not use adjunctive treatments for Fournier's gangrene except in the context of clinical trials.	Weak

Table 7: Suggested regimens for antimicrobial therapy for Fournier's Gangrene of mixed microbiological aetiology

Antimicrobial	Dosage
Piperacillin-tazobactam plus Vancomycin	4.5 g every 6-8 h IV 15 mg/kg every 12 h
Imipenem-cilastatin	1 g every 6-8 h IV
Meropenem	1 g every 8 h IV
Ertapenem	1 g once daily
Gentamicin	5 mg/kg daily
Cefotaxime plus metronidazole or clindamycin	2 g every 6 h IV 500 mg every 6 h IV 600-900 mg every 8 h IV
Cefotaxime plus fosfomycine plus metronidazole	2 g every 6 h IV 5 g every 8 h IV 500 mg every 6 h IV

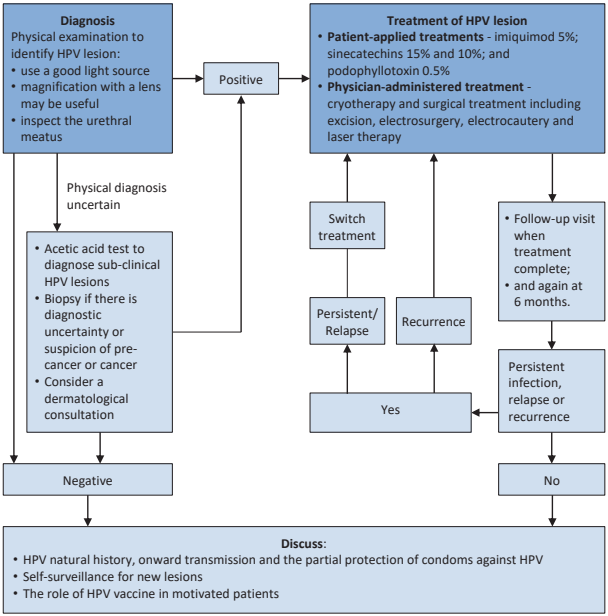
IV = intravenous.

Management of Human papilloma virus in men

Human papilloma virus (HPV) is one of the most frequently sexually transmitted viruses encompassing both oncogenic (low- and high-risk variants) and non-oncogenic viruses.

Recommendations for the treatment of anogenital warts	Strength rating
Use self-administered imiquimd 5% cream applied to all external warts overnight three times each week for sixteen weeks for the treatment of anogenital warts.	Strong
Use self-administered sinecatechins 15% or 10% applied to all external warts three times daily until complete clearance, or for up to sixteen weeks for the treatment of anogenital warts.	Strong
Use self-administered podophyllotoxin 0.5% self-applied to lesions twice daily for three days, followed by four rest days, for up to four or five weeks for the treatment of anogenital warts.	Strong
Use cryotherapy or surgical treatment (excision, electrosurgery, electrocautery and laser therapy) to treat anogenital warts based on an informed discussion with the patient.	Strong
Recommendation male circumcision	
Discuss male circumcision with patients as an additional one-time preventative intervention for HPV-related diseases.	Strong
Recommendation therapeutic HPV vaccination	
Offer HPV vaccine to males after surgical removal of high-grade anal intraepithelial neoplasia.	Weak
Recommendations prophylactic HPV vaccination	
Offer early HPV vaccination to boys with the goal of establishing optimal vaccine-induced protection before the onset of sexual activity.	Strong
Apply diverse communication strategies in order to improve HPV vaccination knowledge in young adult males.	Strong

Figure 1: Diagnostic and treatment algorithm for the management of HPV in men



Peri-Procedural Antibiotic Prophylaxis

The available evidence enabled the panel to make recommendations concerning urodynamics, cystoscopy, stone procedures (extracorporeal shockwave lithotripsy, ureteroscopy and per-cutaneous neprolithotomy), transurethral resection of the prostate, transurethral resection of the bladder and prostate biopsy. For nephrectomy and prostatectomy the scientific evidence was too weak to allow

the panel to make recommendations either for or against antibiotic prophylaxis.

Recommendations for peri-procedural antibiotic prophylaxis	Strength rating
Do not use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following: • urodynamics; • cystoscopy; • extracorporeal shockwave lithotripsy.	Strong
Use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following ureteroscopy.	Weak
Use single dose antibiotic prophylaxis to reduce the rate of clinical urinary infection following percutaneous nephrolithotomy.	Strong
Use antibiotic prophylaxis to reduce infectious complications in men undergoing transurethral resection of the prostate.	Strong
Use antibiotic prophylaxis to reduce infectious complications in high-risk patients undergoing transurethral resection of the bladder.	Weak
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong
Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g. fosfomycin trometamol, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak

Note: As stated in section 3.15.1.4 of the full text guideline the panel have decided not to make recommendations for specific agents for particular procedures, those listed below represent possible choices only. Urologists should choose a specific antimicrobial based on their knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence.

Table 8: Suggested regimens for antimicrobial prophylaxis prior to urological procedures

Procedure	Prophylaxis recommended	Antimicrobial
Urodynamics	No	
Cystoscopy	No	
Extracorporeal shockwave lithotripsy	No	
Ureteroscopy	Yes	Trimethoprim Trimethoprim-sulphamethoxazole Cephalosporin group 2 or 3 Aminopenicillin plus a beta-lactamase inhibitor
Percutaneous nephrolithotomy	Yes (single dose)	
Transurethral resection of the prostate	Yes	
Transurethral resection of the bladder	Yes in patients who have a high risk of suffering post-operative sepsis.	

Transrectal prostate biopsy	Yes	1. Targeted prophylaxis - based on rectal swab or stool culture. 2. Augmented prophylaxis - two or more different classes of antibiotics*. 3. Alternative antibiotics • fosfomycin trometamol (e.g. 3 g before and 3 g 24-48 hrs after biopsy) • cephalosporin (e.g. ceftriaxone 1 g i.m.; cefixime 400 mg p.o. for 3 days starting 24 hrs before biopsy) • aminoglycoside (e.g. gentamicin 3mg/kg i.v.; amikacin 15mg/kg i.m.)

** Note option 2 is against antibiotic stewardship programmes.*

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.

EAU GUIDELINES ON UROLITHIASIS

(Limited text update March 2021)

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Aetiology and classification

Urinary stones can be classified according to the following aspects: aetiology of stone formation, stone composition (mineralogy), stone size, stone location, and X-ray characteristics of the stone. The recurrence risk is basically determined by the disease or disorder causing the stone formation.

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 (Table 1).

Table 1: High-risk stone formers

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones ($CaHPO_4.2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)

Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery
Increased levels of vitamin D
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation
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
Environmental and professional factors
High ambient temperatures
Chronic lead and cadmium exposure

Diagnostic Evaluation

Diagnostic imaging

Standard evaluation of a patient includes taking a detailed medical history and physical examination. The clinical diagnosis should be supported by appropriate imaging.

Recommendation	Strength rating
Immediate imaging is indicated with fever or solitary kidney, and when diagnosis is doubtful.	Strong

Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures, should not be delayed by imaging assessments.

Kidney-ureter-bladder (KUB) urography should not be performed if non-contrast-enhanced computed tomography (NCCT) is being considered, but KUB urography can differentiate between radiolucent and radiopaque stones and should be used for comparison during follow up.

Recommendation for radiologic examinations of patients with acute flank pain/suspected ureteral stones	Strength rating
Use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain, following initial ultrasound assessment.	Strong

Recommendation for radiologic examination of patients with renal stones	Strength rating
Perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	Strong

Diagnostics: Metabolism-related

Each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood; no difference is made between high- and low-risk patients.

Recommendations: basic laboratory analysis - emergency stone patients	Strength rating
Urine	
Dipstick test of spot urine sample: • red cells; • white cells; • nitrites; • approximate urine pH; • urine microscopy and/or culture.	Weak
Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	Strong
Perform a coagulation test (partial thromboplastin time and international normalised ratio) if intervention is likely or planned.	Strong

Examination of sodium, potassium, C-reactive protein (CRP), and blood coagulation time can be omitted if no intervention is planned in non-emergency stone patients. Patients at high risk for stone recurrences should undergo a more specific analytical programme (see section on Metabolic Evaluation).

Recommendations related to non-emergency stone analysis	Strength rating
Perform stone analysis in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	Strong
Repeat stone analysis in patients presenting with: • recurrent stones despite drug therapy; • early recurrence after complete stone clearance; • late recurrence after a long stone-free period because stone composition may change.	Strong

Diagnosis for special groups/conditions

Pregnancy

Recommendations	Strength rating
Use ultrasound as the preferred method of imaging in pregnant women.	Strong
In pregnant women, use magnetic resonance imaging as a second-line imaging modality.	Strong
Use low-dose computed tomography as a last-line option in pregnant women.	Strong

Children

Recommendations	Strength rating
Complete a metabolic evaluation based on stone analysis, in all children.	Strong
Collect stone material for analysis to classify the stone type.	Strong
Perform ultrasound (US) as first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder and the ureter.	Strong
Perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography) if US will not provide the required information.	Strong

In children, the most common non-metabolic disorders facilitating stone formation are vesico-ureteral reflux, UPJ, neurogenic bladder, and other voiding difficulties.

The radiation dose for intravenous urography (IVU) is comparable to that for voiding cysto-urethrography, but the need for contrast medium injection is a major drawback.

Disease Management

Acute treatment of a patient with renal colic

Pain relief is the first therapeutic step in patients with an acute stone episode.

Recommendations	Strength rating
Offer a non-steroidal anti-inflammatory as the first drug of choice; e.g. metamizol* (dipyrone); alternatively paracetamol or, depending on cardiovascular risk factors, diclofenac**, indomethacin or ibuprofen***.	Strong
Offer opiates (hydromorphine, pentazocine or tramadol) as a second choice.	Weak
Offer renal decompression or ureteroscopic stone removal in case of analgesic refractory colic pain.	Strong

** Maximum single oral dose recommended 1,000 mg, total daily dose up to 5,000 mg, not recommended last 3 months of pregnancy and breastfeeding (EMA, Dec. 2018).*

*** Affects glomerular filtration rate (GFR) in patients with reduced renal function.*

**** Recommended to counteract recurrent pain after ureteral colic.*

Administration of daily α-blockers seems to reduce colic episodes, although controversy remains in the published literature.

If analgesia cannot be achieved medically, drainage, using stenting or percutaneous nephrostomy or stone removal, should be performed.

Management of sepsis and anuria in the obstructed kidney

The obstructed, infected, kidney is a urological emergency.

Recommendations	Strength rating
Urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	Strong
Delay definitive treatment of the stone until sepsis is resolved.	Strong

In exceptional cases, with severe sepsis and/or the formation of abscesses, an emergency nephrectomy may become necessary.

Recommendations – Further measures	Strength rating
Collect (again) urine for antibiogram test following decompression.	Strong
Start antibiotics immediately (+ intensive care, if necessary).	Strong
Re-evaluate antibiotic regimen following antibiogram findings.	Strong

Medical expulsive therapy (MET)

Medical expulsive therapy should only be used in informed patients. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function).

Medical expulsive therapy, using α-blockers, seems to be efficacious treating patients with ureteric stones that are amenable to conservative management. Patients benefitting most might be those with larger (distal) stones.

There is no or insufficient evidence to support the use of phosphodiesterase type 5 inhibitor (PDE-5I) or corticosteroids in combination with α-blockers as a standard adjunct to active stone removal.

Recommendation for medical expulsive therapy	Strength rating
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong

Chemolytic dissolution of stones

Oral chemolysis of stones or their fragments can be useful in uric acid stones. It is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate. The pH should be adjusted to 7.0-7.2.

Percutaneous irrigation chemolysis is rarely used any more.

Recommendations – Oral chemolysis of uric acid stones	Strength rating
Inform the patient how to monitor urine-pH by dipstick and to modify the dosage of alkalising medication according to urine pH, as changes in urine pH are a direct consequence of such medication.	Strong
Carefully monitor patients during/after oral chemolysis of uric acid stones.	Strong
Combine oral chemolysis with tamsulosin in case of (larger) ureteral stones (if active intervention is not indicated).	Weak

Shock Wave lithotripsy (SWL)

The success rate for SWL will depend on the efficacy of the lithotripter and on:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones;
- patient's habitus;
- performance of SWL.

Contraindications of SWL

Contraindications are few, but include:

- pregnancy;
- bleeding disorders; which should be compensated for at least 24 hours before and 48 hours after treatment;
- untreated urinary tract infections (UTIs);
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone;
- anatomical obstruction distal to the stone.

Best clinical practice (best performance) in SWL

Stenting prior to SWL

Routine use of internal stents before SWL does not improve stone-free rates (SFRs), nor lowers the number of auxiliary treatments. It may, however, reduce formation of steinstrasse.

Pacemaker

Patients with a pacemaker can be treated with SWL. 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.

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.
- Starting SWL on a lower energy setting with step-wise power ramping prevents renal injury.
- Optimal shock wave frequency is 1.0 to 1.5 Hz.
- Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).

Procedural control

Recommendations - Procedural control	Strength rating
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	Strong
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy.	Strong
Use proper analgesia because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	Strong

Antibiotic prophylaxis

No standard prophylaxis prior to SWL is recommended.

Recommendation	Strength rating
Prescribe antibiotics prior to shock wave lithotripsy in the case of infected stones or bacteriuria.	Strong

Ureteroscopy (URS) (retrograde and antegrade, RIRS)

Apart from general problems, for example, with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

If ureteral access is not possible, insertion of a JJ stent followed by URS after several days is an alternative. During URS, placement of a safety wire is recommended, even though some groups have demonstrated that URS can be performed without it.

Ureteral access sheaths allow easy, multiple, access to the upper urinary tract; however, its insertion may lead to ureteral trauma.

Recommendations	Strength rating
Use holmium: yttrium-aluminium-garnet (Ho:YAG) laser lithotripsy for (flexible) ureteroscopy.	Strong
Perform stone extraction only under direct endoscopic visualisation of the stone.	Strong
Do not insert a stent in uncomplicated cases.	Strong
Offer medical expulsive therapy for patients suffering from stent-related symptoms and after Ho:YAG laser lithotripsy to facilitate the passage of fragments.	Strong

Percutaneous nephrolithotomy (PNL)

Patients with bleeding disorders or receiving anticoagulant therapy must be monitored carefully pre- and post-operatively. Anticoagulant therapy must be discontinued before PNL.

Contraindications to PNL include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy.

Best clinical practice

Both prone and supine positions are equally safe. Percutaneous nephrolithotomy performed with small instruments tends to be associated with significantly lower blood loss, but the duration of procedure tends to be significantly longer.

Recommendations	Strength rating
Perform pre-procedural imaging, including contrast medium where possible or retrograde study when starting the procedure, to assess stone comprehensiveness and anatomy of the collecting system to ensure safe access to the renal stone.	Strong
Perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy procedure, in uncomplicated cases.	Strong

Stone Removal

Recommendations	Strength rating
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	Strong
Exclude or treat urinary tract infections prior to stone removal.	Strong
Offer peri-operative antibiotic prophylaxis to all patients undergoing endourological treatment.	Strong
Offer active surveillance to patients at high risk of thrombotic complications in the presence of an asymptomatic calyceal stone.	Weak
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	Strong

Retrograde (flexible) ureteroscopy is the preferred intervention if stone removal is essential and antithrombotic therapy cannot be discontinued, since it is associated with less morbidity.	Strong

Radiolucent uric acid stones can be dissolved by oral chemolysis.

Ureteral stones

Observation of ureteral stones is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of kidney function).

Recommendations	Strength rating
If active removal is not indicated In patients with newly diagnosed small* ureteral stones, observe patient initially with periodic evaluation.	Strong
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong
Inform patients that ureteroscopy (URS) has a better chance of achieving stone-free status with a single procedure.	Strong
Inform patients that URS has higher complication rates when compared to shock wave lithotripsy.	Strong
Use URS as first-line therapy for ureteral (and renal) stones in cases of severe obesity.	Strong

**See stratification data (J Urol, 2007. 178: 2418).*

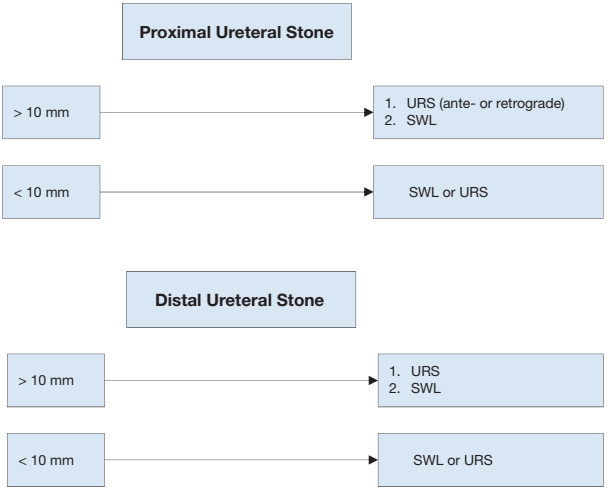
Indication for active stone removal and selection of procedure

Ureter:

- stones with a low likelihood of spontaneous passage;
- persistent pain despite adequate pain medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, single kidney).

The suspected stone composition might influence the choice of treatment modality.

Figure 1: Treatment algorithm for ureteral stones (If active stone removal is indicated) (Strength rating: Strong)



SWL = shock wave lithotripsy; URS = ureteroscopy.

Recommendation	Strength rating
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde ureteroscopy.	Strong

Renal stones

It is still debatable whether all stones should be treated, or whether annual follow-up is sufficient for asymptomatic calyceal stones that have remained stable for six months.

Recommendations	Strength rating
Follow-up periodically in cases where renal stones are not treated (initially after six months then yearly, evaluating symptoms and stone status, either by ultrasound, kidney-ureter bladder radiography or computed tomography).	Strong
Offer active treatment for renal stones in case of stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain.	Weak
Evaluate stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced computed tomography (CT). Stones with density > 1,000 HU on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy.	Strong
Perform percutaneous nephrolithotomy as first-line treatment of larger stones > 2 cm.	Strong

Treat larger stones (> 2 cm) with flexible ureteroscopy or SWL, in cases where PNL is not an option. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong
Perform PNL or retrograde intrarenal surgery (RIRS) for the lower pole, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	Strong

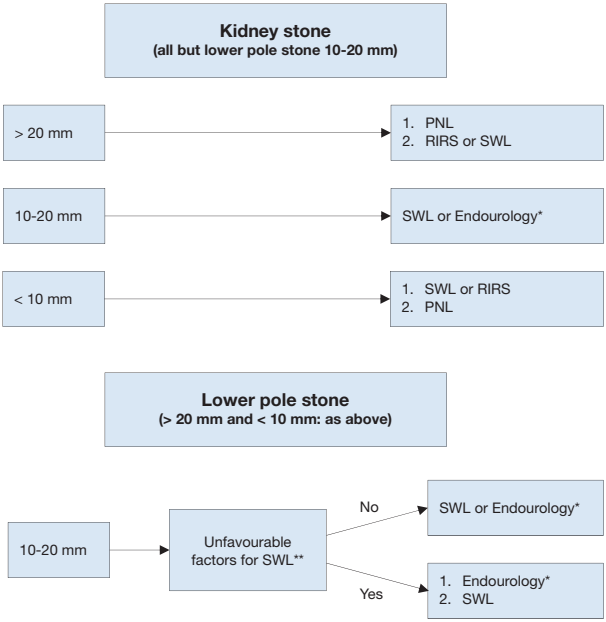
Indication for active stone removal and selection of procedure

Kidney:

- 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 or travelling).

The suspected stone composition might influence the choice of treatment modality.

Figure 2: Treatment algorithm for renal stones (if active treatment is indicated) (Strength rating: Strong)



** The term 'endourology' encompasses all PNL and URS interventions.*

*** See chapter 3.4.5. of full Urolithiasis guideline.*

PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureteroscopy.

Recommendation	Strength rating
Treat larger stones (> 2 cm) with flexible ureteroscopy or shock wave lithotripsy, in cases where percutaneous nephrolithotomy is not an option. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong

Open and laparoscopic surgery

Recommendation	Strength rating
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	Strong

Steinstrasse

The major factor in steinstrasse formation is stone size. Medical expulsion therapy increases the stone expulsion rate of steinstrasse. When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.

Recommendations	Strength rating
Treat steinstrasse associated with urinary tract infection (UTI)/fever preferably with percutaneous nephrostomy.	Weak
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureteroscopy (in absence of signs of UTI).	Weak

Management of patients with residual stones

Following initial treatment with SWL, URS or PNL residual fragments may remain and require additional intervention. The indications for active removal of residual stones and selection of the procedure are based on the same criteria as for primary stone treatment. For well-disintegrated stone material in the lower calyx, inversion therapy with simultaneous mechanical percussion manoeuvre under enforced diuresis may facilitate stone clearance.

Recommendation in case of residual fragments	Strength rating
Perform imaging after shock wave lithotripsy, ureteroscopy or percutaneous antegrade ureteroscopy to determine presence of residual fragments.	Strong

Management of urinary stones and related problems during pregnancy

Recommendation	Strength rating
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except where there are clinical indications for intervention).	Strong

If intervention becomes necessary, placement of a ureteral stent or a percutaneous nephrostomy tube are readily available primary options. Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage. There is a higher tendency for stent encrustation during pregnancy.

Management of stones in patients with urinary diversion

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter, or in the conduit or continent reservoir.

Recommendation	Strength rating
Perform percutaneous lithotomy to remove large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach, or that are not amenable to shock wave lithotripsy.	Strong

Management of stones in patients with neurogenic bladder

Patients with neurogenic bladder are more prone to development of urinary calculi.

In myelomeningocele patients, latex allergy is common so appropriate measures need to be taken regardless of the treatment.

Management of stones in transplanted kidneys

Transplanted patients are at additional risk due to their dependency on a solitary kidney, immunosuppression therapy and possible metabolic impairments. Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.

Stones causing urinary stasis/obstruction require immediate intervention or drainage of the transplanted kidney.

Recommendation	Strength rating
Offer patients with transplanted kidneys, any of the contemporary management options, including shock wave lithotripsy, flexible ureteroscopy and percutaneous nephrolithotomy.	Weak

Special problems in stone removal

Calyceal diverticulum stones	• Shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL) (if possible) or retrograde renal surgery (RIRS). • Laparoscopic retroperitoneal surgery. • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow calyceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above. • Passage of fragments after SWL might be poor. • Acceptable stone-free rates (SFRs) can be achieved with flexible ureteroscopy.
Stones in pelvic kidneys	• SWL, RIRS, PNL or laparoscopic surgery. • In obese patients, the options are RIRS, PNL or open surgery.
Stones formed in a continent reservoir	• Each stone must be considered and treated individually.

Patients with obstruction of the uretero-pelvic junction (UPJ)	• When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • Ureteroscopy together with endopyelotomy with holmium:yttrium-aluminium-garnet laser. • Incision with an Acucise® balloon catheter might be considered, provided the stones can be prevented from falling into the pelvic-ureteral incision. • Open surgery with correction of the UPJ obstruction (pyeloplasty) and stone removal is a feasible option.

Management of urolithiasis in children

In children, the indication for SWL and for PNL is similar to those in adults. Compared to adults, children pass fragments more rapidly after SWL. For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS.

Children with renal stones of a diameter up to 20 mm (~300 mm^2) are ideal candidates for SWL.

Recommendations	Strength rating
Offer children with single ureteral stones less than 10 mm shock wave lithotripsy (SWL) if localisation is possible as first-line option.	Strong
Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL.	Strong
Offer children with renal stones with a diameter of up to 20 mm (~300 mm^2) SWL.	Strong
Offer children with renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm^2) percutaneous nephrolithotomy.	Strong
Retrograde renal surgery is a feasible alternative for renal stones smaller than 20 mm in all locations.	Weak

Metabolic evaluation and recurrence prevention

After stone passage, every patient should be assigned to a low- or high-risk group for stone formation. For correct classification, two analyses are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis.

Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. For both groups, general preventive measures apply (see below).

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: < 1,010 L/day
Nutritional advice for a balanced diet	• Rich in vegetables 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 • Avoid excessive consumption of vitamin supplements
Lifestyle advice to normalise general risk factors	• Body mass index (BMI): Retain a normal BMI level • Adequate physical activity • Balancing of excessive fluid loss

Caution: Protein need is age-group dependent; therefore, protein restriction in childhood should be handled carefully.

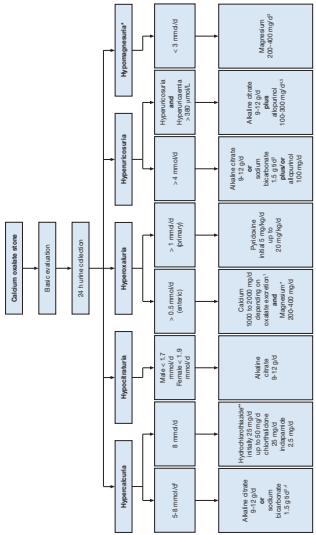
Calcium oxalate stones

Hyperparathyroidism is excluded by blood analysis.

Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition (based on 24-hour urine samples)		
Urinary risk factor	**Suggested treatment**	**Strength rating**
Hypercalcuria	Thiazide* + alkaline citrate	Strong
Hyperoxaluria	Oxalate restriction	Weak
Enteric hyperoxaluria	Potassium citrate	Weak
	Calcium supplement	Weak
	Diet reduced in fat and oxalate	Weak
Hypocitraturia	Alkaline citrate	Strong
Hypocitraturia	Sodium bicarbonate if intolerant to alkaline citrate	Strong
Hyperuricosuria	Allopurinol	Strong
	Febuxostat	Strong
High sodium excretion	Restricted intake of salt	Strong
Small urine volume	Increased fluid intake	Strong
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	Strong

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk of developing a non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed.*

Figure 3: Diagnostic and therapeutic algorithm for calcium oxalate stones



[1] *Be aware of excess calcium excretion*

[2] *tid = three times/day (24h).*

[3] *No magnesium therapy for patients with renal insufficiency*

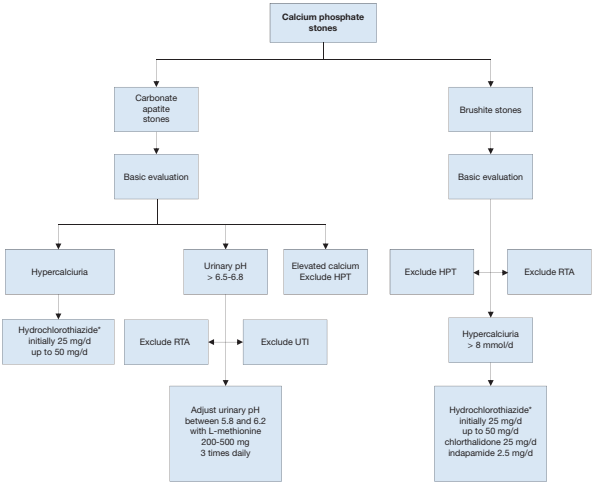
[4] *There is no evidence that combination therapy (thiazide + citrate) or (thiazide + allopurinol) is superior to thiazide therapy alone.*

[5] *Febuxostat 80 mg/day.*

** low evidence (see text)*

*** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk for developing NMSC. In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed.*

Figure 4: Diagnostic and therapeutic algorithm for calcium phosphate stones



HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk of developing NMSC. In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed.*

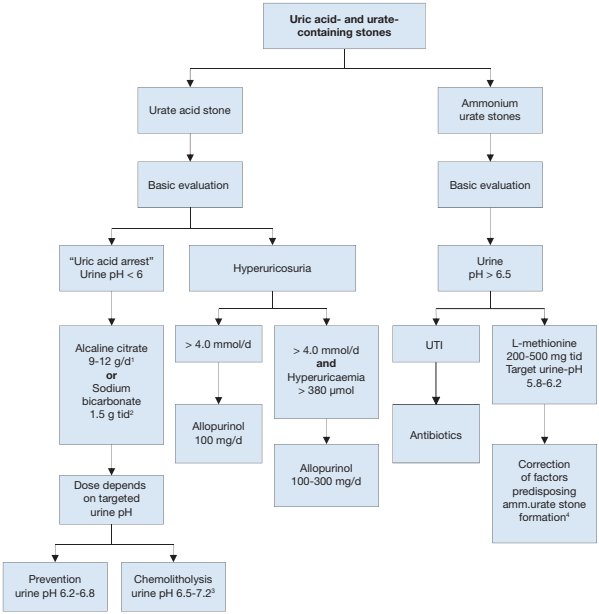
Recommendations	Strength rating
Prescribe thiazide* in case of hypercalciuria.	Strong
Advise patients to acidify their urine in case of high urine pH.	Weak

Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk for developing NMSC. In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed.

Hyperparathyroidism

Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact parathyroid hormone to confirm or exclude suspected hyper-parathyroidism (HPT). Primary HPT can only be cured by surgery.

Figure 5: Diagnostic and therapeutic algorithm for uric acid and urate-containing stones



UTI = urinary tract infection.

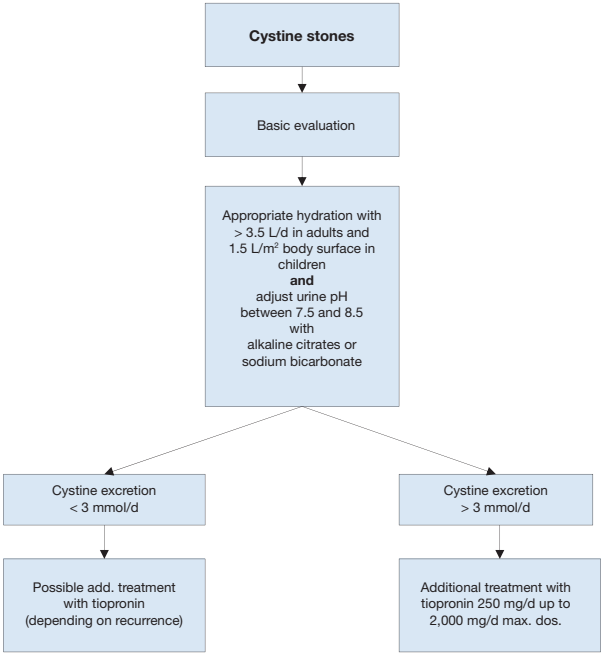
[1] d: day

[2] tid: three times a day

[3] A higher pH may lead to calcium phosphate stone formation.

[4] In patients with high uric acid excretion, allopurinol may be helpful.

Figure 6: Metabolic management of cystine stones



Struvite/infection stones

Recommendations for therapeutic measures of infection stones	Strength rating
Surgically remove the stone material as completely as possible.	Strong
Prescribe antibiotics in case of persistent bacteriuria.	Strong
Prescribe ammonium chloride, 1 g, two or three times daily, to ensure urinary acidification.	Weak
Prescribe methionine, 200-500 mg, one to three times daily, as an alternative, to ensure urinary acidification.	Weak

2,8-Dihydroyadenine stones and xanthine stones

Both stone types are rare. In principle, diagnosis and specific prevention is similar to that of uric acid stones.

Drug stones

Drug stones are induced by pharmacological treatment. Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Treatment includes general preventive measures and the avoidance of the respective drugs.

Unknown stone composition

Investigation	Rationale for investigation
Medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart
Diagnostic imaging	• Ultrasound in the case of a suspected stone • Un-enhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition
Blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid
Perform a urinalysis	• Dipstick test: leukocytes, erythrocytes, nitrites, protein, urine pH, specific weight • Urine cultures • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion). Further examinations depend on the results of the investigations listed above.

Further examinations depend on the results of the investigations listed above.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON BLADDER STONES

(Limited text update March 2021)

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Prevalence and stratification

The prevalence of bladder stones is higher in males (male:female ratio between 10:1 and 4:1). The age distribution is bimodal: incidence peaks at three years in children in developing countries and 60 years in adulthood.

Primary or endemic bladder stones occur in the absence of other urinary tract pathology, typically seen in children in areas with a diet deficient in animal protein, poor hydration and recurrent diarrhoea.

Secondary bladder stones occur in the presence of other urinary tract abnormalities, which include bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies including catheters, bladder diverticula, and bladder augmentation or urinary diversion.

Migratory bladder stones are those which have passed from the upper urinary tract where they formed and may then serve as a nidus for bladder stone growth.

Diagnostic imaging

There is a paucity of evidence for the investigation of bladder

stones, particularly in children. Ultrasound (US) of the (filled) bladder has a reported sensitivity and specificity for detecting bladder stones between 20-83% and 98-100%, respectively. Plain X-ray of kidney ureter bladder (KUB) has a sensitivity of 21-78% in adults and this increases for stones ≥ 2.0 cm. In adults, besides US, computed tomography and/or cystoscopy are the benchmark diagnostic investigations.

Disease management

Asymptomatic migratory bladder stones in adults may be left untreated. Primary and secondary bladder stones are usually symptomatic and are unlikely to pass spontaneously; active treatment is usually indicated.

Uric acid stones can be dissolved by oral urinary alkalinisation when a pH > 6.5 is consistently achieved. Irrigation chemolysis is possible for struvite or uric acid stones. For further details see chapter 3.4.4 in the full EAU Guidelines on Urolithiasis.

Bladder stones can be removed with open, laparoscopic or robotic assisted laparoscopic or endoscopic (transurethral or percutaneous) surgery, or extracorporeal shock wave lithotripsy (SWL).

Summary of evidence	LE
The incidence of bladder stones peaks at three years in children (endemic/primary stones in developing countries) and 60 years in adults.	2c
The aetiology of bladder stones is typically multi-factorial. Bladder stones can be classified as primary (endemic), secondary (associated with lower urinary tract abnormalities e.g. BPO, neuropathic bladder, foreign body, chronic bactiuria) or migratory (having formed in the upper tract).	4

In adults, BOO is the most common predisposing factor for bladder stone formation.	2c
Of men undergoing surgery for BPO, 3-4.7% form bladder stones.	2b
Metabolic abnormalities are also likely to contribute to bladder stone formation in patients with secondary bladder stones.	2b
Primary (endemic) bladder stones typically occur in children in areas with poor hydration, recurrent diarrhoea and a diet deficient in animal protein. The following measures are proposed to reduce their incidence: maintenance of hydration, avoidance of diarrhoea, and a mixed cereal diet with milk and Vitamins A and B supplements; with the addition of eggs, meat and boiled cows' milk after one year of age.	5
In adults, US has a sensitivity of 20-83% for diagnosing bladder stones.	2b
In adults, XR-KUB has a sensitivity of 21-78%; sensitivity increases with stone size.	2b
Computed tomography has a higher sensitivity than US for the detection of bladder stones.	2b
Cystoscopy has a higher sensitivity than XR-KUB or US for the detection of bladder stones.	2b
Endoscopic bladder stone treatments are associated with comparable stone-free rates (SFRs), but a shorter length of hospital stay, duration of procedure and duration of catheterisation, compared to open cystolithotomy in adults.	1a
Stone-free rates are lower in patients treated with SWL than those treated with open or endoscopic procedures in both adults and children.	2a

Transurethral cystolithotripsy is associated with a shorter length of hospital stay, less pain and a shorter convalescence period than percutaneous cystolithotripsy in adults.	1b
Transurethral cystolithotripsy with a nephroscope is quicker than when using a cystoscope, with no difference in SFR in adults.	1a
Transurethral cystolithotripsy with a resectoscope is quicker than when using a cystoscope, with no difference in SFR in adults.	2a
Mechanical, pneumatic and laser appear equivalent lithotripsy modalities for use in endoscopic bladder stone treatments in adults and children.	2a
Open cystolithotomy without a retropubic drain or urethral catheter ("tubeless") is associated with a shorter length of hospital stay than traditional cystolithotomy and can be performed safely in children with primary stones and no prior bladder surgery or infections.	2b
Bladder stone removal with concomitant treatment for BOO is associated with no significant difference in major post-operative complications when compared to BOO treatment alone in adults. However, concomitant bladder stone treatment does increase the rates of short-term post-operative incontinence and urinary infection.	2b
The incidence of bladder stone formation in spinal cord injury patients is 15-36% after eight to ten years. The absolute annual risk of stone formation in spinal cord injury patients is significantly higher with an indwelling catheter compared to those voiding with CISC or spontaneously.	2b
The incidence of bladder stone formation after bladder augmentation or vesico-entero-cystostomy is between 2-53% in adults and children.	2b

Urinary diversion including orthotopic ileal neobladders, ileocaecal continent cutaneous urinary diversion and rectosigmoid reservoirs is associated with stone formation in 0-43% of cases.	2b
The risk of bladder stone formation in spinal cord injury, bladder augmentation or continent urinary diversion patients is reduced by performing regular bladder irrigation.	2b

Recommendations	**Strength rating**
Use ultrasound (US) as first-line imaging with symptoms suggestive of a bladder stone.	Strong
Use cystoscopy or computed tomography (CT), kidney ureter bladder X-Ray (KUB) to investigate adults with persistent symptoms suggestive of a bladder stone if US is negative.	Strong
Use X-Ray KUB for adults with confirmed bladder stones to guide treatment options and follow-up.	Weak
All patients with bladder stones should be examined and investigated for the cause of bladder stone formation, including: • uroflowmetry and post-void residual; • urine dipstick, pH, ± culture; • metabolic assessment and stone analysis (see sections 3.3.2.3 and 4.1 of the Urolithiasis guideline for further details). In selected patients, consider: • upper tract imaging (in patients with a history of urolithiasis or loin pain); • cysto-urethroscopy or urethrogram.	Weak

Offer oral chemolitholysis for radiolucent or known uric acid bladder stones in adults.	Weak
Offer adults with bladder stones trans-urethral cystolithoplasty where possible.	Strong
Perform transurethral cystolithotripsy with a continuous flow instrument in adults (e.g. nephroscope or resectoscope) where possible.	Weak
Offer adults percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or advisable.	Strong
Suggest open cystolithotomy as an option for very large bladder stones in adults and children.	Weak
Offer children with bladder stones trans-urethral cystolithotripsy where possible.	Weak
Offer children percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or is associated with a high risk of urethral stricture (e.g., young children, previous urethral reconstruction and spinal cord injury).	Weak
Open, laparoscopic and extracorporeal shock wave lithotripsies are alternative treatments where endoscopic treatment is not advisable in adults and children.	Weak
Prefer "tubeless" procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery or bladder dysfunction, where open cystolithotomy is indicated in children.	Weak

Perform procedures for the stone and underlying bladder outlet obstruction (BOO) simultaneously in adults with bladder stones secondary to BOO, where possible.	Strong
Individualise imaging follow up for each patient as there is a paucity of evidence. Factors affecting follow up will include: • whether the underlying functional predisposition to stone formation can be treated (e.g., TURP); • metabolic risk.	Weak
Recommend regular irrigation therapy with saline solution to adults and children with bladder augmentation, continent cutaneous urinary reservoir or neuropathic bladder dysfunction, and no history of autonomic dysreflexia to reduce the risk of stone recurrence.	Weak

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EAU GUIDELINES ON PAEDIATRIC UROLOGY

(Text update March 2021)

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Introduction

Due to the scope of the extended Guidelines on Paediatric Urology, only a short introduction of the individual chapter in combination with recommendations can be given in this pocket version. Additionally, some algorithms and flow charts are enclosed. For further details please refer to the full length version.

PHIMOSIS

Phimosis is either primary (physiological), with no sign of scarring, or secondary (pathological), resulting from scarring due to conditions such as balanitis xeroticaobliterans.

Childhood circumcision should not be recommended without a medical reason. An absolute indication for circumcision is secondary phimosis. Contraindications are congenital anomalies of the penis, particularly hypospadias or buried penis, as the foreskin may be required for a reconstructive procedure.

Paraphimosis is characterised by retracted foreskin with the constrictive ring localised at the level of the sulcus.

Recommendations	Strength rating
Offer corticoid ointment or cream to treat primary symptomatic phimosis.	Strong
Circumcision will also solve the problem.	Strong
Treat primary phimosis in patients with recurrent urinary tract infection and/or with urinary tract abnormalities.	Strong
Circumcise in case of lichen sclerosus or scarred phimosis.	Strong
Treat paraphimosis by manual reposition and proceed to surgery if it fails.	Strong
Avoid retraction of asymptomatic preputial adhesions.	Weak

UNDESCENDED TESTIS

Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates with an incidence of 1.0-4.6% of full-term neonates. Boys with one undescended testis have a lower fertility rate whereas boys with bilateral undescended testes suffer both, lower fertility and paternity rates. In addition, boys who are treated for an undescended testis have an increased risk of developing testicular malignancy. Therefore, screening and self-examination both during and after puberty is recommended.

Figure 1: Classification of undescended testes

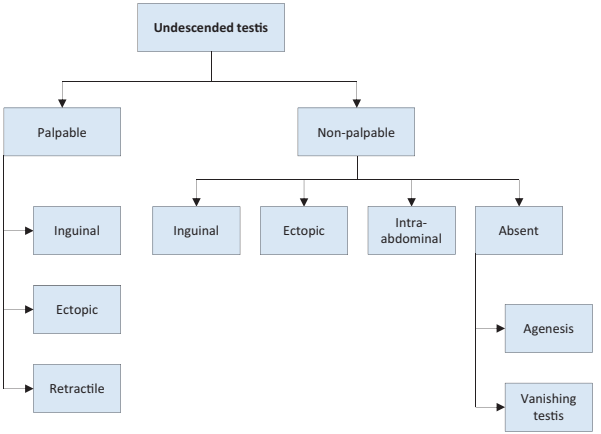
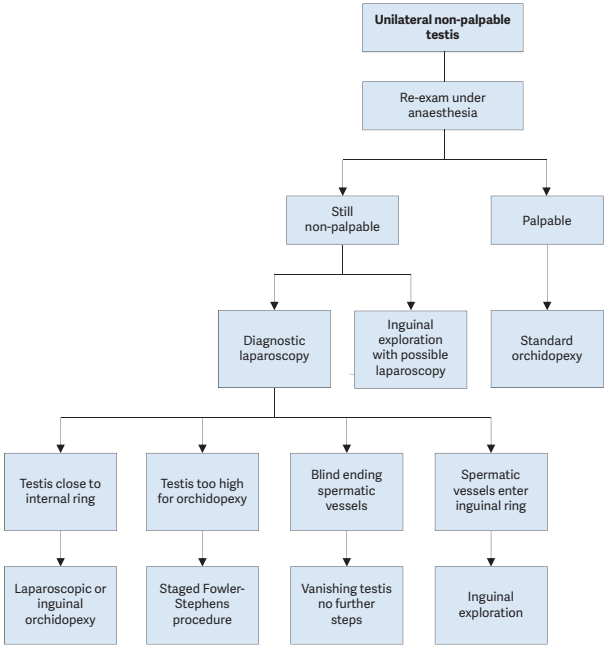


Figure 2: Treatment of unilateral non-palpable undescended testes



Recommendations	Strength rating
Do not offer medical or surgical treatment for retractile testes instead undertake close follow-up on a yearly basis until puberty.	Strong
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	Strong
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development.	Strong
Perform a diagnostic laparoscopy to locate an intra-abdominal testicle.	Strong
Hormonal therapy in unilateral undescended testes is of no benefit for future paternity.	Strong
Offer endocrine treatment in case of bilateral undescended testes.	Weak
Inform the patient/caregivers about the increased risk of a later malignancy with an undescended testis in a post-pubertal boy or older and discuss removal in case of a contralateral normal testis in a scrotal position.	Weak

TESTICULAR TUMOURS IN PREPUBERTAL BOYS

Testicular tumours account for approximately 1-2% of all paediatric solid tumours. In prepubertal boys most intratesticular tumours are benign and teratomas and yolk sac tumours more common than germ cell tumours, whereas post-puberty the tumours are most likely malignant.

Recommendations	Strength rating
High-resolution ultrasound (7.5 – 12.5 MHz), preferably a doppler ultrasound, should be performed to confirm the diagnosis.	Strong
Alpha-fetoprotein should be determined in prepubertal boys with a testicular tumour before surgery.	Strong
Surgical exploration should be done with the option for frozen section, but not as an emergency operation.	Strong
Organ-preserving surgery should be performed in all benign tumours.	Strong
Staging (MRI abdomen/CT chest) should only be performed in patients with a malignant tumour to exclude metastases.	Strong
Magnetic resonance imaging should only be performed in patients with the potential malignant Leydig or Sertoli-cell-tumours to rule out lymph node enlargement.	Weak
Patients with a non-organ confined tumour should be referred to paediatric oncologists post-operatively.	Weak

HYDROCELE

A communicating hydrocele vacillates in size, usually relative to activity. It is diagnosed by medical history and physical investigation, the swelling is translucent, and transillumination of the scrotum confirms the diagnosis. Non-communicating hydroceles are found secondary to minor trauma, testicular torsion, epididymitis, or varicocele operation, or may appear as a recurrence after primary repair of a communicating hydrocele.

Recommendations	Strength rating
In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	Strong
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	Strong
Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	Strong
Do not use sclerosing agents because of the risk for chemical peritonitis.	Strong

ACUTE SCROTUM

Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis.

Recommendations	Strength rating
Testicular torsion is a paediatric urological emergency and requires immediate treatment.	Strong
In neonates with testicular torsion perform orchidopexy of the contralateral testicle. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	Weak
Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	Strong

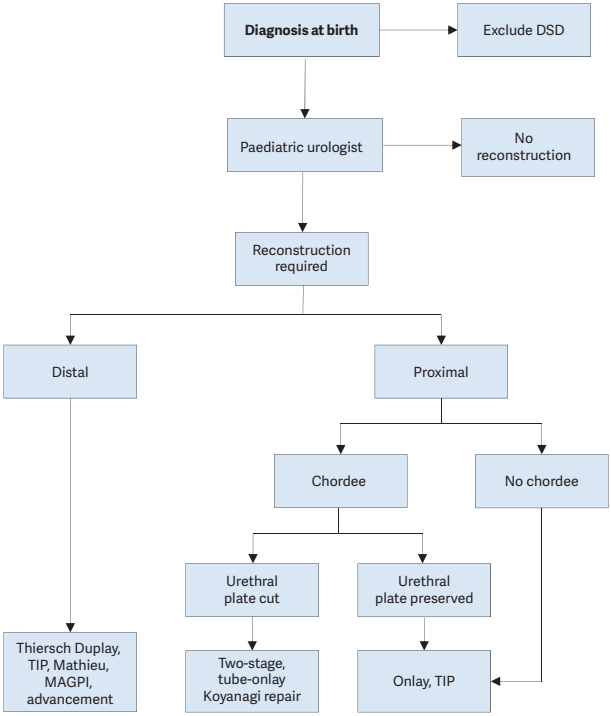
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	Strong
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	Strong

HYPOSPADIAS

Hypospadias are usually classified according to the anatomical location of the proximally displaced urethral orifice.

Patients with hypospadias should be diagnosed at birth. The diagnostic evaluation also includes an assessment of associated anomalies, which include cryptorchidism and open processus vaginalis or inguinal hernia. 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 disorders of sex development, especially congenital adrenal hyperplasia.

Figure 3: Algorithm for the management of hypospadias



DSD = disorders of sex development; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

Recommendations	Strength rating
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	Strong
Counsel caregivers on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	Strong
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option but the body of evidence to accentuate its harms and benefits is inadequate.	Weak
For distal hypospadias, offer Duplay-Thiersch urethroplasty, original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (Figure 3). Correct significant (> 30°) curvature of the penis.	Weak
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, ejaculation disorder, and to evaluate patient's satisfaction.	Strong
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	Strong

CONGENITAL PENILE CURVATURE

Congenital penile curvature presents penile bending of a normally formed penis due to corporal disproportion. Most of the cases are ventral deviations. Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood. The treatment is surgical.

Recommendations	Strength rating
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	Strong
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	Strong
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	Weak
At the beginning as well as at the end of surgery, perform artificial erection tests.	Strong

VARICOCELE IN CHILDREN AND ADOLESCENTS

Varicocele is unusual in boys under ten years of age, but becomes more frequent at the beginning of puberty. Fertility problems will arise in about 20% of adolescents with varicocele. Testicular catch-up growth and improvement in sperm parameters after varicocelectomy has been reported in adolescents. Varicocele is mostly asymptomatic, rarely causing pain at this age. Diagnosis and classification depends upon the clinical finding and US investigation.

Figure 4: Algorithm for the diagnosis of varicocele in children and adolescents

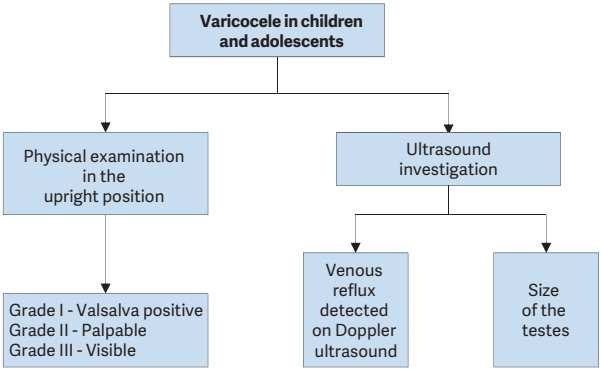
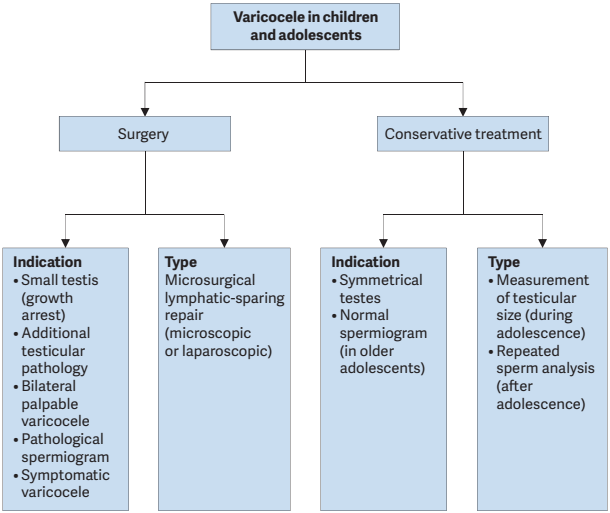


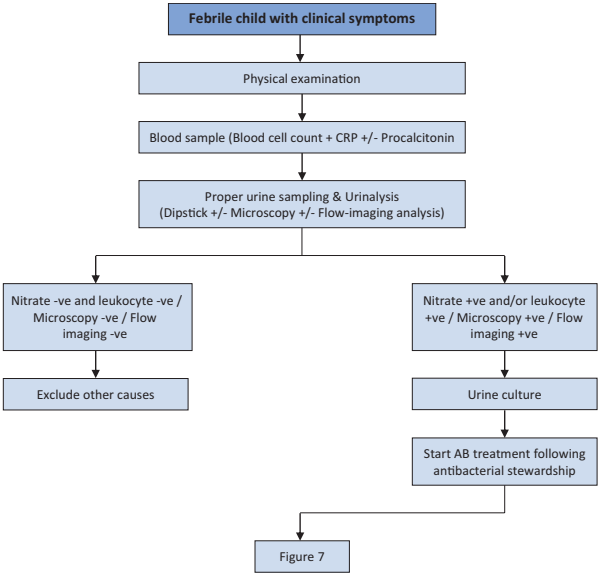
Figure 5: Algorithm for the management of varicocele in children and adolescents



Recommendations	Strength rating
Examine varicocele in the standing position and classify into three grades.	Strong
Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.	Strong
In all pre-pubertal boys with a varicocele and in all isolated right varicoceles perform standard renal ultrasound to exclude a retroperitonal mass.	Strong

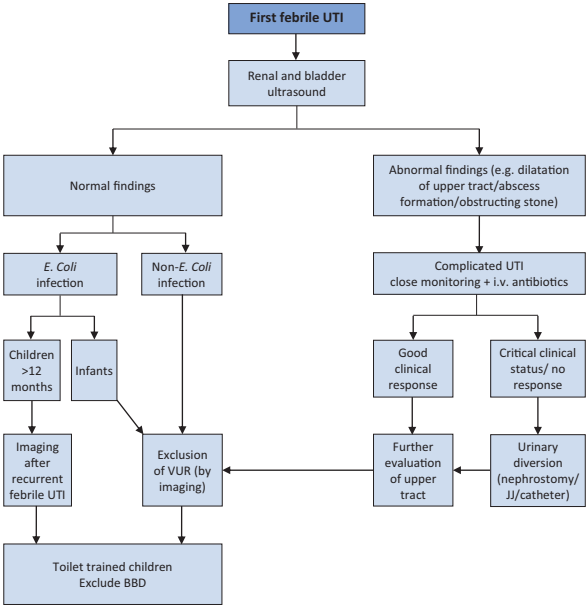
Inform caregivers and patients and offer surgery for: • varicocele associated with a persistent small testis (size difference of > 2 mL or 20%); • varicocele associated with additional testicular condition affecting fertility (cryptorchidism, history of torsion, trauma); • varicocele associated with pathological sperm quality (in older adolescents); • symptomatic varicocele.	Weak
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	Strong
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	Strong

Figure 6: Algorithm for the management of a first febrile UTI



CRP = C-reactive protein; AB = antibiotic

Figure 7: Diagnosis strategy for first febrile UTI



BBD = bladder and bowel dysfunction; VUR = vesicoureteral reflux; i.v. = intravenous.

Recommendations	Strength rating
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	Strong

Exclude bladder- and bowel dysfunction in any toilet-trained child with febrile and/or recurrent UTI.	Strong
Clean catch urine can be used for screening for UTI. Bladder catheterisation and suprapubic bladder aspiration to collect urine can be used for urine cultures.	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results.	Strong
Midstream urine is an acceptable technique for toilet-trained children.	Strong
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; complicated pyelonephritis.	Strong
Treat febrile UTIs with four to seven day courses of oral or parenteral therapy.	Strong
Treat complicated febrile UTI with broad-spectrum antibiotics.	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	Strong
In selected cases consider dietery supplements as an alternative or add-on preventive measure.	Strong
In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract within 24 hours.	Strong

In infants, exclude vesicoureteral reflux after first epidose of febrile UTI with a non-*E. Coli* infection. In children more than one year of age with an *E. Coli* infection, exclude VUR after the second febrile UTI.	Strong

DAY-TIME LOWER URINARY TRACT DYSFUNCTION

Urinary incontinence in children may be caused by congenital or neurologic abnormalities, however, many children have functional bladder problems for which the term day-time lower urinary tract (LUT) conditions is used. Day-time LUTD has a high prevalence ranging between 1%-20%. Symptoms can be classified as filling-phase (storage) dysfunctions and voding-phase (emptying) dysfunctions.

Table 1: Management algorithm

Children above 5 years of age applying with LUTS
DIAGNOSTIC WORK-UP
Voiding diary 2-3 full days minimum
Bristol Stool scale
Physical exam - To exclude neurogenic pathology or anatomic problems (meatal stenosis, labial fusion)
Urinalysis - To exclude presence of UTO or any other pathology (DM, DI)
Uroflowmetry and PVR determination (USG or bladder scan) - To evaluate urine flow and emptying efficacy
Questionnaires (optional) - To evaluate voiding and bowel habits, wetting severity/ frequency, fluid intake, quality of life

Ultrasonography (optional) - To determine bladder wall thickness, upper tract changes, signs of constipation
Urodynamic studies (not required unless refractory to management)
VCUG (only required if recurrent febrile UTI is present)
MANAGEMENT
- If UTI is present, treat UTI first - If constipated, treat bowel first with dietary changes and laxatives - Urotherapy is initial therapy in all cases to maintain controlled fluid intake, regular and efficient bladder emptying - Medical treatment (anticholinergics); if OAB symptoms dominate and persist despite urotherapy - Antibiotic prophylaxis: in case of recurrent UTI - Biofeedback is optional as first line therapy as part of urotherapy program; otherwise it is recommended if refractory to urotherapy - Neural stimulation or Botulinum Toxin A injection in detrusor is suggested if refractory to urotherapy and medical treatment but is still experimental

Recommendations	Strength rating
Use two day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits and response to treatment.	Strong
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction in children.	Weak

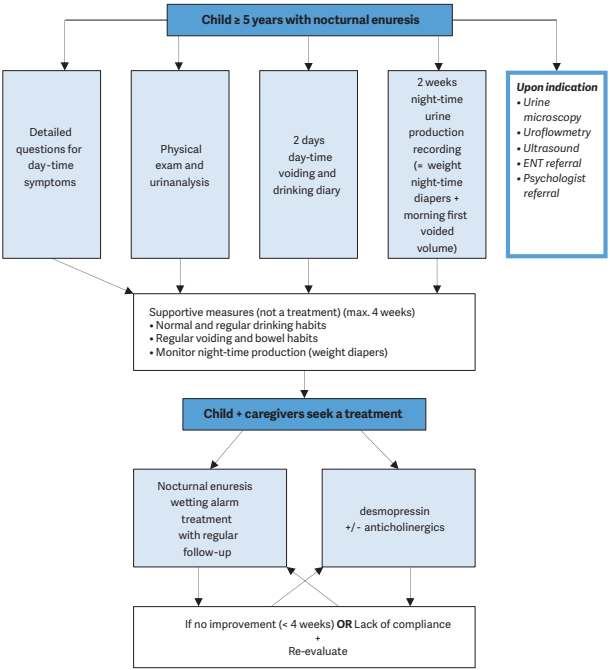
Initially offer urotherapy involving bladder rehabilitation and bowel management.	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second-line therapy in overactive bladder.	Strong
Use antibiotic prophylaxis if there are recurrent infections.	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics MRI of lumbosacral spine and other diagnostic modalities, guiding to off-label treatment which should only be offered in highly experienced centres.	Weak

MONOSYMPTOMATIC NOCTURNAL ENURESIS - BEDWETTING

Monosymptomatic nocturnal enuresis is incontinence during the night without daytime symptoms above the age of five years. Due to an imbalance between night-time urine output and night-time bladder capacity, the bladder can easily become full at night, and the child will either wake-up to empty the bladder or will void during sleep.

A voiding diary, registering the day-time bladder function and the night-time urine output will help guide the treatment.

Figure 8: A stepwise assessment and management options for nocturnal enuresis



ENT = ear, nose, throat

Recommendations	Strength rating
Do not treat children less than five years of age in whom spontaneous cure is likely, but inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition.	Strong
Use voiding diaries or questionnaires to exclude day-time symptoms.	Strong
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	Strong
Offer desmopressin in proven night-time polyuria.	Strong
Offer alarm treatment in motivated and compliant families.	Strong

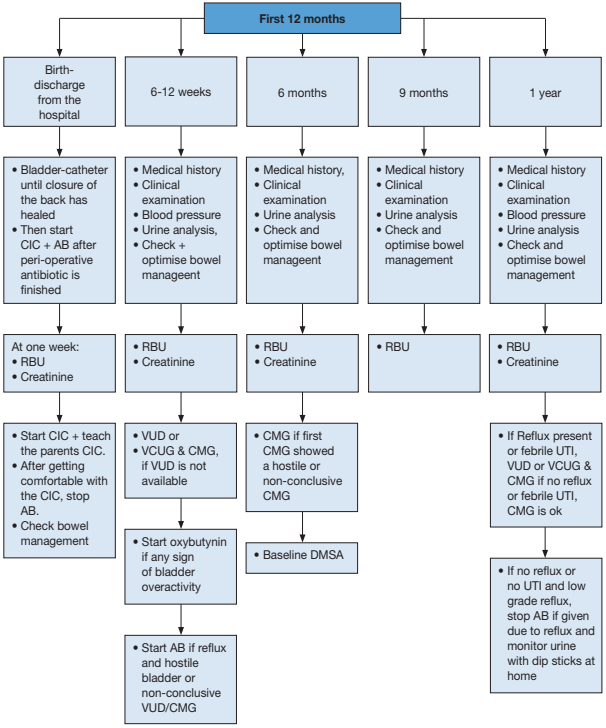
MANAGEMENT OF NEUROGENIC BLADDER

Neurogenic detrusor-sphincter dysfunction may result in different forms of lower urinary tract dysfunctions and in incontinence, urinary tract infections, vesico-ureteral reflux, renal scarring and renal insufficiency. The most common cause in children is myelodysplasia. Bladder and bowel dysfunction correlates poorly with the type and level of the spinal cord lesion. Therefore, urodynamic and functional classifications are required to define the extent of the pathology and in guiding treatment planning. Children with neurogenic bladder can also have disturbances of bowel and sexual function. The main goals of treatment are prevention of

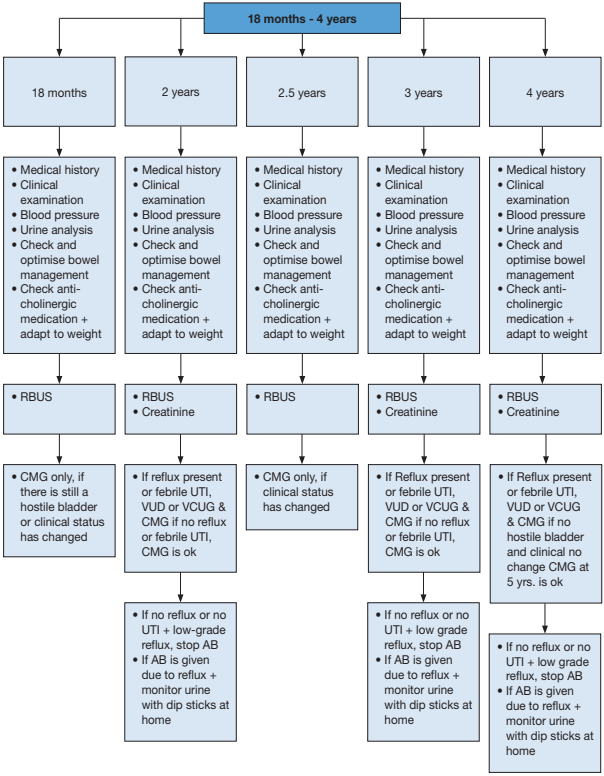
urinary tract deterioration, achievement of continence at an appropriate age and also improving quality of life.

Figure 9: Management of children with myelodysplasia with a neurogenic bladder

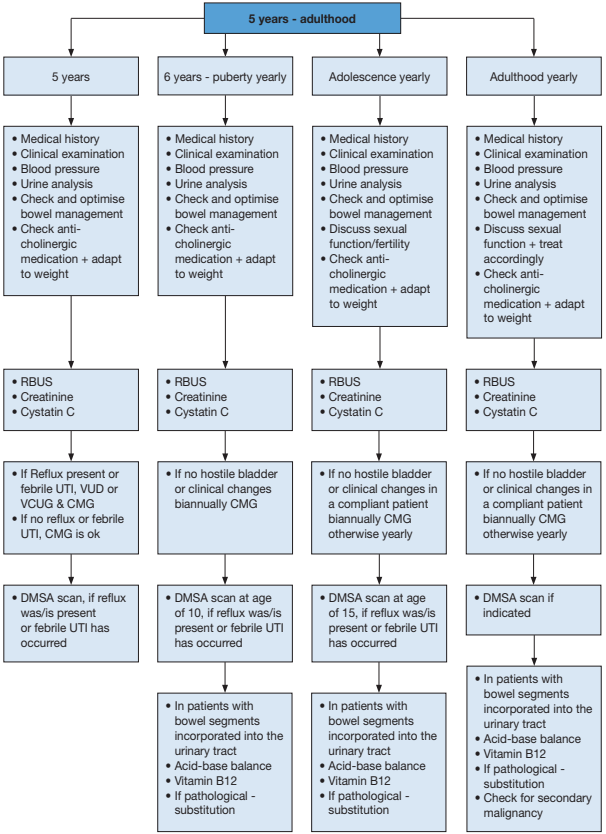
Flowchart - First year of life



Flowchart - 18 months – 4 years of age

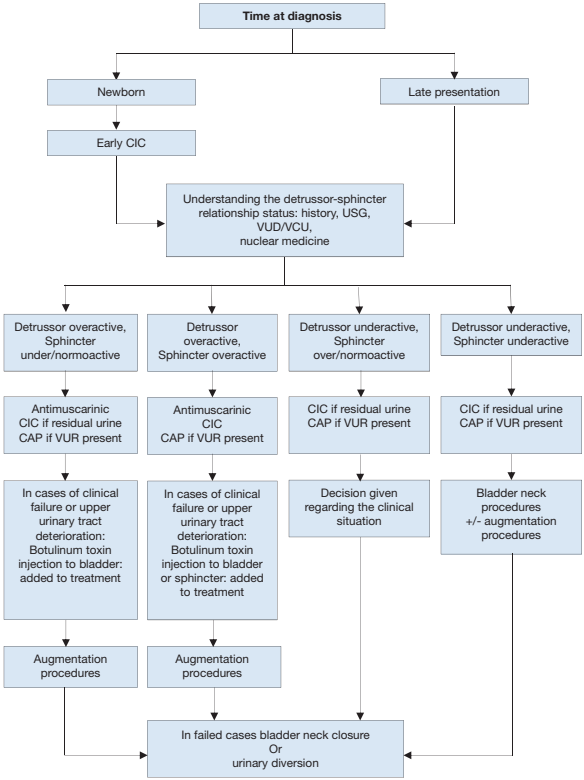


Flowchart - 5 years to adulthood



RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid.

Figure 10: Algorithm for the management of children with myelodysplasia with a neurogenic bladder



CAP = continuous antibiotic prophylaxis;
CIC = clean intermittent catheterisation; US = ultrasound;
VCUG = voiding cystourethrography; VUD = videourodynamic;
VUR = vesicoureteric reflux.

Recommendations	Strength rating
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and lower tract (UD).	Strong
Start early anticholinergic medication in the newborns with suspicion of an overactive detrusor.	Strong
The use of suburothelial or intradetrusoral injection of onabotulinum toxin A is an alternative and a less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	Strong
Treatment of faecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	Strong

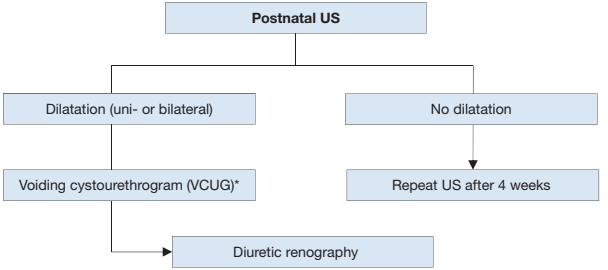
Ileal or colonic bladder augmentation is recommended in patients with therapy-resistant overactivity of the detrusor, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risk of surgical and non-surgical complications and consequences outweigh the risk of permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing an IC through the urethra.	Weak
A life-long follow-up of renal and reservoir function should be available and offered to every patient. Addressing sexuality and fertility starting before/during puberty should be offered.	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	Weak

DILATATION OF THE UPPER URINARY TRACT (UPJ AND UVJ OBSTRUCTION)

Dilatation of the upper urinary tract remains a significant clinical challenge in deciding which patient will benefit from treatment. Ureteropelvic junction obstruction is the most common pathological cause of neonatal hydronephrosis.

Megaureters (obstruction at the level of the ureterovesical junction) are the second most likely cause of pathological neonatal hydronephrosis. The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis. The challenge in the management of dilated upper tracts is to decide which child should be observed, which managed medically, and which requires surgical intervention.

Figure 11: Diagnostic algorithm for dilatation of the upper urinary tract



** A diagnostic work-up including VCUG must be discussed with the caregivers, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of prenatally detected cases.*

US = ultrasound.

Recommendations	Strength rating
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourethrography in post-natal investigations.	Strong

Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection like uncircumcised infants, children diagnosed with hydroureteronephrosis and highgrade hydronephrosis, respectively.	Weak
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	Weak
Offer surgical intervention in case of an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the US, and grade IV dilatation as defined by the Society for Fetal Urology.	Weak
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	Weak
Do not offer surgery as a standard for primary megaureters since the spontaneous remission rates are as high as 85%.	Weak

VESICOURETERIC REFLUX IN CHILDREN

Vesicoureteric reflux presents with a wide range of severities, and the majority of reflux (VUR) patients will not develop renal scars and probably will not need any intervention. The main goal in management is the preservation of kidney function.

The diagnostic work-up should evaluate the overall health and development of the child including a detailed medical history

(including family history, and screening for lower urinary tract dysfunction [LUTD]), physical examination together with blood pressure measurement, urinalysis (assessing proteinuria), urine culture, and serum creatinine in patients with bilateral renal parenchymal abnormalities. Voiding cystourethrography still remains the gold standard in diagnosing VUR.

Recommendations	Strength rating
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	Strong
Use renal ultrasound (US) for screening of sibling(s).	Strong
Use voiding cystourethrography if there is evidence of renal scarring on US or a history of urinary tract infection.	Weak
Do not screen older toilet-trained children since there is no added value in screening for VUR.	Weak

Recommendations	Strength rating
Initially treat all patients diagnosed within the first year of life with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	Weak
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	Weak

Offer open surgical correction to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
Initially manage all children presenting at age one to five years conservatively.	Strong
Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all and especially in children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	Strong
Offer surgical correction, if parents prefer definitive therapy to conservative management.	Strong

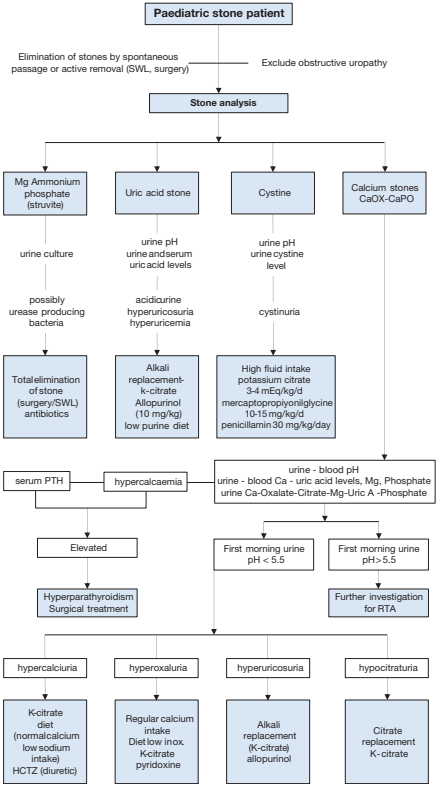
Select the most appropriate management option based on: • the presence of renal scars; • clinical course; • the grade of reflux; • ipsilateral renal function; • bilaterality; • bladder function; • associated anomalies of the urinary tract; • age and gender; • compliance; • parental preference. Refer to full guideline for risk factors and follow-up.	Weak
In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.	Strong

URINARY STONE DISEASE

Paediatric stone disease is an important clinical problem in paediatric urology practice. Due to its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately.

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. Adequate fluid intake and restricting the use of salt within daily allowance range are the general recommendations besides the specific medical treatment against the detected metabolic abnormalities.

Figure 12: Algorithm for metabolic investigations in urinary stone disease in children



Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = oxalate; PTH = parathyroid hormone; SWL = extracorporeal shockwave lithotripsy; RTA = renal tubular acidosis; Uric A = uric acid.

Table 2: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	Secondary treatment options	Comment
Staghorn stones	PCNL	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	RIRS/PCNL/ MicroPerc	
Pelvis 10-20 mm	SWL	PCNL/RIRS/ MicroPerc/ Open	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
Lower pole calyx	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
< 10 mm	SWL	RIRS/PCNL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.

Lower pole calyx	SWL	RIRS/PCNL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.
> 10 mm	PCNL	SWL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	PCNL/URS/ Open	
Upper ureteric stones	URS	SWL/Open	Additional inter-vention need is high with SWL.
Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.
Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.

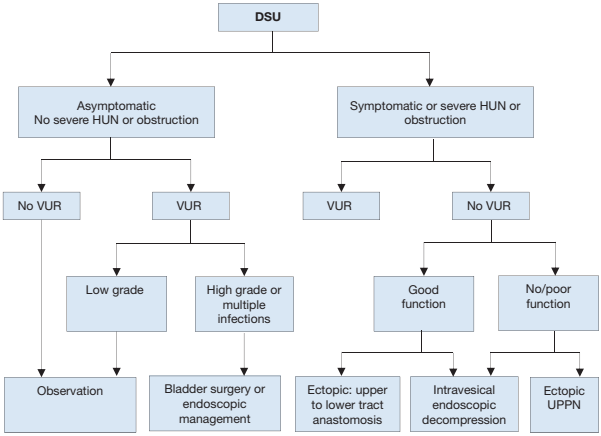
** Cystine and uric acid stones excluded.*
PCNL = percutaneous nephrolithostomy; SWL = shockwave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

Recommendations	Strength rating
Use plain abdominal X-ray and ultrasound as the primary imaging techniques for the diagnosis and follow-up of stones.	Strong
Use low-dose non-contrast computed tomography in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	Strong
Perform a metabolic evaluation in any child with urinary stone disease. Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	Strong
Limit open surgery under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopaedic deformities that limit positioning for endoscopic procedures.	Strong

OBSTRUCTIVE PATHOLOGY OF RENAL DUPLICATION: URETEROCELE AND ECTOPIC URETER

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication. Antenatal US detects both conditions in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth. 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). Ectopic ureter is less frequent than ureterocele and more common in females with some remaining asymptomatic.

Figure 13: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life



DSU = duplex system ureterocele; HUN = hydroureteronephrosis; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

Recommendations			Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/ dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, complete primary reconstruction. Offer, early endoscopic decompression to patients with an obstructing ureterocele.	Weak

Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	Weak
	Treatment	In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ ureteroureterostomy/ ureteropyelostomy and upper-pole ureterectomy) are other therapeutic option especially in cases in which the upper pole has function worth preserving.	Weak

DISORDERS OF SEX DEVELOPMENT

The term 'disorders of sex development' is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex. Dealing with neonates with DSD requires a multidisciplinary approach, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers with each team member specialised in DSD.

Table 3: Findings in a newborn suggesting the possibility of DSD

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 4: Diagnostic work-up of neonates with disorders of sex development

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 to confirm presence of testicular tissue
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone.

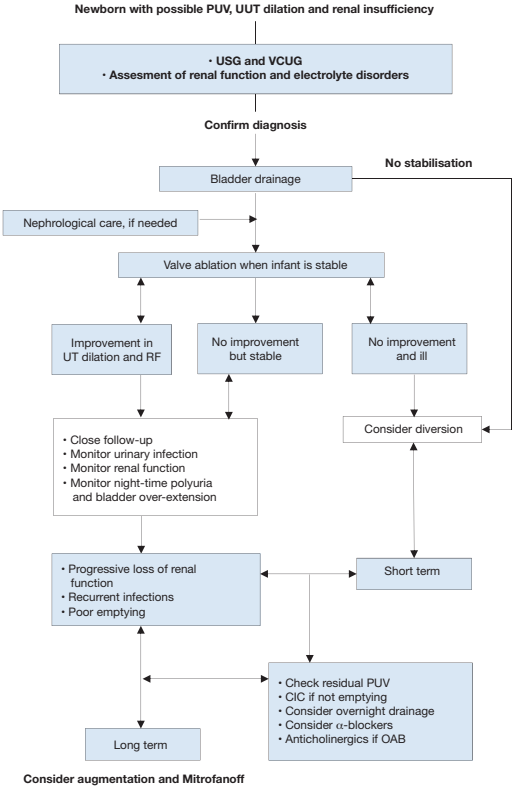
Recommendations	Strength rating
Newborns with DSD conditions warrant a multidisciplinary team approach.	Strong
Refer children to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.	Strong
Do not delay diagnosis and treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.	Strong

CONGENITAL LOWER URINARY TRACT OBSTRUCTION (CLUTO)

The term congenital lower urinary tract obstruction (CLUTO) is used for a foetus, which during intrauterine US screening shows a dilatation of the upper and lower urinary tract. During pregnancy the diagnosis is usually based on US examinations

only. There is a broad spectrum of conditions causing such a condition. Postpartum diagnosis comprises any anatomical and functional disorder, anomaly, and malformation causing a dilatation such as posterior and anterior urethral valves, urethral atresia, dysplasia and stenosis, Prune Belly syndrome, and dilating reflux. Moreover cloacal malformation, ureterocele, a Megacystis-Microcolon-intestinal hypoperistalsis or Megacystis-Megaureter syndrome belong to the CLUTO spectrum as well.

Figure 14: Algorithm the assessment, management and follow-up of newborns with possible PUV



CIC = clean intermittent catheterisation; OAB = overactive bladder; PUV = posterior urethral valve; RF = renal function; UT = urinary tract; UUT = upper urinary tract; VCUG = voiding cystourethrogram.

Recommendations	Strength rating
Diagnose posterior urethral valves (PUV) initially by ultrasound but a voiding cystourethrogram (VCUG) is required to confirm the diagnosis.	Strong
Assess split renal function by dimercaptosuccinic acid scan or mercaptoacetyltriglycine (MAG3) clearance. Use serum creatinine as a prognostic marker.	Strong
Vesico-amniotic shunt antenatally is not recommended to improve renal outcome.	Weak
Offer endoscopic valve ablation after bladder drainage and stabilisation of the child.	Strong
Offer suprapubic diversion for bladder drainage if the child is too small for valve ablation.	Strong
Offer a high urinary diversion if bladder drainage is insufficient to drain the upper urinary tract and the child remains unstable.	Strong
Monitor bladder and renal function lifelong, in all patients.	Strong

RARE CONDITIONS:

Urachal remants

Urachal remnants originate from failure of the obliteration of the allantois, resulting in a urachal anomaly such as urachal sinus, urachal cyst, vesico-urachal diverticulum, and patent urachus, respectively. Most often the urachal anomaly is asymptomatic, but it occasionally may become infected, may cause urinary symptoms, or may develop a urachal carcinoma in later life.

Recommendations	Strength rating
Urachal remnants with no epithelial tissue carry little risk of malignant transformation.	Strong
Asymptomatic and non-specific atretic urachal remnants can safely be managed non-operatively.	Strong
Urachal remnants incidentally identified during diagnostic imaging for non-specific symptoms should also be observed non-operatively since they tend to resolve spontaneously.	Strong
A small urachal remnant, especially at birth, may be viewed as physiological.	Strong
Urachal remnants in patients younger than six months are likely to resolve with non-operative management.	Strong
Follow-up is necessary only when symptomatic for six to twelve months.	Strong
Surgical excision of urachal remnants solely as a preventive measure against later malignancy appears to have minimal support in the literature.	Strong
Only symptomatic urachal remnants should be safely removed by open or laparoscopic approach.	Strong
A VCUG is only recommended when presenting with febrile urinary tract infections.	Strong

Papillary tumours of the bladder

Papillary tumours of the bladder in children and adolescents are extremely rare and are different from papillary tumours in adults.

Recommendations	Strength rating
Ultrasound is the first investigation of choice for the diagnosis of paediatric bladder tumours.	Strong
Cystoscopy should be reserved if a bladder tumor is suspected on imaging for diagnosis and treatment.	Strong
After histological confirmation, inflammatory myofibroblastic bladder tumours should be resected locally.	Weak
Follow-up should be every 3-6 months in the first year, and thereafter at least annually with urinanalysis and an ultrasound for at least 5 years.	Weak

Penile lesions

Paediatric lesions of the penis are uncommon but an important part of the paediatric urological practice. The commonest of these lesions are cystic penile lesions followed by vascular malformations and neurogenic lesions. Soft tissue tumours of the male external genitalia are uncommon, but have been described in the paediatric age group and can be malignant.

Recommendations	Strength rating
Treatment of penile cystic lesions is by total surgical excision, it is mainly indicated for cosmetic or symptomatic (e.g. infection) reasons.	Weak
Propranolol is currently first-line treatment for infantile haemangiomas.	Strong

Penile lymphedema

Paediatric lymphedema is usually primary and generally very rare. Inefficient lymphatic drainage leads to accumulation of subcutaneous lymph causing tissue swelling and inflammation and subsequently stimulates adipose deposition and fibrosis further exacerbating enlargement. With time the edematous tissue becomes vulnerable to infection, chronic cutaneous changes and disfigurement. Complications may ensue such as phimosis, haematuria, bleeding, bladder outlet obstruction, pain, dysuria, lymphorrhea and severe psychological distress due to resultant deformity.

Recommendations	Strength rating
Conservative management is the first-line treatment for penile lymphedema.	Weak
In symptomatic cases or in patients with functional impairment, surgical intervention may become necessary for penile lymphedema.	Weak

PAEDIATRIC UROLOGICAL TRAUMA

In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract. This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, and sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

Paediatric renal trauma

Table 5: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma

Grade	Type of injury	Description
I	Contusion	Non-visible or visible haematuria
	Haematoma	Normal urological studies
II	Haematoma	Non-expanding subcapsular haematoma
	Laceration	Laceration of the cortex of < 1.0 cm
III	Laceration	Laceration > 1.0 cm without rupture of collecting system
IV	Laceration	Through the cortex, medulla and collecting system
	Vascular	Vascular injury
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of the renal hilum

Recommendations	Strength rating
Use imaging in all children who have sustained a blunt or penetrating trauma with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	Strong
Use rapid spiral computed tomography with delayed images scanning for diagnostic and staging purposes.	Strong
Manage most injured kidneys conservatively.	Strong
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	Strong

Paediatric ureteral trauma

Recommendations	Strength rating
Diagnose suspected ureteral injuries by retrograde pyelogram.	Strong
Manage ureteral injuries endoscopically, using internal stenting or drainage of an urinoma, either percutaneously or via a nephrostomy tube.	Weak

Paediatric bladder injuries

Recommendations	Strength rating
Use retrograde cystography to diagnose suspected bladder injuries.	Strong
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	Strong
Manage extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	Strong
Do not delay treatment of intra-peritoneal bladder ruptures by surgical exploration and repair as well as post-operative drainage for seven to ten days.	Strong

Paediatric urethral injuries

Recommendations	Strength rating
Assess the urethra by retrograde urethrogram in case of suspected urethral trauma.	Strong

Perform a rectal examination to determine the position of the prostate.	Strong
Manage bulbous urethral injuries conservatively with a transurethral catheter.	Strong
Manage posterior urethral disruption by either: • primary reconstruction; • primary drainage with a suprapubic catheter alone and delayed repair; • primary re-alignment with a transurethral catheter.	Weak

PERI-OPERATIVE FLUID MANAGEMENT

Children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms, compared to adults. Therefore special child specific requirements regarding preoperative fasting and intra- as well as post-operative fluid have to be considered and close monitoring is essential. This is especially true for interventions relieving any kind of obstruction as this may result in substantial polyuria.

Table 6: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (hours)
Clear liquids	1
Breast milk	4
Light meal	6

Table 7: Intra-operative fluid management

	Solution for infusion	Initial/repeated dose
Background infusion	Balanced isotonic solution + 1-2% glucose	10mL/kg/h
Fluid therapy	Balanced isotonic solution	X 10-20 mL/kg
Volume therapy	Albumin, Gelatine, HES	X 5-10 mL/kg
Transfusion	Red blood cells, fresh frozen plasma, platelets	X 10 mL/kg

Recommendations	Strength rating
Ensure shorter pre-operative fasting periods for elective surgeries (up to one hour for clear liquids).	Strong
Use ERAS protocols for abdominal surgery in children with normal bowel movement.	Strong
Use isotonic solutions in hospitalised children because they are at high risk of developing hyponatraemia.	Strong
Assess the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen since there is an increased risk of electrolyte abnormalities in children undergoing such surgery.	Strong
Start early oral fluid intake in all patients scheduled for minor surgical procedures.	Strong

POST-OPERATIVE PAIN MANAGEMENT

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia.

A proposed strategy for post-operative analgesia may be as follows:

1. Intra-operative regional or caudal block.
2. Paracetamol + NSAID.
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine).
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine).

Recommendations	Strength rating
Prevent/treat pain in children of all ages.	Strong
Evaluate pain using age-compatible assessment tools.	Strong
Inform patients and caregivers accurately.	Strong
Use pre-emptive and balanced analgesia in order to decrease the side effects of opioids.	Strong

BASIC PRINCIPLES OF LAPAROSCOPIC SURGERY IN CHILDREN

Laparoscopy in children requires specific anaesthetic precautions. Physiological effects of CO2 pneumoperitoneum, positioning of the patient and operative time need to be considered by the anaesthesiology team.

Recommendations	Strength rating
Use lower intra-abdominal pressure (6-8 mmHg) during laparoscopic surgery in infants and smaller children.	Strong
Use open access for laparoscopy in infants and smaller children.	Strong
Monitor for laparoscopy-related cardiac, pulmonary and diuretic responses.	Strong

This short booklet text is based on the more comprehensive EAU Paediatric Urology Guidelines (978-94-92671-13-4), available at their website, http://www.uroweb.org/guidelines.

EAU GUIDELINES ON UROLOGICAL TRAUMA

(Limited text update March 2021)

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Introduction

Traumatic injuries are classified according to the basic mechanism of the injury into **penetrating** and blunt injuries. Penetrating trauma is further classified according to the velocity of the projectile into high- and medium-velocity projectiles (e.g. rifle and handgun bullets, respectively), and low-velocity items (e.g. knife stab). High-velocity weapons inflict greater damage due to a temporary expansive cavitation that causes destruction in a much larger area than the projectile tract itself. In lower velocity injuries, the damage is usually confined to the projectile tract. **Blast injury** is a complex cause of trauma which includes blunt and penetrating trauma and burns.

Urological trauma is often associated with significant injuries in the polytraumatised patient. Advances in trauma care include the widespread acceptance of damage control principles and trauma centralisation to major trauma centres staffed by dedicated trauma teams. Urologists increasingly understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients.

Renal Trauma

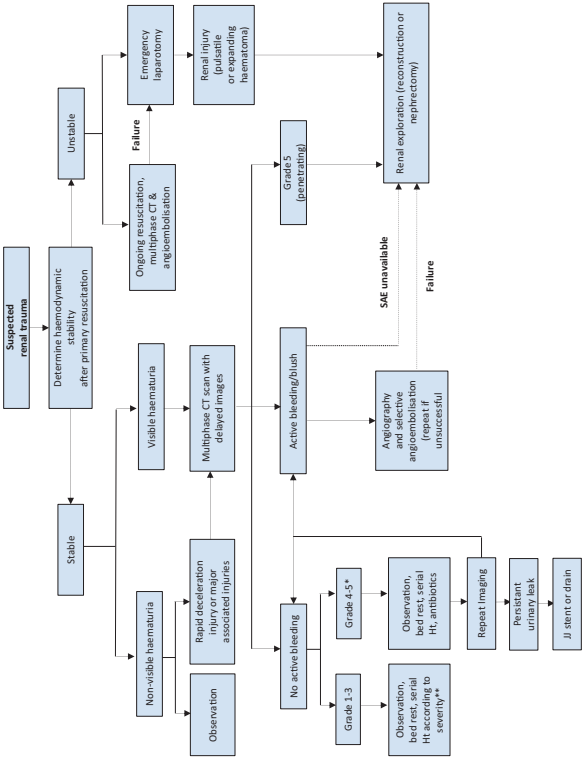
Renal trauma is present in to up 5% of all trauma cases. It is most common in young males and has an overall population incidence of 4.9 per 100,000. Most injuries can be managed non-operatively with successful organ preservation. The most commonly used classification system is that of the American Association for the Surgery of Trauma. It is validated and predicts morbidity and the need for intervention.

Recommendations for evaluation and management of renal trauma

Recommendations	Strength rating
Evaluation	
Assess haemodynamic stability upon admission.	Strong
Record past renal surgery, and known pre-existing renal abnormalities (ureteropelvic junction obstruction, solitary kidney, lithiasis).	Strong
Test for haematuria in a patient with suspected renal injury.	Strong
Perform a multiphase computed tomography scan in trauma patients with: • visible haematuria; • non-visible haematuria and one episode of hypotension; • a history of rapid deceleration injury and/or significant associated injuries; • penetrating trauma; • clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.	Strong

Management	
Manage stable patients with blunt renal trauma non-operatively with close monitoring and re-imaging as required.	Strong
Manage isolated Grade 1-4 stab and low-velocity gunshot wounds in stable patients non-operatively.	Strong
Use selective angioembolisation for active renal bleeding if there are no other indications for immediate surgical exploration.	Strong
Proceed with renal exploration in the presence of: • persistent haemodynamic instability; • Grade 5 vascular or penetrating injury; • expanding or pulsatile peri-renal haematoma.	Strong
Attempt renal reconstruction if haemorrhage is controlled and there is sufficient viable renal parenchyma.	Weak
Repeat imaging in high-grade injuries and in cases of fever, worsening flank pain, or falling haematocrit.	Strong
Follow-up approximately three months after major renal injury with: • physical examination; • urinalysis; • individualised radiological investigation including nuclear scintigraphy; • blood pressure measurement; • renal function tests.	Weak
Measure blood pressure annually to diagnose renovascular hypertension.	Strong

Figure 1: Management of renal trauma



* *Excluding Grade 5 penetrating injuries.*
** *Antibiotics should for administered for all penetrating injuries.*
--- *If haemodynamically unstable.*
CT = computed tomography; Ht = haematocrit; SAE = selective angioembolisation.

Ureteral Trauma

Ureteral injuries are quite rare - most are iatrogenic. They are often missed intra-operatively, usually involve the lower ureter, and may result in severe sequelae. Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma. Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, as it occurs in 2-3% of cases. It should also be suspected in blunt trauma with a deceleration mechanism, as the renal pelvis can be torn away from the ureter.

Diagnostic evaluation

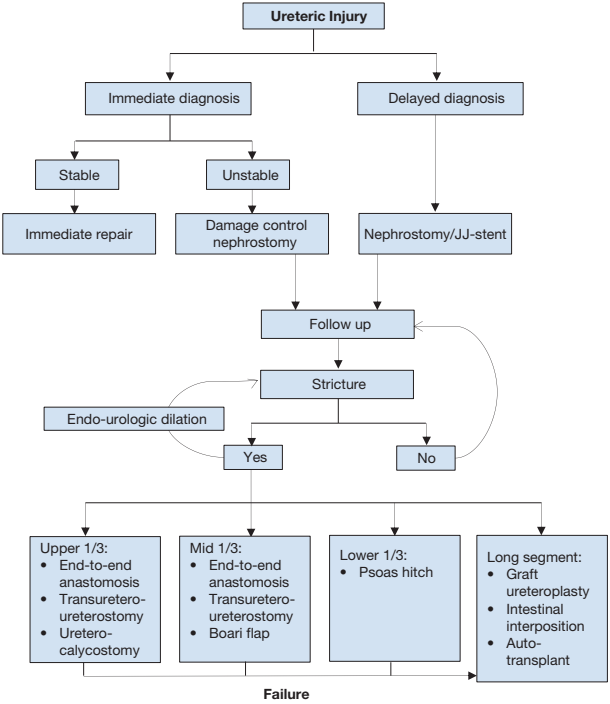
- A high index of suspicion of ureteral injury should be maintained as the majority of cases are diagnosed late, predisposing the patient to pain, infection, and renal function impairment.
- Haematuria is an unreliable indicator.
- Extravasation of contrast material in computed tomography (CT) is the hallmark sign of ureteral trauma.
- In unclear cases, a retrograde or antegrade urography is required for confirmation.

Management of ueteral trauma

Recommendations	Strength rating
Visually identify the ureters to prevent ureteral trauma during abdominal and pelvic surgery.	Strong
Beware of concomitant ureteral injury in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	Strong
Use pre-operative prophylactic stents in high-risk cases.	Strong

Repair iatrogenic ureteral injuries recognised during surgery immediately.	Strong
Treat iatrogenic ureteral injuries with delayed diagnosis by nephrostomy tube/JJ stent urinary diversion.	Strong
Manage ureteral strictures by ureteral reconstruction according to the location and length of the affected segment.	Strong

Figure 2: Management of ureteric injuries



Bladder Trauma

Bladder trauma is primarily classified according to the location of the injury: **intraperitoneal, extraperitoneal**, and **combined** intra-extraperitoneal as it guides further management. Bladder trauma is categorised by aetiology: **non-iatrogenic** (blunt and penetrating) and **iatrogenic** (external and internal). Extraperitoneal injury is almost always associated with pelvic fractures. Intraperitoneal injury is caused by a sudden rise in intravesical pressure of a distended bladder, secondary to a blow to the pelvis or lower abdomen.

Diagnostic evaluation

The principal sign of bladder injury is visible haematuria. Absolute indications for bladder imaging include: visible haematuria and a pelvic fracture or non-visible haematuria combined with high-risk pelvic fracture or posterior urethral injury. In the absence of these absolute indications, further imaging is based on clinical signs and symptoms including:

- inability to void or inadequate urine output;
- abdominal tenderness or distension due to urinary ascites, or signs of urinary ascites in abdominal imaging;
- uraemia and elevated creatinine level due to intraperitoneal re-absorption;
- entry/exit wounds at lower abdomen, perineum or buttocks in penetrating injuries.

Intra-operative signs of external iatrogenic bladder injury include: extravasation of urine, visible laceration, visible bladder catheter, and blood and/or gas in the urine bag during laparoscopy. Internal bladder injury is recognised by cystoscopic identification of fatty tissue, dark space, or bowel.

Imaging – Cystography and Cystoscopy

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected iatrogenic

bladder trauma in the post-operative setting. Intraperitoneal extravasation is visualised by free contrast medium in the abdomen outlining bowel loops or abdominal viscera. Extraperitoneal bladder injury is typically diagnosed by flame-shaped areas of contrast extravasation in the peri-vesical soft tissues. **Cystoscopy** is the preferred method for detection of intra-operative bladder injuries as it may directly visualise the laceration and can localise the lesion in relation to the position of the trigone and ureteral orifices.

Management of bladder trauma

Recommendations	Strength rating
Perform cystography in the presence of visible haematuria and pelvic fracture.	Strong
Perform cystography in case of suspected iatrogenic bladder injury in the post-operative setting.	Strong
Perform cystography with active retrograde filling of the bladder with dilute contrast (300-350 mL).	Strong
Perform cystoscopy to rule out bladder injury during retropubic sub-urethral sling procedures.	Strong
Manage uncomplicated blunt extra-peritoneal bladder injuries conservatively.	Weak
Manage blunt extraperitoneal bladder injuries operatively in cases of bladder neck involvement and/or associated injuries that require surgical intervention.	Strong
Manage blunt intraperitoneal injuries by surgical exploration and repair.	Strong

Manage small uncomplicated intra-peritoneal bladder injuries during endoscopic procedures conservatively.	Weak
Perform cystography to assess bladder wall healing after repair of a complex injury or in case of risk factors for wound healing.	Strong

Urethral Trauma

- Injuries to the anterior urethra are caused by straddle injuries, trauma during sexual intercourse (associated with penile fracture), penetrating trauma and from iatrogenic trauma e.g. endoscopic instruments, catheterisation.
- Pelvic fractures are the predominant cause of male posterior and female urethral injury.
- Pelvic fracture and penetrating urethral injuries have a high likelihood of life-threatening concomitant injuries.
- Female urethral injuries are often associated with vaginal injuries.
- Insertion of a synthetic sub-urethral sling for the treatment of stress urinary incontinence is an important cause of iatrogenic **female** urethral injury.

Diagnostic evaluation

- Blood at the external urethral meatus is the most common clinical sign, and indicates the need for further diagnostic work up.
- Inability to void is usually a sign of a complete injury.
- Incomplete injuries are associated with pain on urination and haematuria in the majority of cases.
- Blood at the vaginal introitus is present in the majority of female patients with pelvic fractures and co-existing urethral injuries.
- Rectal examination may reveal a "high-riding" prostate. However, this is an unreliable finding. Blood on the examination finger is suggestive of a rectal injury

associated with pelvic fracture.

- Urethral bleeding or urinary extravasation can cause penile and scrotal swelling and haematoma, but these findings are usually delayed (> 1 hr).
- Retrograde urethrography is the standard in the early evaluation of a male urethral injury, except for penile fracture related injuries for which cysto-urethroscopy is preferred.
- Cysto-urethroscopy combined with vaginoscopy is the preferred diagnostic modality in case of suspected female urethral injury.

Management

Male urethral injuries

- The management of male anterior and posterior urethral injuries are summarised in Figure 3 and 4, respectively.

Female urethal injuries

- In case of haemodynamic instability, provide urinary diversion by suprapubic catherisation or a single attempt at urethral catheterisation.
- Early repair within seven days has the highest succes rate and the lowest complication rate in comparison with delayed repair or early endoscopic re-aligment.

Management of urethral trauma

Recommendations	Strength rating
Provide appropriate training to reduce the risk of traumatic catheterisation.	Strong
Evaluate male urethral injuries with flexible cysto-urethroscopy and/or retrograde urethrography.	Strong
Evaluate female urethral injuries with cysto-urethroscopy and vaginoscopy.	Strong

Treat iatrogenic anterior urethral injuries by transurethral or suprapubic urinary diversion.	Strong
Treat partial blunt anterior urethral injuries by suprapubic or urethral catheterisation.	Strong
Treat complete blunt anterior urethral injuries by immediate urethroplasty, if surgical expertise is available, otherwise perform suprapubic diversion with delayed urethroplasty.	Weak
Treat pelvic fracture urethral injuries (PFUIs) in haemodynamically unstable patients by transurethral or suprapubic catheterisation initially.	Strong
Perform early endoscopic re-alignment in male PFUIs when feasible.	Weak
Do not repeat endoscopic treatments after failed re-alignment for male PFUI.	Strong
Treat partial posterior urethral injuries initially by suprapubic or transurethral catheter.	Strong
Do not perform immediate urethroplasty (< 48 hours) in male PFUIs.	Strong
Perform early urethroplasty (two days to six weeks) for male PFUIs with complete disruption in selected patients (stable, short gap, soft perineum, lithotomy position possible).	Weak
Manage complete posterior urethral disruption in male PFUIs with suprapubic diversion and deferred (at least three months) urethroplasty.	Strong
Perform early repair (within seven days) for female PFUIs (not delayed repair or early re-alignment).	Strong

Figure 3: Management of anterior urethral injuries in men

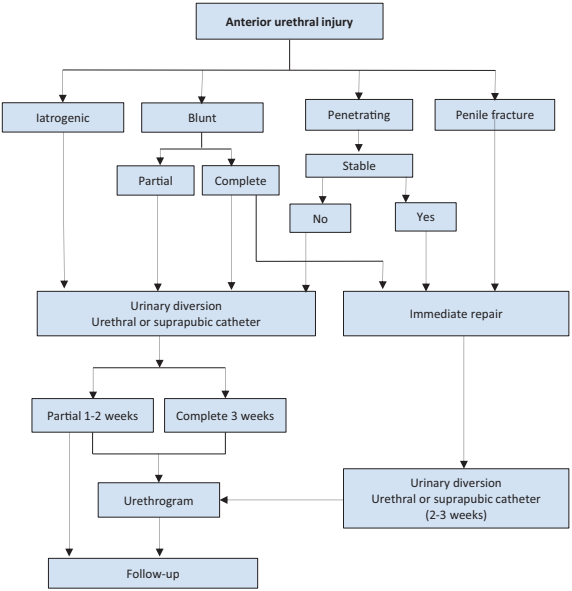
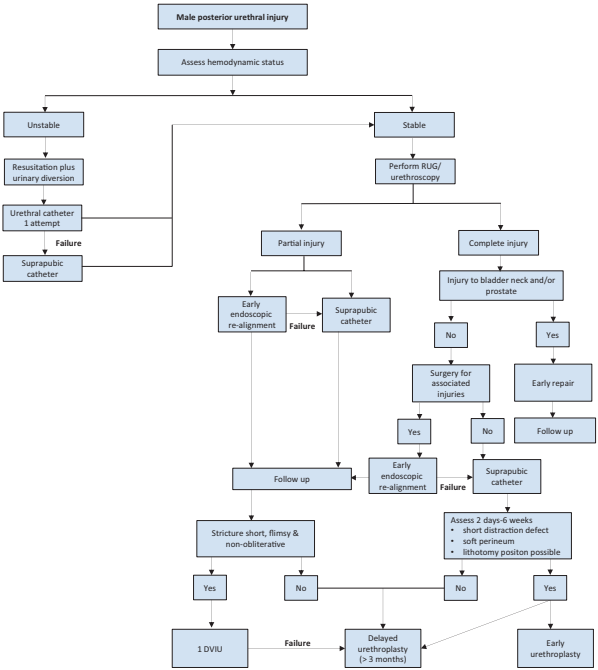


Figure 4: Management of posterior urethral injuries in men



RUG = retrograde urethrography; DVIU = direct visual internal urethrotomy.

Genital Trauma

Of all urological injuries, 33-66% involve the external genitalia. Genital trauma is much more common in males than in females this is due to anatomical differences, increased frequency of road traffic accidents and increased participation in physical sports, war and crime. The majority of genital trauma is caused by blunt injuries (80%).

Diagnostic evaluation

A summary of key points for penile fracture and testicular trauma are provided in Table 1. Blunt vulvar or perineal trauma in women may be associated with bleeding, pain and voiding problems. In genital trauma:

- Urinalysis should be performed.
- Visible haematuria requires a retrograde urethrogram in males, whilst flexible or rigid cystoscopy is recommended to exclude urethral and bladder injury in females.
- In women with genital injuries and blood at the vaginal introitus, further gynaecologic investigation to exclude vaginal injury is required.

Management

Penetrating penile trauma

- Non-operative management is recommended for small superficial injuries with intact Buck's fascia.
- More significant injuries require surgical exploration and debridement of necrotic tissue.
- Surgical approach depends upon the site and extent of the injury, but a subcoronal incision with penile degloving usually gives good exposure. Initially, a defect in the tunica albuginea should be closed after copious irrigation.
- In penile avulsion injuries acute management involves resuscitation of the patient, and preparation for surgical re-implantation of the penis if it has been recovered and is not too badly damaged.

Blunt scrotal trauma

- May result in testicular dislocation, haematocoele, testicular rupture and/or scrotal haematoma.
- Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.
- If haematocele is smaller than three times the size of the contralateral testis – conservative management.
- If large haematocele – explore.
- If testicular rupture suspected, explore, evacuate clot and any necrotic testicular tubules and close the tunica albuginea.

Penetrating scrotal trauma

- Surgical exploration with conservative debridement of non-viable tissue.
- Primary reconstruction of testis and scrotum can be performed in most cases.
- In complete disruption of the spermatic cord, re-alignment without vaso-vasostomy may be considered.
- In extensive destruction of the tunica albuginea, mobilisation of a free tunica vaginalis flap can be performed for testicular closure.
- If reconstruction cannot be achieved, orchiectomy is indicated.
- In improvised explosive device blast injury, the extensive loss of genital tissue often requires complex and staged reconstructive surgical procedures.

Table 1. Summary of key points for penile fracture and testicular trauma

Penile fracture
The most common causes of penile fracture are sexual intercourse, forced flexion, masturbation and rolling over.
Penile fracture is associated with a sudden cracking or popping sound, pain, immediate detumescence and local swelling.
Magnetic resonance imaging is superior to all other imaging techniques in diagnosing penile fracture.
Management of penile fracture is surgical intervention with closure of the tunica albuginea.
Testicular trauma
Blunt testicular injury may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea.
Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting.
Scrotal ultrasound is the preferred imaging modality for the diagnosis of testicular trauma.
Surgical exploration in patients with testicular trauma ensures preservation of viable tissue when possible.

Recommendations for the management of genital trauma

Recommendations	Strength rating
Exclude urethral injury in the case of penile fracture.	Strong
Perform ultrasound (US) for the diagnosis of testis trauma.	Strong
Treat penile fractures surgically, with closure of tunica albuginea.	Strong
Explore the injured testis in all cases of testicular rupture and in those with inconclusive US findings.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.

EAU GUIDELINES ON URETHRAL STRICTURES

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Introduction

The European Association of Urology (EAU) Urethral Strictures Guidelines aim to provide a comprehensive overview of urethral strictures in male, female and transgender patients. In this Guideline, the Panel agreed to avoid the term "success" as this is poorly defined and subjective. Instead, the term "patency rate" or "stricture recurrence rate" are used to clarify that only stricture recurrence was taken into consideration.

Aetiology and Prevention

The following pathologies are frequent causes of urethral stricture disease in males:

- Sexually transmitted infection;
- Inflammation;
- External urethral trauma;
- Iatrogenic urethral injury: urethral catheterisation, transurethral prostate surgery, radical prostatectomy, prostate radiation and ablative treatments;
- Failed hypospadias repair;
- Congenital;
- Idiopathic.

Urethral stricture disease in females is mainly idiopathic. Other etiologies are iatrogenic injury, trauma, infection and radiation therapy.

Recommendations	Strength rating
Advise safe sexual practices, recognise symptoms of sexually transmitted infection and provide access to prompt investigation and treatment for men with urethritis.	Strong
Avoid unnecessary urethral catheterisation.	Strong
Implement training programmes for physicians and nurses performing urinary catheterisation.	Strong
Do not use catheters larger than 18 Fr if urinary drainage only is the purpose.	Weak
Avoid using non-coated latex catheters.	Strong
Do not routinely perform urethrotomy when there is no pre-existent urethral stricture.	Strong

Classification

Classification according to stricture location will affect further management. The male urethra is divided into:

- Anterior urethra (surrounded by spongious tissue): meatus, penile urethra and bulbar urethra.
- Posterior urethra: membranous urethra, prostatic urethra and bladder neck.

For classification according to stricture tightness see Table 1.

Table 1: EAU classification according to the degree of urethral narrowing

Category	Description	Urethral lumen (French [Fr.])	Degree
0	Normal urethra on imaging	-	-
1	Subclinical strictures	Urethral narrowing but ≥ 16 Fr	Low
2	Low grade strictures	11-15 Fr	
3	High grade or flow significant strictures	4-10 Fr	High
4	Nearly obliterative strictures	1-3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

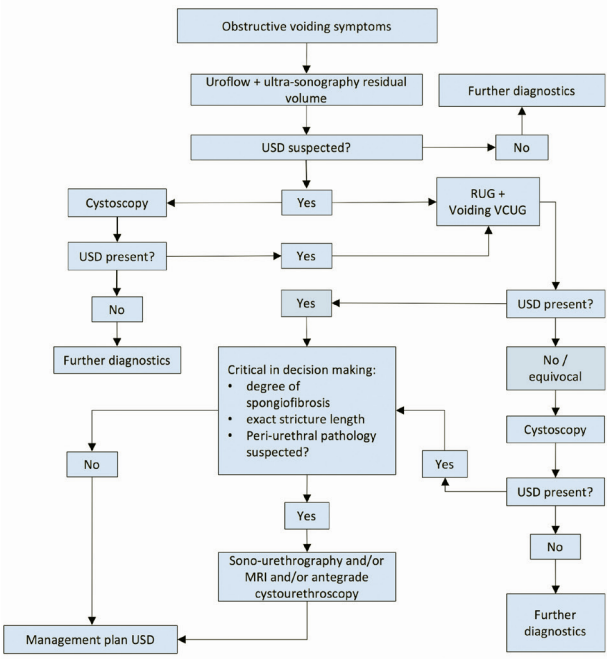
Diagnostic Evaluation

History taking and physical examination

Recommendations	Strength rating
Use a validated patient reported outcome measure (PROM) to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease.	Strong
Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease.	Strong

Further diagnostic evaluation

Figure 1: Diagnostic flowchart of patients with suspected urethral stricture disease



**Use VCUG in case of (nearly-) obliterative strictures or stenosis.*
MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cystourethrogram.

Recommendations	Strength rating
Perform uroflowmetry and estimation of post-void residual in patients with suspected urethral stricture disease.	Strong
Perform retrograde urethrography to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery.	Strong
Combine retrograde urethrography with voiding cystourethrography to assess (nearly)-obliterative strictures, stenoses and pelvic fracture urethral injuries.	Strong
Use clamp devices in preference to the Foley catheter technique for urethrographic evaluation to reduce pain.	Weak
Perform cystourethroscopy as an adjunct to imaging if further information is required.	Weak
Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required.	Weak
Consider MRI urethrography as an ancillary test in posterior urethral stenoses.	Strong

Disease Management In Males

Conservative treatment

Patients with a stricture or stricture recurrence (≥ 16 Fr) will rarely develop symptoms or need surgical intervention.

Recommendations	Strength rating
Do not intervene patients with asymptomatic incidental (> 16 Fr) strictures.	Weak
Consider long-term suprapubic catheter in patients with radiation-induced bulbomembranous strictures and/or poor performance status.	Weak

Endoluminal treatment of anterior urethral strictures in males

Direct vision internal urethrotomy and dilatation

Direct vision internal urethrotomy (DVIU)/dilatation is commonly performed as 1st line treatment of non-obliterative urethral strictures. There is no difference in patency rate between dilatation and DVIU.

The best patency rates with DVIU/dilatation are reported among untreated patients with a single, short (max. 2 cm) bulbar stricture. Direct vision internal urethrotomy/dilatation performs poorly in penile and long segment strictures. Direct vision internal urethrotomy of the penile urethra might provoke venous leakage from the corpora cavernosa with subsequent risk of erectile dysfunction (ED).

Repetitive dilatations/DVIU have no long-term freedom of recurrence and might increase stricture complexity.

Recommendations	Strength rating
Do not use direct vision internal urethrotomy (DVIU) for penile strictures.	Strong
Do not use DVIU/dilatation as solitary treatment for long (>2 cm) segment strictures.	Strong

Perform DVIU/dilatation for a primary, single, short (<2 cm) and non-obliterative stricture at the bulbar urethra.	Weak
Perform DVIU/dilatation for a short recurrent stricture after prior bulbar urethroplasty.	Weak
Use either "hot" or "cold" knife techniques to perform DVIU depending on operator surgeon experience and resources.	Weak
Use visually controlled dilatation in preference to blind dilatation.	Weak
Do not perform repetitive (>2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option.	Strong

Post-dilatation/direct vision internal urethrotomy strategies

Intermittent self dilatation (ISD) is able to reduce stricture recurrence and need for reintervention but at the cost of impairment of quality of life (QoL) in a substantial proportion of patients. Intra-urethral corticosteroids via steroid ointment on the dilatator device in addition to ISD delay the time to recurrence.

Intralesional injections with steroids and mitomycin C (MMC) have been proposed to reduce stricture recurrence after DVIU. For steroid injections, there was no difference in recurrence rate although the time to recurrence was longer. Mitomycin C injection might reduce stricture recurrence although, anecdotally, severe complications have been reported.

Permanent stainless-steel mesh stents are no longer commercially available. Temporary stent insertion after DVIU/dilatation prolongs time to recurrence for bulbar strictures. The use of stents in the penile urethra is anecdotal and appears to be associated with a higher recurrence rate.

Recommendations	Strength rating
Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/ direct vision internal urethrotomy (DVIU) if urethroplasty is not a viable option.	Weak
Use intra-urethral corticosteroids in addition to ISD to stabilise the urethral stricture.	Weak
Do not use intralesional injections outside the confines of a clinical trial.	Weak
Do not use permanent urethral stents.	Strong
Do not use urethral stents for penile strictures.	Strong
Use a temporary stent for recurrent bulbar strictures after DVIU to prolong time to next recurrence only if urethroplasty is not a viable option.	Weak

Urethroplasty in males

The role of urethroplasty in the management of penile urethral strictures

Single-stage vs. staged augmentation urethroplasty vs. anastomotic urethroplasty

Staged augmentation urethroplasty is favoured in men with more complex urethral stricture disease (multiple interventions in the past, unfavourable clinical findings such as significant spongiofibrosis or scarring that requires excision, poor quality of the urethral plate). In the absence of these factors, a single-stage approach might be possible.

Leave an interval of four to six months before proceeding to tubularisation of the urethra in the case of staged urethroplasty.

Revision (usually due to graft contracture) after the 1st stage has been reported in 0-20% of cases.

Anastomotic urethroplasty of the penile urethra is associated with a risk of chordee, especially if the stricture is longer than 1 cm.

Recommendations	Strength rating
Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or staged approach taking into consideration previous interventions and stricture characteristics.	Strong
Offer an interval of at least 4-6 months before proceeding to the second stage of the procedure and provided that the outcome of the first stage is satisfactory.	Weak
Do not offer anastomotic urethroplasty to patients with penile strictures > 1 cm due to the risk of penile chordee post-operatively.	Strong
Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in the face of adverse intra-operative findings.	Strong

Specific considerations for failed hypospadias repair-related and lichen sclerosus-related strictures

The management of failed hypospadias repair is challenging and complex as the urethral plate, penile skin and dartos fascia are often deficient/non-existent.

Given the fact that LS affects the skin, the use of genital skin as a flap or graft is not advised.

Recommendations	Strength rating
Consider men with failed hypospadias repair (FHR) as complex patients and refer them to specialist centres for further management.	Weak
Propose psychological and/or psychosexual counselling to men with unsatisfactory cosmesis and sexual or urinary dysfunction related to FHR.	Weak
Do not use penile skin grafts or flaps in FHR patients with lichen sclerosus (LS) or scarred skin.	Strong
Do not use genital skin in augmentation penile urethroplasty in men with LS-related strictures.	Strong
Perform single-stage oral mucosal graft urethroplasty in the absence of adverse local conditions in men with LS-related strictures.	Weak

Distal urethral strictures (meatal stenosis, fossa navicularis strictures)

Open repair of distal urethral strictures can be in the form of Malone meatoplasty, skin flap meatoplasty or graft (skin [SG]/oral mucosal graft [OMG]) urethroplasty.

Recommendations	Strength rating
Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures.	Weak

Urethroplasty for bulbar strictures

Shorter bulbar strictures

"Short" bulbar strictures are those amenable to excision and primary anastomosis (EPA), with a limit of around 2-3 cm.

Recommendations	Strength rating
Use transecting excision and primary anastomosis (tEPA) for short post-traumatic bulbar strictures with (nearly) complete obliteration of the lumen and full thickness spongiofibrosis.	Strong
Use non-transecting excision and primary anastomosis or free graft urethroplasty instead of tEPA for short bulbar strictures not related to straddle injury.	Weak

"Longer" bulbar strictures

Free graft urethroplasty

There is insufficient evidence to routinely recommend the nerve and muscle sparing modifications of bulbar urethroplasty.

Recommendations	Strength rating
Use free graft urethroplasty for bulbar strictures not amendable to excision and primary anastomosis (EPA).	Strong
Use oral mucosa free graft urethroplasty for ReDo urethroplasty in the case of a long stricture.	Strong
Use augmented anastomotic repair for bulbar strictures not amenable to EPA but with a short, nearly obliterative segment within the whole strictured segment.	Weak

Use dorsal, dorsal-lateral or ventral approach according to surgical practice, expertise and intra-operative findings.	Strong

Staged urethroplasty for bulbar urethral strictures

Staged urethroplasty may be considered when:

- there are locally adverse conditions such as fistula, false passage, abscess or cancer;
- there has been a previously unsuccessful complex urethroplasty including failed hypospadias repair;
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient;
- the stricture is radiotherapy induced;
- the stricture is consequent to LS (this is controversial and for some groups LS is a contraindication for a staged urethroplasty;
- severe spongiofibrosis.

Late complications of 1st stage urethroplasty include a need for revision in up to 19% - consequent to recurrence of LS in graft(s) (8.8%), graft contracture (6.6%) and stomal stenosis (3.3%).

Recommendations	**Strength rating**
Offer staged urethroplasty to men with complex anterior urethral stricture disease not suitable for single stage urethroplasty and who are fit for reconstruction.	Weak
Do not perform staged bulbar urethroplasty for lichen sclerosis if single stage urethroplasty is possible.	Weak

Consider staged procedure in patients unsure about perineal urethrostomy versus urethral reconstruction.	Weak
Warn men that staged urethroplasty may comprise more than two stages.	Weak

Urethroplasty for penobulbar or panurethral strictures

Generally, only high-volume centres publish series on panurethral urethroplasties. Alternative techniques and grafts may be required.

Recommendations	Strength rating
Offer panurethral urethroplasties in specialised centres because different techniques and materials might be needed.	Weak
Combine techniques to treat panurethral strictures if one technique is not able to treat the whole extent of the stricture.	Weak

Perineal urethrostomy

Perineal urethrostomy (PU) offers a permanent or temporary solution for restoration of voiding in men with complex urethral stricture disease in whom:

- there are no further options to restore urethral patency either due to multiple previous failed urethroplasties or multiple co-morbidities precluding a more expansive surgical undertaking after failed endoscopic management;
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient;
- following urethrectomy and/or penectomy for cancer.

Recommendations	Strength rating
Offer perineal urethrostomy (PU) as a management option to men with complex anterior urethral stricture disease.	Strong
Offer PU to men with anterior urethral stricture disease who are not fit or not willing to undergo formal reconstruction.	Weak
Choose type of PU based on personal experience and patient characteristics.	Weak
Consider augmented Gil-Vernet-Blandy PU or "7-flap" PU in men with proximal bulbar or membranous urethral stricture disease.	Weak
Consider "7-flap" urethroplasty in obese men.	Weak

Posterior urethra

Non-traumatic posterior urethral stenosis

Endoluminal management of non-traumatic posterior urethral stenosis

Endoluminal treatment of complete obliterative strictures is not advised because of a very low likelihood of durable patency and the risk of false passage towards the rectum.

Recommendations	Strength rating
Perform visually controlled dilatation or direct vision internal urethrotomy (DVIU) as 1st line treatment for a non-obliterative vesico-urethral anastomosis stricture (VUAS) or radiation-induced bulbomembranous strictures (BMS).	Weak
Do not perform deep incisions at the 6 and 12 o' clock position during DVIU for VUAS or radiation-induced BMS.	Strong

Perform transurethral resection (TUR) or "hot-knife" DVIU as 1st line treatment for patients with non-obliterative bladder neck stenosis (BNS) after surgery for benign prostatic obstruction.	Strong
Perform repetitive endoluminal treatments in non-obliterative VUAS or BNS in an attempt to stabilise the stricture.	Weak
Warn patients about the risk of *de novo* urinary incontinence or exacerbation of existing urinary incontinence after endoluminal treatment.	Weak
Do not perform endoluminal treatment in case of VUAS, BMS and BNS with complete obliteration.	Strong
Do not use stents for strictures at the posterior urethra.	Weak

Lower urinary tract reconstruction for non-traumatic posterior urethral stenosis

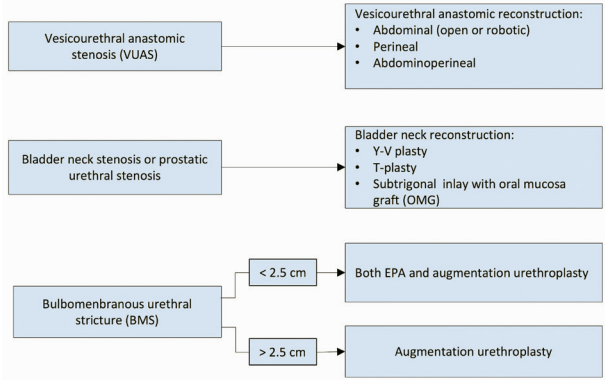
De novo urinary incontinence (UI) with transperineal ReDo vesico-urethral anastomosis (VUA) is universal and artificial urinary sphincter placement can be offered after 3-6 months. *De novo* UI with retropubic ReDo VUA is 0-58%.

Urinary incontinence rates are up to 14% with bladder neck reconstruction and up to 25% after reconstruction of BMS after surgery for benign prostatic obstruction (BPO).

De novo UI and new onset ED after urethral surgery for radiation-induced BMS are reported in 11-50% and 0-35% of cases, respectively.

Salvage prostatectomy is able to achieve patency in 67% of patients for prostatic strictures after irradiation or high-energy treatments but morbidity is substantial.

Figure 2: Options for lower urinary tract reconstruction of non-traumatic posterior urethral obstruction (stenosis)



Recommendations	Strength rating
Perform ReDo vesico-urethral anastomosis (VUA) in non-irradiated patients and irradiated patients with adequate bladder function with obliterative vesico-urethral anastomosis stricture or vesico-urethral anastomosis stricture refractory to endoluminal treatment.	Weak
Warn patient that urinary incontinence (UI) is inevitable after transperineal ReDo VUA and that subsequent anti-UI surgery might be needed in a next stage, after at least three to six months.	Strong
Offer ReDo VUA by retropubic approach if the patient is pre-operatively continent.	Weak

Perform bladder neck reconstruction with Y-V or T-plasty for treatment refractory bladder neck stenosis.	Weak
Warn patients about *de novo* UI after reconstruction for bladder neck stenosis or bulbomembranous strictures (BMS) with previous benign prostatic obstruction surgery as aetiology.	Strong
Use either excision and primary anastomosis or augmentation urethroplasty for short (< 2.5 cm) radiation-induced BMS refractory to endoscopic treatment depending on surgeon's experience.	Weak
Perform augmentation urethroplasty for long (> 2.5 cm) radiation-induced BMS.	Weak
Warn patients about the risk of *de novo* UI and new onset erectile dysfunction after urethroplasty for radiation-induced BMS.	Strong
Offer salvage prostatectomy in motivated and fit patients with adequate bladder function in case of a prostatic stricture due to prior irradiation or high-energy treatment.	Weak

Extirpative surgery and urinary diversion for non-traumatic posterior urethral stenosis

This is reserved for complex and/or recurrent cases associated with severe necrosis, calcification and significant morbidity, especially severe pain, intractable haematuria or fistulation.

Recommendations	**Strength rating**
Perform urinary diversion in recurrent or complex cases with loss of bladder capacity and/or incapacitating local symptoms.	Weak

Perform cystectomy during urinary diversion in case of intractable bladder pain, spasms and/or haematuria.	Weak

Post-traumatic posterior stenosis

The acute and early management of pelvic fracture urethral injuries (PFUIs) is discussed in the EAU Guidelines on Urological Trauma. The deferred management of PFUI is at earliest three months after the trauma at the time a stable post-traumatic posterior stenosis has been formed.

Endoluminal treatment for post-traumatic posterior stenosis

Endoluminal treatment of an obliterative stenosis will not be not successful and has a risk of creating a false passage towards the bladder base or rectum.

Endoluminal treatment of short (≤ 1.5 cm), non-obliterative stenoses has a 20-96.5% stricture-free rate, with a 4% *de novo* UI rate.

DVIU has stricture-free rates of 22.9-77.3% for a short and non-obliterative recurrence after EPA.

Recommendations	**Strength rating**
Do not perform endoscopic treatment for an obliterative stenosis.	Strong
Perform one attempt at endoluminal treatment for a short, non-obliterative stenosis.	Weak
Do not perform more than two direct vision internal urethrotomies and/or dilatations for a short and non-obliterative recurrence after excision and primary anastomosis for a traumatic posterior stenosis if long-term urethral patency is the desired intent.	Weak

Urethroplasty for post-traumatic posterior stenosis

It has been calculated that to achieve and maintain sufficient experience in the reconstruction of PFUI, one centre per twelve million inhabitants is sufficient (for well-resourced countries).

In case of a recurrent stenosis, a repeat ("ReDo") urethroplasty is possible in motivated patients. Several different types of urethroplasty have been described for this with a 37.5-100% patency rate.

Recommendations	Strength rating
Perform open reconstruction for post-traumatic posterior stenosis only in high-volume centres.	Weak
Perform progressive perineal excision and primary anastomosis (EPA) for obliterative stenosis.	Strong
Perform progressive perineal EPA for non-obliterative stenosis after failed endoluminal treatment.	Strong
Perform a midline perineal incision to gain access to the posterior urethra.	Strong
Do not perform total pubectomy during abdomino-perineal reconstruction.	Strong
Reserve abdomino-perineal reconstruction for complicated situations including very long distraction defect, para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	Weak

Perform another urethroplasty after 1st failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion.	Weak
Use a local tissue flap to fill up excessive dead space or after correction of a concomitant recto-urethral fistula.	Weak

Female Urethral Strictures

Female urethral stricture (FUS) symptoms are long-standing and non-specific but most commonly reported are frequency, urgency, poor flow, incomplete emptying and UI. It is important to exclude FUS in female patients with lower urinary tract symptoms.

It is important to assess flow rate and postvoid residuals. All suspected of having FUS should have voiding cystourethrography (VCUG) or video-urodynamics (VUDS) to confirm the diagnosis.

Recommendations	Strength rating
Perform flow rate, post-void residual and voiding cystourethrogram or video-urodynamics in all women with refractory lower urinary tract symptoms.	Strong
Perform urethral dilatation to 30-41 Fr as initial treatment of female urethral stricture (FUS).	Strong
Perform repeat urethral dilatation and start planned weekly intermittent self-dilatation (ISD) with a 16-18 Fr catheter for the 1st recurrence of FUS.	Strong

Perform urethroplasty in women with a 2nd recurrence of FUS and who cannot perform ISD or wish definitive treatment. The technique for urethroplasty should be determined by the surgeon's experience, availability and quality of graft/flap material and the quality of the ventral vs. dorsal urethra.	Strong
Treat meatal strictures by meatotomy/ meatoplasty.	Strong

Disease Management In Transgender Patients

In trans men, stricture treatment depends on the time after neophallic reconstruction, stricture location, stricture length and quality of local tissues. Endoscopic incision has been performed for short (< 3 cm) strictures in trans men, usually at the anastomotic site with a 45.5% patency rate. Endoscopic incision shortly after neophallic reconstruction and repetitive incisions are not successful. After failure of endoscopic incision or in case of a (nearly-) obliterative short stricture at the anastomosis, excision and primary anastomosis has been proposed with a 57.1% patency rate. Strictures of the neophallic urethra are usually treated with staged urethroplasty (+/- graft augmentation).

In trans women, It is acceptable to start with dilatation of a short and non-obliterative stricture. If this is not possible or if it fails, a short (< 1 cm) meatal stricture can be treated by Y-V meatoplasty with an 85% stricture-free rate. Somewhat longer (1-2 cm) meatal strictures can be treated by a neovaginal advancement flap.

Recommendations	Strength rating
Do not perform endoscopic incision or urethroplasty within six months after neophalloplasty.	Strong
Do not perform more than two endoscopic incisions for strictures in trans men unless with palliative intent.	Strong
Perform staged urethroplasty for strictures at the neophallic urethra if open reconstruction is indicated.	Weak
Perform Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women if open reconstruction is indicated.	Weak

Tissue Transfer

Different local flaps have been described: penile skin, perineal and scrotal flaps (hair-bearing). Flaps have a higher urogenital morbidity but a comparable patency rate compared to grafts. When complete tubularisation is needed in a single stage approach, grafts have a significantly higher complication rate compared to flaps. Hair-bearing flaps have a lower urethral patency rate compared to non-hair-bearing flaps.

Possible grafts are oral mucosa, penile skin, and a multitude of other autologous grafts. Patency rates of buccal mucosa and lingual mucosa are comparable. Different types of oral grafts have different types of oral morbidity and some of the oral complications might last in the long-term. Patency rates with penile skin grafts are 79-81.8% vs. 85.9-88.1% with buccal mucosa. In LS-related strictures, the use of genital skin graft is associated with poor patency rates (4%).

The post-operative morbidity of closure vs. non-closure of the buccal mucosa harvesting site has been evaluated and no clear recommendation can be provided whether or not to close the harvesting site.

Recommendations	Strength rating
Use a graft above a flap when both are equally indicated.	Strong
Do not use grafts in a tubularised fashion in a single-stage approach.	Strong
Use flaps in case of poor vascularisation of the urethral bed.	Weak
Do not use hair-bearing perineal or scrotal flaps unless no other option is feasible.	Strong
Use buccal or lingual mucosa if a graft is needed and these grafts are available.	Weak
Inform the patient about the potential complications of the different types of oral grafting (buccal versus lingual versus lower lip) when an oral graft is proposed.	Strong
Use penile skin if buccal/lingual mucosa is not available, suitable or accepted by the patient for reconstruction.	Weak
Do not use genital skin graft in case of lichen sclerosus.	Strong
Do not use cell free tissue engineered grafts in case of extensive spongiofibrosis, after failed previous urethroplasty or stricture length > 4 cm.	Weak
Do not use autologous tissue-engineered oral mucosa grafts outside the frame of a clinical trial.	Strong

Peri-Operative Care Of Urethral Surgery

After any form of urethral manipulation (urethral catheter, ISD, dilatation, DVIU), a period of urethral rest is necessary in order to allow tissue recovery and stricture "maturation" before considering urethroplasty.

A urine culture is performed one to two weeks prior to surgery and if infection is present, a therapeutic course with antibiotics is recommended pre-operatively. An intra-operative prophylactic regimen with antibiotics is effective in reducing the rate of post-operative surgical site infection and UTIs.

Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation.

Recommendations	Strength rating
Do not perform urethroplasty within three months of any form of urethral manipulation.	Weak
Administer an intra-operative prophylactic regimen with antibiotics at the time of urethral surgery.	Strong
Perform a form of validated urethrography after urethroplasty to assess for urinary extravasation prior to catheter removal.	Strong
Remove the catheter within 72 hours after uncomplicated direct vision internal urethrotomy or urethral dilatation.	Weak
Consider 1st urethrography seven to ten days after uncomplicated urethroplasty to assess whether catheter removal is possible, especially in patients with bother from their urethral catheter.	Weak

Follow-Up

After urethroplasty surgery, recurrent strictures appear with different frequency depending on stricture features and urethroplasty techniques.

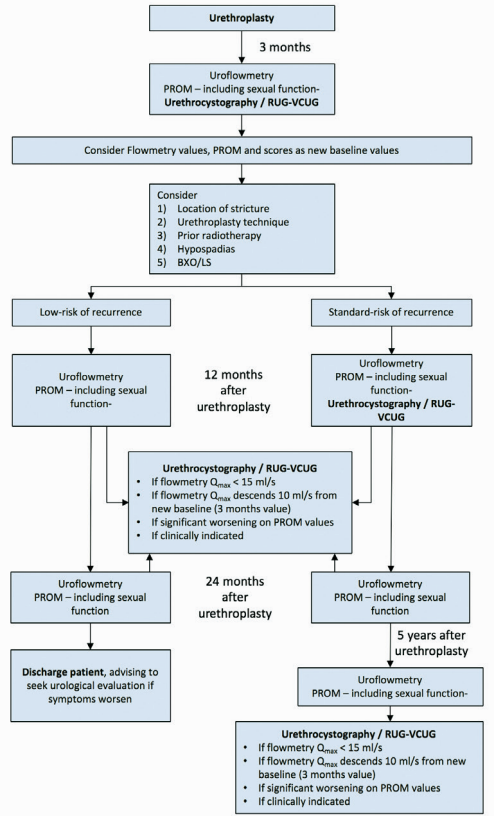
Follow-up, should not only focus on detection of stricture recurrence but should also assess functional outcomes and patient satisfaction.

The same tools used for the primary diagnosis of urethral stricture disease can be used to detect stricture recurrence (Figure 3).

The majority of stricture recurrences present within one year after surgery although late recurrences are, especially after augmentation urethroplasty.

Risk-adapted follow-up protocols are cost-effective and safe for the patients (Tables 2 and 3).

Figure 3: Follow-up after urethroplasty



BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient reported outcome measure; Q_{max} = maximum flow rate; RUG = retrograde urethrography; VCUG = voiding cystourethrography.

Table 2: Follow-up protocol for urethroplasty with low risk of recurrence

- Anastomotic urethroplasties in the bulbar/(bulbo) membranous segment with no history of radiotherapy, hypospadias or balanitis xerotica obliterans (BXO)/LS features.

Surgery	3 months	12 months	24 months*
Uroflowmetry	+	+	+
PROM (incl. sexual function)	+	+	+
Anatomic evaluation: (Urethrocystoscopy/RUG-VCUG)	+**	On indication	On indication

**Follow-up could be discontinued after two years, advising the patient to seek urological evaluation if symptoms worsen. Academic centres could increase the length of follow-up for research purposes.*

***The Panel suggests performing an anatomic assessment at three months.*

Table 3: Follow-up protocol for urethroplasty with standard-risk of recurrence

- Anastomotic urethroplasties in the bulbar segment with prior history of radiotherapy, hypospadias or BXO/LS features;
- Penile urethroplasties;
- Non-traumatic posterior urethroplasties;
- Graft or/and flap – substitution – urethroplasties.

Surgery	3 months	12 months	24 months	5 years *
Uroflowmetry	+	+	+	+
PROM (incl. sexual function)	+	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+	+	+	On indication

*Follow-up could be discontinued after two years, advising the patient to seek urological evaluation if symptoms worsen. Academic centres could increase the length of follow-up for research purposes.

**The Panel suggests performing an anatomic assessment at three months.

Recommendations	Strength rating
Offer follow-up to all patients after urethroplasty surgery.	Strong
Use cystoscopy or retrograde urethrography to assess anatomic success after urethroplasty surgery.	Weak
Use PROM questionnaires to assess subjective outcomes and patient satisfaction.	Strong
Use validated questionnaires to evaluate sexual function after urethral stricture surgeries.	Strong
Offer a routine follow-up of at least one year after urethroplasty.	Strong
Adopt a risk-based follow-up protocol.	Weak

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON CHRONIC PELVIC PAIN

(Limited text update March 2021)

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Introduction

The EAU Guideline for Chronic Pelvic Pain plays an important role in the process of consolidation and improvement of care for patients with abdominal and pelvic pain. From both literature and daily practice it has become clear that abdominal and pelvic pain are areas still under development. The EAU Guideline aims to expand the awareness of caregivers in the field of abdominal and pelvic pain and to assist those who treat patients with abdominal and pelvic pain in their daily practice. The guideline is a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

This pocket version aims to synthesise the important clinical messages described in the full text and is presented as a series of 'strength rated recommendations', which follow the standard for levels of evidence used by the EAU (see Introduction chapter of the EAU Guidelines book and online at the EAU website http://www.uroweb.org/guideline/).

Chronic pelvic pain syndromes

Classification

Much debate over the classification of chronic pelvic pain has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition: phenotyping, terminology and taxonomy.

Definition of chronic pelvic pain

Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction.

*(*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) have localised the pain as being perceived in the specified anatomical pelvic area).*

Definition of CPPPS

Chronic primary pelvic pain syndrome (CPPPS) is the occurrence of chronic pelvic pain 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. CPPPS is a sub-division of chronic pelvic pain.

Table 1: Classification of chronic pelvic pain syndromes

Axis I Region		Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix	
Chronic pelvic pain	Chronic secondary pelvic pain syndrome, formally known as specific disease associated pelvic pain OR Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Urological	Prostate	
			Bladder	
			Scrotal Testicular Epididymal	
			Penile Urethral	
			Post-vasectomy	
		Gynaecological	Vulvar Vestibular Clitoral	
			Endometriosis associated	
			CPPPS with cyclical exacerbations	
			Dysmenorrhoea	
		Gastrointestinal	Irritable bowel	
			Chronic anal	
			Intermittent chronic anal	
		Peripheral nerves	Pudendal pain syndrome	
		Sexological	Dyspareunia	
			Pelvic pain with sexual dysfunction	
		Psychological	Any pelvic organ	
		Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal	
			Coccyx	

	Axis IV Referral character-istics	AAxis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
	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 Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urgency 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 Catastrophic thinking about Pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance

Table 2: Chronic Primary Pelvic Pain Syndromes

Primary Urological Pain Syndromes	
Primary prostate pain syndrome	Primary prostate pain syndrome (PPPS) 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. PPPS 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 PPPS. In the authors' 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 includes infection (types I and II), which the authors feel should not be considered under PPPS, 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 CPPPS of the male is used instead of PPPS, which has been agreed by the majority.

Primary bladder pain syndrome	Primary bladder pain syndrome (PBPS) 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. PBPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. PBPS 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 sub-classifications 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.
Primary scrotal pain syndrome	Primary scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised to the scrotum or a structure within it, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Primary 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.

Primary testicular pain syndrome	Primary testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.
Primary epididymal pain syndrome	Primary epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of lower 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.
Primary penile pain syndrome	Primary 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. Primary 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.
Primary urethral pain syndrome	Primary 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. Primary 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. Primary urethral pain syndrome may occur in men and women.

Post-vasectomy scrotal 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. Post-vasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and for that reason it is considered by some a special form of primary scrotal pain syndrome.
Primary Gynaecological Pain Syndromes: External Genitalia	
Primary vulvar pain syndrome	Primary 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 included 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 the panel use the term primary 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 sub-divided vulvodynia based on pain location and temporal characteristics of the pain (e.g., provoked or unprovoked). The following definitions are based on that approach.

Primary generalised vulvar pain syndrome	Primary 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.
Primary localised vulvar pain syndrome	Primary 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). Primary localised vulvar pain syndrome can be sub-divided into primary vestibular pain syndrome and primary clitoral pain syndrome.
Primary vestibular pain syndrome	Primary 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.
Primary clitoral pain syndrome	Primary 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	
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.
Chronic primary pelvic pain syndrome with cyclical exacerbations	Chronic primary pelvic pain syndrome 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.
Primary dysmenorrhoea	Primary dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic primary pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.

Gastrointestinal Pelvic Pain Syndromes	
Irritable bowel syndrome (IBS)	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 pre-occupation 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: three 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 (> three bowel movements per day or < three 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 primary anal pain syndrome	Chronic primary 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 primary 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 primary anal pain syndrome	Intermittent chronic primary 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 sub-group of the chronic primary anal pain syndromes. It was previously known as "proctalgia fugax" but this term is no longer recommended.
Musculoskeletal System	
Primary pelvic floor muscle pain syndrome	Primary 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 over-activity 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.
Primary coccyx pain syndrome	Primary 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. Primary 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.
Chronic Pain Post Surgery	
Chronic post-surgical pain syndrome	The definition of chronic post-surgical pain is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least three months after the surgery. There is a separate category for this in the ICD-11 classification.

Epidemiology, Aetiology and Pathophysiology
Chronic visceral pain, pelvic pain and abdominal aspects of pelvic pain

Recommendations	Strength rating
All of those involved in the management of chronic pelvic pain should have knowledge of peripheral and central pain mechanisms.	Strong
The early assessment of patients with chronic pelvic pain should involve investigations aimed at excluding disease-associated pelvic pain.	Strong
Assess functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation, early in patients with chronic pelvic pain and address these issues as well as the pain.	Strong
Build up relations with colleagues so as to be able to manage Chronic Primary Pelvic Pain Syndrome comprehensively in a multi-specialty and multi-disciplinary environment with consideration of all their symptoms.	Strong

Diagnostic Evaluation
History and physical examination
History is very important for the evaluation of patients with chronic pelvic pain. Pain syndromes are symptomatic diagnoses which are derived from a history of pain perceived in the region of the pelvis, and absence of other pathology, for a minimum of three out of the past six months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, primary anatomical or functional disease of the pelvic organs, and neurogenic disease must be

ruled out. The history should be comprehensive covering functional as well as pain related symptoms. The clinical examination often serves to confirm or refute the initial impressions gained from a good history. The examination should be aimed at specific questions where the outcome of the examination may change management. As well as a local examination, a general musculoskeletal and neurological examination should be considered an integral part of the assessment and be undertaken, if appropriate.

Figure 1: Diagnosing chronic pelvic pain

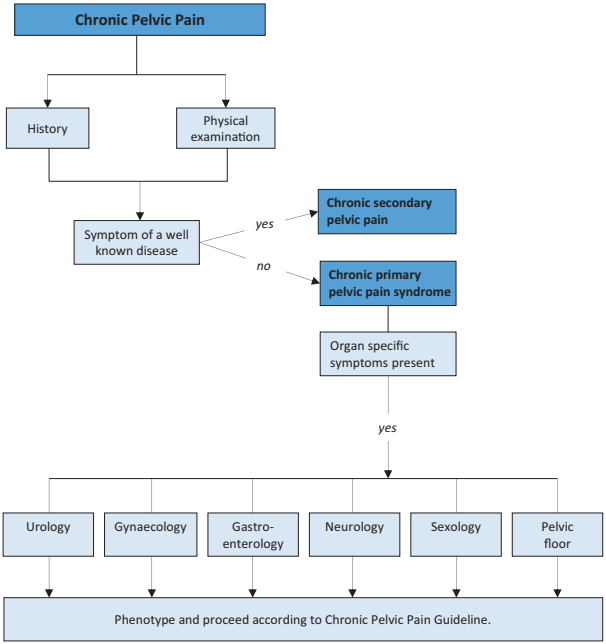

Figure 2: Phenotyping of pelvic pain

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry.
Psychology	Anxiety about pain, depression and loss of function, history of negative sexual experiences.
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.
Sexological	Erectile function, ejaculatory function, post-orgasmic pain.

Recommendations for diagnostic evaluation

Recommendation – general	Strength rating
Take a full history and evaluate to rule out a treatable cause in all patients with chronic pelvic pain.	Strong

Recommendations for the diagnostic evaluation of Primary Prostate Pain Syndrome	Strength rating
Adapt diagnostic procedures to the patient. Exclude specific diseases with similar symptoms.	Strong
Use a validated symptom and quality of life scoring instrument, such as the National Institutes of Health Chronic Prostatitis Symptom Index, for initial assessment and follow-up.	Strong

Assess primary prostate pain syndrome associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	Strong

Recommendations for the diagnostic evaluation of Primary Bladder Pain Syndrome	**Strength rating**
Perform general anaesthetic rigid cystoscopy in patients with bladder pain to subtype and rule out confusable disease.	Strong
Diagnose patients with symptoms according to the EAU definition, after primary exclusion of specific diseases, with primary bladder pain syndrome (PBPS) by subtype and phenotype.	Strong
Assess PBPS associated non-bladder diseases systematically.	Strong
Assess PBPS associated negative cognitive, behavioural, sexual, or emotional consequences.	Strong
Use a validated symptom and quality of life scoring instrument for initial assessment and follow-up.	Strong

Recommendations for the diagnostic evaluation of gynaecological aspects of chronic pelvic pain	**Strength rating**
Take a full uro-gynaecological history in those who have had a continence or prolapse non-absorbable mesh inserted and consider specialised imaging of the mesh.	Strong

Refer to a gynaecologist if clinical suspicion of a gynaecological cause for pain following complete urological evaluation. Laparoscopy should be undertaken in accordance with gynaecological guidelines.	Strong

Recommendation for the diagnostic evaluation of Anorectal Pain Syndrome	**Strength rating**
Anorectal function tests are recommended in patients with anorectal pain.	Strong

Recommendations for the diagnostic evaluation of nerves to the pelvis	**Strength rating**
Rule out confusable diseases, such as neoplastic disease, infection, trauma and spinal pathology.	Strong
If a peripheral nerve pain syndrome is suspected, refer early to an expert in the field, working within a multi-disciplinary team environment.	Weak
Imaging and neurophysiology help diagnosis but image and nerve locator guided local anaesthetic injection is preferable.	Weak

Recommendation for the diagnostic evaluation of sexological aspects in CPP	**Strength rating**
Screen patients presenting with symptoms suggestive for chronic pelvic pain syndrome for abuse, without suggesting a causal relation with the pain.	Weak

Recommendations for the diagnostic evaluation of psychological aspects of CPP	Strength rating
Assess patient psychological distress in relation to their pain.	Strong
Ask patients what they think is the cause of their pain and other symptoms to allow the opportunity to inform and reassure.	Strong

Recommendations for the diagnostic evaluation of pelvic floor function	Strength rating
Use the International Continence Society classification for pelvic floor muscle function and dysfunction.	Strong
In patients with chronic primary pelvic pain syndrome, it is recommended to actively look for the presence of myofascial trigger points.	Weak

Management

The philosophy for the management of CPP is based on a bio-psychosocial model. This is a holistic approach with the patients' active involvement. Single interventions rarely work in isolation and need to be considered within a broader personalised management strategy. The management strategy may well have elements of self-management. Pharmacological and non-pharmacological interventions should be considered with a clear understanding of the potential outcomes and end points. These may include: psychology, physiotherapy, drugs and more invasive interventions. Providing information that is personalised and responsive to the patient's problems, conveying belief and concern, is a powerful way to allay anxiety. Additional written information or direction to reliable sources is useful; practitioners tend to rely on locally

produced material or pharmaceutical products of variable quality while endorsing the need for independent materials for patients.

Recommendations for management

Recommendations for the management of Primary Prostate Pain Syndrome	Strength rating
Offer multimodal and phenotypically directed treatment options for Primary Prostate Pain Syndrome (PPPS).	Weak
Use antimicrobial therapy (quinolones or tetracyclines) over a minimum of six weeks in treatment-naïve patients with a duration of PPPS less than one year.	Strong
Use α-blockers for patients with a duration of PPPS less than one year.	Strong
Offer high-dose oral pentosane polysulphate in PPPS.	Weak
Offer acupuncture in PPPS.	Strong
Offer non-steroidal anti-inflammatory drugs in PPPS, but long-term side-effects have to be considered.	Weak

Recommendations for the management of Primary Bladder Pain Syndrome	Strength rating
Offer subtype and phenotype-oriented therapy for the treatment of Primary Bladder Pain Syndrome (PBPS).	Strong
Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of PBPS.	Strong

Offer dietary advice.	Weak
Administer amitriptyline for treatment of PBPS.	Strong
Offer oral pentosane polysulphate for the treatment of PBPS.	Strong
Offer oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosane polysulphate alone.	Weak
Do not recommend oral corticosteroids for long-term treatment.	Strong
Offer intravesical hyaluronic acid or chondroitin sulphate before more invasive measures.	Weak
Offer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	Weak
Offer intravesical heparin before more invasive measures alone or in combination treatment.	Weak
Do not use bladder distension alone as a treatment of PBPS.	Weak
Offer submucosal bladder wall and trigonal injection of botulinum toxin type A (BTX-A) plus hydrodistension if intravesical instillation therapies have failed.	Strong
Offer neuromodulation before more invasive interventions.	Weak
Only undertake ablative and/or reconstructive surgery as the last resort and only by experienced and PBPS-knowledgeable surgeons, following a multi-disciplinary assessment including pain management.	Strong

Offer transurethral resection (or coagulation or laser) of bladder lesions, but in PBPS type 3 C only.	Strong

Recommendations for the management of Scrotal Pain Syndrome	**Strength rating**
Inform about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	Strong
Do open instead of laparoscopic inguinal hernia repair, to reduce the risk of scrotal pain.	Strong
In patients with testicular pain improving after spermatic block, offer microsurgical denervation of the spermatic cord.	Weak

Recommendations for the management of gynaecological aspects of chronic pelvic pain	**Strength rating**
Involve a gynaecologist to provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	Strong
Provide a multi-disciplinary approach to pain management in persistent disease states.	Strong
All patients who have developed complications after mesh insertion should be referred to a multi-disciplinary service (incorporating pain medicine and surgery).	Strong

Recommendations for functional anorectal pain	Strength rating
Undertake biofeedback treatment in patients with chronic anal pain.	Strong
Offer Botulinum toxin type A in chronic primary anal pain syndrome.	Weak
Offer percutaneous tibial nerve stimulation in chronic primary anal pain syndrome.	Weak
Offer sacral neuromodulation in chronic primary anal pain syndrome.	Weak
Offer inhaled salbutamol in intermittent chronic primary anal pain syndrome.	Weak

Recommendation for the management of nerves to the pelvis	Strength rating
Neuropathic pain guidelines are well-established. Use standard approaches to management of neuropathic pain.	Strong

Recommendations for the management of sexological aspects in chronic pelvic pain	Strength rating
Offer behavioural strategies to the patient and his/her partner to reduce sexual dysfunctions.	Weak
Offer pelvic floor muscle therapy as part of the treatment plan to improve quality of life and sexual function.	Weak

Recommendation for the management of psychological aspects in chronic pelvic pain	Strength rating
For chronic pelvic pain with significant psychological distress, refer patient for chronic pelvic pain-focused psychological treatment.	Strong

Recommendations for the management of pelvic floor dysfunction	Strength rating
Apply myofascial treatment as first-line treatment.	Weak
Offer biofeedback as therapy adjuvant to muscle exercises, in patients with anal pain due to an overactive pelvic floor.	Strong

Recommendations for the management of chronic/non-acute urogenital pain by opioids	Strength rating
Opioids and other drugs of addiction/ dependency should only be prescribed following multi-disciplinary assessment and only after other reasonable treatments have been tried and failed.	Strong
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with the patient and their family doctor.	Strong
Where there is a history or suspicion of drug abuse, involve a psychiatrist or psychologist with an interest in pain management and drug addiction.	Strong

This short booklet is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4, available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.

EAU GUIDELINES ON RENAL TRANSPLANTATION

(Text update March 2021)

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Introduction

The European Association of Urology (EAU) Renal Transplantation Guidelines aim to provide a comprehensive overview of the medical and technical aspects relating to renal transplantation.

Organ retrieval and transplantation surgery

Living-donor nephrectomy

Recommendations	Strength rating
Offer pure or hand-assisted laparoscopic/ retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	Strong
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	Strong
Perform laparo-endoscopic single site surgery, robotic and natural orifice trans-luminal endoscopic surgery-assisted living-donor nephrectomy in highly-specialised centres only.	Strong

Organ preservation

Recommendations for kidney storage solutions	Strength rating
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	Strong
Use Celsior or Marshall's solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	Strong

Recommendations for kidney preservation: static and dynamic preservation	Strength rating
Minimise ischemia times.	Strong
Use hypothermic machine-perfusion (where available) in deceased donor kidneys to reduce delayed graft function.	Strong
Hypothermic machine-perfusion may be used in standard criteria deceased donor kidneys.	Strong
Use low pressure values in hypothermic machine perfusion preservation.	Strong
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	Strong
Do not discard grafts due to only increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine perfusion preservation.	Weak

Donor kidney biopsies

Recommendations	Strength rating
Do not base decisions on the acceptance of a donor organ on histological findings alone, since this might lead to an unnecessary high rate of discarded grafts. Interpret histology in context with clinical parameters of donor and recipient including perfusion parameters where available.	Strong
Use paraffin histology for histomorphology as it is superior to frozen sections; however, its diagnostic value has to be balanced against a potential delay of transplantation.	Strong
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	Strong

Living and deceased donor implantation surgery

Recommendations	Strength rating
Immediate pre-op haemodialysis	
Use dialysis or conservative measures to manage fluid and electrolyte imbalance prior to transplant surgery taking into consideration the likelihood of immediate graft function.	Weak
Operating on patients taking anti-platelet and anticoagulation agents	
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	Weak

Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/ haematologist /nephrologist.	Weak
Prevention of venous thrombosis including deep vein thrombosis during and after renal transplant	
Do not routinely give post-operative prophylactic unfractionated or low-molecular-weight heparin to low-risk living donor transplant recipients.	Weak
Peri-operative antibiotics in renal transplant	
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	Strong
Specific fluid regimes during renal transplantation	
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	Strong
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	Weak
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	Strong
Dopaminergic drugs in renal transplantation	
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	Weak

Surgical approaches for first, second, third and further transplants

Single kidney transplant – living and deceased donors

Recommendations	Strength rating
Assess the utility (including inspection) of the kidney for transplantation before commencement of immunosuppression and induction of anaesthesia for deceased donor kidney transplantation.	Strong
Choose either iliac fossa for placement of a first or second single kidney transplant.	Weak
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	Weak
Assess the length of the donor renal vein and if it is short consider one of a variety of surgical techniques to optimise the venous anastomosis.	Weak
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	Weak
Use an end-to-end anastomosis to the internal iliac artery as an alternative to external or common iliac arteries.	Weak
Check the intima of the donor and recipient arteries prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to/as part of the arterial anastomosis.	Strong

Pre-operatively plan the surgical approach in third or further transplants, to ensure that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.	Strong

Emerging surgical technologies

Robot-assisted kidney transplant (RAKT) surgery is being evaluated in prospective non-randomised trials (using IDEAL consortium principles). Whilst potential advantages may exist (decreased post-operative pain, length of hospital stay, incision length and lymphocele rate), evidence is too premature to recommend RAKT.

Dual kidney transplants

Dual kidney transplant is performed when the quality of a single deceased donor kidney is thought to be insufficient for appropriate long-term graft function and that the outcome with both kidneys would be better. A variety of surgical techniques have been described to implant a pair of donor kidneys these include: unilateral extra-peritoneal or intra-peritoneal and bilateral extra-peritoneal or intra-peritoneal that can be via a midline or two lateral incisions. No randomised controlled trials exist to recommend one technique for all patients or situations.

Ureteric implantation in normal urinary tract

Ureteric anastomotic techniques described for renal transplant recipients with no underlying urological abnormality include: extra (Lich-Gregoir) or intra (Ledbetter-Politano) vesical uretero-neo-cystotomy and uretero-ureterostomy using native ureter.

Recommendations	Strength rating
Perform Lich-Gregoir-like extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	Strong
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	Strong
Use transplant ureteric stents prophylactically to prevent major urinary complications.	Strong
Use the same surgical principals for single ureters to manage duplex ureters and anastomose them either separately or combined.	Strong

Transplantation/ureteric implantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter.
- The technique used to implant transplant ureter(s) into an ileal conduit is the same as the method used with native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extravesically (Lich-Gregoir). The latter is favoured in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the

catheterisable stoma (umbilical or iliac fossa - usually right-side) with clear communication with the transplant surgeons so that the position of any future transplant kidney is not compromised. If an intraperitoneal placement of a future kidney transplant is likely, then placement of a Mitrofanoff exiting in the iliac fossa is preferable at the umbilicus. If a future kidney transplant is likely in the right iliac fossa then placement of a Mitrofanoff exiting at the umbilicus or left iliac fossa may be preferable.

Donor complications

Living-donor nephrectomy, like any other intervention, is potentially associated with complications and mortality. However, the fact that the operation is performed on a healthy individual amplifies the relevance of any complications. Intra-operative complications occur in 2.2% (the most common being bleeding in 1.5% and injury to other organs in 0.8%) and post-operative complications occur in 7% (infectious complications in 2.6% and bleeding in 1%). Potential complications should be included in the process of informed consent. Long term complications are mostly related to the single-kidney condition. Health related quality of life, including mental condition, remains on average better than the general population after donation.

Recommendations	Strength rating
Restrict living donor nephrectomy to specialised centres.	Strong
Offer long-term follow-up to all living kidney donors.	Strong

Recipient complications

Surgical complications during and after kidney transplantation may expose the recipient to an increased risk of morbidity and mortality. The incidence and management of such

complications is therefore of primary importance. The most common surgical complications in renal transplantation are summarised below.

Haemorrhage

The incidence of haematomas is reported to be between 0.2-25%. Small and asymptomatic haematomas do not usually require any intervention. In case of larger haematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessels complications can be present. These cases may be treated by percutaneous drainage under computed tomography or ultrasound guidance or may require surgical treatment.

Arterial thrombosis

Transplant renal artery thrombosis is a rare complication (prevalence 0.5-3.5%).

Recommendations	Strength rating
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Strong
Perform a surgical thrombectomy in case of a salvageable graft if arterial thrombosis is confirmed intra-operatively.	Weak
Perform an allograft nephrectomy in case of a non-viable graft.	Strong

Venous thrombosis

Transplant renal vein thrombosis is an early complication (prevalence 0.5-4%) and one of the most important causes of graft loss during the first post-operative month.

Recommendations	Strength rating
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Weak
If venous thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft.	Weak
Do not routinely use pharmacologic prophylaxis to prevent transplant renal vein thrombosis.	Strong

Transplant renal artery stenosis

The incidence of transplant renal artery stenosis is 1-25%. Risk factors include small calibre and atherosclerosis of the donor artery, trauma to donor artery at procurement, absence of arterial patch, suturing technique (interrupted versus continuous), and damage to the iliac artery during transplantation.

Recommendations	Strength rating
Perform ultrasound-colour-doppler to diagnose an arterial stenosis, in case of undetermined results on ultrasound consider a magnetic resonance or computed tomography angiogram.	Strong
Perform percutaneous transluminal angioplasty/stent, if feasible, as first-line treatment for an arterial stenosis.	Strong
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	Strong

Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

Percutaneous biopsy may result in arteriovenous fistulae and/or intra-renal pseudo-aneurysms in 1-18% of cases.

Recommendations	Strength rating
Perform a ultrasound-colour-doppler if a arteriovenous fistulae or pseudo-aneurysm is suspected.	Strong
Perform angiographic embolisation as first-line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	Strong

Lymphocele

Lymphocele is a relatively common complication (prevalence 1-26%). There is a significant aetiological association with diabetes, m-TOR inhibitors (i.e sirolimus) therapy, and acute rejection.

Recommendations	Strength rating
Perform percutaneous drainage placement as first-line treatment for large and symptomatic lymphocele.	Strong
Perform fenestration when percutaneous treatments fail.	Strong

Urinary leak

Urinary leakage occurs in 0-9.3% of cases.

Recommendations	Strength rating
Manage urine leak by JJ-stent and bladder catheter and/or percutaneous nephrostomy tube.	Strong
Perform surgical repair in cases of failure of conservative management.	Strong

Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5%. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Late stenosis (after six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection.

Recommendations	Strength rating
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	Strong
Manage strictures < 3 cm in length either with surgical reconstruction or endoscopically (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision).	Strong
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	Strong

Haematuria

The incidence of haematuria ranges from 1-34%. The Lich-Gregoire technique provides the lowest incidence of haematuria. Bladder irrigation is the first-line of treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites.

Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86%. Acute graft pyelonephritis occurs in 13% of graft recipients. Patients with lower tract urinary infections and cytomegalovirus infection present a higher risk of acute graft pyelonephritis.

Recommendation	Strength rating
Use an endoscopic approach as first-line treatment for symptomatic reflux.	Weak

Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients.

Recommendations	Strength rating
Evaluate the causes of urolithiasis in the recipient.	Strong
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	Strong
Perform shockwave lithotripsy or antegrade/retrograde ureteroscopy for stones < 15 mm.	Strong
Perform percutaneous nephrolithotomy for stones > 20 mm.	Weak

Wound infection

Wound infections occur in about 4% of cases. Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load, and avoiding sirolimus/everolimus therapy can decrease wound complication rates.

Incisional hernia

Incisional hernia occurs in approximately 4% of open kidney transplantations. Mesh infection is a risk factor for incisional hernia recurrence. Open and laparoscopic repair approaches are safe and effective.

Malignancy and renal transplantation*

Recommendations	Strength rating
In the recipient	
List for renal transplantation patients with a history of appropriately treated low stage/grade renal cell carcinoma or prostate cancer without additional delay.	Weak
In the potential donor kidney	
Do not discard a kidney for potential transplantation on the basis of a small renal mass alone.	Weak
Malignancy after renal transplantation	
Be aware of the presence of a kidney transplant in the pelvis and the possibility of subsequent transplants when planning treatment for prostate cancer.	Strong
Refer kidney transplant patients with prostate cancer to an integrated transplant urology centre.	Strong

**The following section is limited to a synopsis of three systematic reviews conducted by the Panel.*

Matching of donors and recipients

Histocompatibility antigens show remarkable polymorphism and human leukocyte antigen (HLA) matching is still very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches.

Recommendations	Strength rating
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	Strong
Test both the donor and recipient for human leukocyte antigen DQ. Human leukocyte antigen DP testing may be performed for sensitised patients.	Strong
Perform thorough testing for HLA antibodies before transplantation.	Strong
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	Strong

Immunosuppression after kidney transplantation

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.

The currently recommended standard initial immuno-suppression regime provides excellent efficacy with good tolerability.
It is given to most patients and consists of:

- calcineurin inhibitors (preferably tacrolimus, alternatively cyclosporine);
- mycophenolate (MMF or enteric-coated mycophenolate sodium;
- steroids (prednisolone or methylprednisolon);
- induction therapy (preferably basiliximab in low and standard risk patients and anti-thymocyte globulin (ATG) in high-risk patients).

Recommendations	Strength rating
General immunosuppression after kidney transplantation	
Perform initial rejection prophylaxis with a combination therapy of a calcineurin inhibitor (preferably tacrolimus), mycophenolate, steroids and an induction agent (either basiliximab or anti-thymocyte globulin).	Strong
Calcineurin inhibitors	
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	Strong
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	Strong
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	Strong
Mycophenolates	
Administer mycophenolate as part of the initial immunosuppressive regimen.	Strong
Azathioprine	
Azathioprine may be used in a low-risk population as an immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	Weak
Steroids	
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	Strong

Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	Weak
Inhibitors of the mammalian target of rapamycin (m-TOR)	
The m-TOR inhibitors may be used to prevent rejection in patients who are intolerant to standard therapy.	Weak
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	Strong
Do not convert patients with proteinuria and poor renal function to m-TOR inhibitors.	Strong
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment.	Strong
Induction with Interleukin-2 receptor antibodies	
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	Weak
T-cell depleting induction therapy	
T-cell depleting antibodies may be used for induction therapy in immunologically high-risk patients.	Weak
Belatacept	
Belatacept may be used for immuno-suppressive therapy in immunologically low-risk patients, who have a positive Epstein-Barr virus serology.	Weak

Immunological complications

Immunological rejection is a common cause of early and late transplant dysfunction. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Two main types of immunological reactions are distinguished: T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR). Antibody-mediated rejection and TCMR may be diagnosed together, called mixed acute rejection. Antibody-mediated rejection may occur as hyperacute rejection, acute rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

Recommendations	Strength rating
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	Strong
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	Strong
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	Strong
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	Strong
Only if contraindications to renal biopsy are present, can 'blind' steroid bolus therapy be given.	Strong
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	Strong

Reassess the immunosuppressive therapy of all patients with rejection, including patient adherence to the medication, which is of particular importance in late rejections.	Strong

Hyper-acute rejection

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft. It results from circulating, complement-fixing IgG antibodies, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium within minutes or hours after vascularisation.

Recommendation	Strength rating
Prevent hyper-acute rejection by adequate ABO blood group and HLA matching of donor and recipients.	Strong

Treatment of T-cell mediated acute rejection

Recommendations	Strength rating
Use steroid bolus therapy as first-line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	Strong
In severe or steroid-resistant rejection, use intensified immunosuppression, high-dose steroid treatment, and eventually T-cell depleting agents.	Strong

Treatment of antibody mediated rejection

Recommendation	Strength rating
Treatment of antibody mediated rejection should include antibody elimination.	Strong

Follow-up after transplantation

Long-term graft function is of critical importance for the success of a transplant. Therefore, regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen.

Recommendations	Strength rating
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	Strong
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immuno-suppressive regimen.	Strong
Regularly monitor (approximately every four to eight weeks) serum creatinine, estimated glomerular filtration rate, blood pressure, urinary protein excretion, immuno-suppression and complications after renal transplantation. Changes in these parameters over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	Strong

Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	Strong
In patients with interstitial fibrosis and tubular atrophy undergoing calcineurin inhibitor therapy and/or with histological signs suggestive for calcineurin inhibitor toxicity (e.g. arteriolar hyalinosis, striped fibrosis) consider calcineurin inhibitor reduction or withdrawal.	Strong
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-13-4) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.

EAU GUIDELINES ON THROMBOPROPHYLAXIS IN UROLOGICAL SURGERY

(March 2017)

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Introduction

Utilising recent studies and newly summarised evidence, the EAU Guidelines on Thromboprophylaxis provide practical evidence-based guidance regarding post-surgery thromboprophylaxis and peri-operative management of antithrombotic agents in urology.

The Thromboprophylaxis Panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence and grading of recommendations. GRADE offers four levels of evidence quality, reflecting the degree of certainty or confidence in the evidence: high, moderate, low, and very low. The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. GRADE classifies recommendations as strong or weak.

Thromboprophylaxis post-surgery

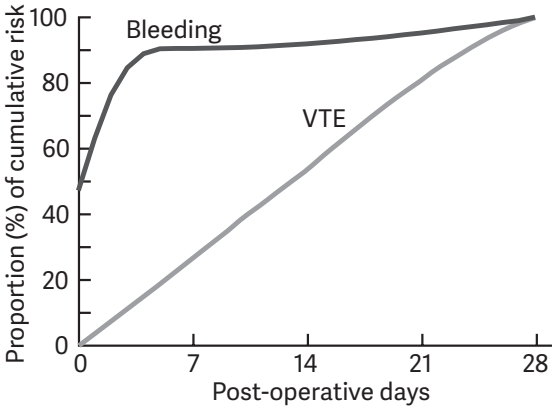
This guideline provides procedure and patient risk-specific guidance weighing the benefit of reduced venous thromboembolism (VTE) against the harm of increased bleeding. The Panel provides recommendations for numerous urologic procedures, with variation across patient risk

strata (Table 1). When creating recommendations, the Panel first calculated the net benefit (absolute reduction in VTE risk – absolute increase in bleeding risk) and then considered quality of evidence for both pharmacological and mechanical prophylaxis (Figure 1).

Table 1: Venous thromboembolism (VTE) according to patient risk factors

	Risk factors
Low risk	No risk factors
Medium risk	Any one of the following: age 75 years or more; body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child).
High risk	Prior VTE Patients with any combination of two or more risk factors

Figure 1: Proportion of cumulative risk (%) of venous thromboembolism (VTE) and major bleeding by week since surgery during the first four post-operative weeks



	Proportion of 28-day cumulative bleeding risk
Operation day	47.4%
Post-operative day 1	63.3%
Post-operative day 2	76.6%
Post-operative day 3	84.9%
Post-operative day 4	89.2%
Post-operative day 28	100.0%

The bleeding pattern depicted applies to most bleeds for most surgeries. However, some urological surgeries, such as transurethral resection of the the prostate (TURP), are associated with later bleeding. This is typically minor and occurs around ten days post-surgery.

General statements for all procedure-specific recommendations

The following apply to all recommendations for pharmacological prophylaxis:

- All recommendations are based on a starting time of the morning after surgery.
- The optimal duration of pharmacological prophylaxis for all recommendations is approximately four weeks post-surgery.
- There are number of acceptable alternatives for pharmacologic prophylaxis (Table 2).
- All recommendations for mechanical prophylaxis are until ambulation.

Table 2: Alternative regimens for pharmacological prophylaxis

Pharmacological agent	Dosage*
Low molecular weight heparins:	
Dalteparin	5,000 IU injection once a day
Enoxaparin	40 mg injection once a day
Tinzaparin	3,500/4,500 IU injection once a day
Unfractionated heparin	5,000 IU injection two or three times a day
Fondaparinux†	2.5 mg injection once a day
Direct acting oral anticoagulants†:	
Dabigatran	220 mg tablet once a day
Apixaban	2.5 mg tablet once a day
Edoxaban	30 mg tablet once a day
Rivaroxaban	10 mg tablet once a day

** Dosages may not apply in renal impairment.*

† Fondaparinux and direct acting oral anticoagulants have not been sufficiently studied in urology to warrant on-label use for post-surgery thromboprophylaxis.

Recommendations for prophylaxis in specific procedures according to patient risk

Ambulatory day surgery
R1. In all patients undergoing minor ambulatory day surgery (for example, circumcision, hydrocelectomy and vasectomy), the Panel recommends against use of pharmacological prophylaxis ***(strong, moderate-quality evidence)***, and against use of mechanical prophylaxis ***(strong, moderate-quality evidence)***.

Open radical cystectomy
R2. In all patients undergoing open radical cystectomy, the Panel recommends use of pharmacological prophylaxis ***(strong, moderate or high-quality evidence depending on risk stratum)***, and suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

Robotic radical cystectomy
R3. In all patients undergoing robotic radical cystectomy, the Panel suggests use of pharmacological prophylaxis ***(weak, low-quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

Laparoscopic radical prostatectomy
R4. For patients undergoing laparoscopic radical prostatectomy without pelvic lymph node dissection (PLND), for those at low risk of VTE, the Panel recommends against use of pharmacological prophylaxis ***(strong, moderate-quality evidence)*** and suggests against use of mechanical prophylaxis ***(weak, low-quality evidence)***; for those at moderate and high risk, the Panel suggests against use of pharmacological prophylaxis ***(weak, moderate- or high-quality evidence)*** and suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R5. For patients undergoing laparoscopic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacological prophylaxis ***(strong, moderate-quality evidence)***; for those at medium risk, the Panel suggests against use of pharmacological prophylaxis ***(weak, moderate-quality evidence)***; for those at high risk, the Panel recommends use of pharmacological prophylaxis ***(strong, high-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R6. For patients undergoing laparoscopic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacological prophylaxis ***(weak, moderate-quality evidence)***; for those at medium risk, the Panel suggests use of pharmacological prophylaxis ***(weak, high-quality evidence)***; for those at high risk, the Panel recommends use of pharmacological prophylaxis ***(strong, high-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

Open radical prostatectomy

R7. For patients undergoing open radical prostatectomy without PLND or with standard PLND, for those at low risk of VTE, the use of pharmacological prophylaxis is suggested ***(weak, moderate-quality evidence)***; for those at medium and high risk, use of pharmacological prophylaxis is recommended ***(strong, moderate- or high-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R8. For all patients undergoing open radical prostatectomy with extended PLND, the Panel recommends use of pharmacological prophylaxis ***(strong, moderate or high-quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

Robotic radical prostatectomy

R9. For patients undergoing robotic radical prostatectomy without PLND, for those at low risk of VTE, the Panel recommends against use of pharmacological prophylaxis ***(strong, moderate-quality evidence)*** and suggests against use of mechanical prophylaxis ***(weak, low-quality evidence)***; for those at medium and high risk, the Panel suggests against use of pharmacological prophylaxis ***(weak, moderate-quality evidence)*** and suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R10. For patients undergoing robotic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis ***(strong, moderate-quality evidence)***; for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis ***(weak, moderate-quality evidence)***; for those at high risk, the Panel suggests use of pharmacologic prophylaxis ***(weak, moderate-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R11. For patients undergoing robotic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis ***(weak, moderate-quality evidence)***; for those at medium risk, the Panel suggests use of pharmacologic prophylaxis ***(weak, moderate-quality evidence)***; for those at high risk, the Panel recommends use of pharmacologic prophylaxis ***(strong, moderate-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

Nephrectomy

R12. For patients undergoing laparoscopic partial nephrectomy, for those at low and medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis ***(weak, low-quality evidence)***; for those at high risk, the Panel recommends use of pharmacologic prophylaxis ***(strong, moderate-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R13. For all patients undergoing open partial nephrectomy, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, very low quality evidence)***.

R14. For patients undergoing robotic partial nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis ***(weak, moderate-quality evidence)***; for those at medium risk, the Panel suggests use of pharmacologic prophylaxis ***(weak, moderate-quality evidence)***; for those at high risk, the Panel recommends use of pharmacologic prophylaxis ***(strong, high-quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R15. For patients undergoing laparoscopic radical nephrectomy, for those at low or medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis ***(weak, very low quality evidence)***; for those at high risk, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low quality evidence)***; and for all patients, the Panel suggests use of mechanical prophylaxis ***(weak, very low quality evidence)***.

R16. For patients undergoing open radical nephrectomy, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R17. For all patients undergoing radical nephrectomy with thrombectomy, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, very low quality evidence)***.

R18. For all patients undergoing open nephroureterectomy, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, very low quality evidence)***.

R19. For all patients undergoing primary nerve sparing retroperitoneal lymph node dissection, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, very low quality evidence)***.

Non-cancer urological procedures

R20. For all patients undergoing transurethral resection of the prostate (TURP) or equivalent procedures, the Panel suggests against use of pharmacologic prophylaxis ***(weak, very low quality evidence)***; for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis ***(weak, low-quality evidence)***; and for those at high risk, the Panel suggests use of mechanical prophylaxis ***(weak, low-quality evidence)***.

R21. For patients undergoing laparoscopic donor nephrectomy or open donor nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis ***(weak, very low or low -quality evidence)***, and suggests against use of mechanical prophylaxis ***(weak, very low or low -quality evidence)***; for medium-risk patients, the Panel suggests against use of pharmacologic prophylaxis ***(weak, very low or low -quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, very low or low -quality evidence)***; and for high-risk patients, the Panel suggests use of pharmacologic prophylaxis ***(weak, very low or low -quality evidence)***, and suggests use of mechanical prophylaxis ***(weak, very low or low -quality evidence)***.

R22. For all patients undergoing open prolapse surgery or reconstructive pelvic surgery, the Panel suggests against the use of pharmacologic prophylaxis ***(weak, very low quality evidence)***; for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis ***(weak, very low or low -quality evidence)***; while for those at high risk, the Panel suggests use of mechanical prophylaxis ***(weak, very low or low -quality evidence)***.

R23. For all patients undergoing percutaneous nephrolithotomy, the Panel suggests against use of pharmacologic prophylaxis ***(weak, very low quality evidence)***; for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis ***(weak, very low quality evidence)***; while for those at high risk, the Panel suggests use of mechanical prophylaxis ***(weak, very low quality evidence)***.

Peri-operative management of antithrombotic agents in urology

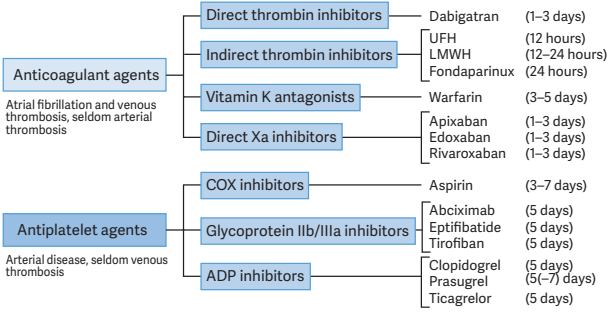
In principle, there are four options to manage use of antithrombotic agents (Figure 2) during the peri-operative period:

1) to defer surgery until antithrombotic agents are not needed;
2) stop antithrombotic agents prior to surgery and restart sometime after surgery;
3) continue through the surgical procedure;
4) administer alternative antithrombotic agents that may still reduce the risk of thrombosis but with less risk of bleeding than agents patients are currently using ("bridging").

Recent evidence has demonstrated that bridging increases bleeding without preventing thrombosis. The Panel therefore makes one of two recommendations for patients receiving antithrombotic agents regularly and contemplating surgery:

1) discontinue antithrombotic therapy for the period around surgery;
2) in those with a temporary very high risk of thrombosis, delay surgery until that risk decreases. If it is not possible to delay, continuing antithrombotic therapy or bridging through surgery may be advisable.

Figure 2: The most widely used antithrombotic agents in patients undergoing urologic surgery
Required period of stopping drug before surgery (if desired) provided in parentheses.



Recommendations for peri-operative management

Five days is an appropriate time to stop antiplatelet agents before surgery, while the optimal time to stop varies across anticoagulants (for details, see Figure 2).

R24. In all patients receiving antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor), except those with very high risk of thrombosis (see recommendations 26 and 27), the Panel recommends stopping antiplatelet agents before surgery and not initiating any alternative antithrombotic therapy ***(strong, high-quality evidence)***.

R25. In patients in whom antiplatelet agents have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk - typically four days post-surgery - rather than withholding for longer periods ***(strong, moderate-quality evidence)***.

R26. In patients with very high risk of thrombosis receiving antiplatelet agents (those with drug-eluting stent placement within six months, those with bare metal stent placement within six weeks, those with transient ischemic attack (TIA) or stroke within 30 days) in whom surgery can be delayed, the Panel recommends delaying surgery ***(strong, high-quality evidence)***.

R27. In patients with very high risk of thrombosis receiving antiplatelet agents (those with drug-eluting stent placement within six months, those with bare metal stent placement within six weeks, those with TIA or stroke within 30 days) in whom surgery cannot be delayed, the Panel suggests continuing the drugs through surgery ***(weak, low-quality evidence)***.

R28. In all patients receiving anticoagulant agents (unfractionated heparin, low molecular weight heparin [LMWH], warfarin, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban), except those with very high risk of thrombosis (see recommendation 26), the Panel recommends stopping drugs before surgery (see Figure 2) and not initiating any alternative antithrombotic therapy ***(strong, high-quality evidence)***.
Note: Patients with creatinine clearance <30 ml/min should not receive dabigatran, apixaban, rivaroxaban or edoxaban.

R29. In patients in whom anticoagulants have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk - typically four days post-surgery - rather than withholding for longer periods ***(strong, moderate-quality evidence)***.

R30. In patients with a new VTE, it is recommended that surgery is delayed for at least one month, and if possible three months, to permit discontinuation of anticoagulation pre-operatively, rather than operating within one month of thrombosis ***(strong, high-quality evidence)***.

R31. In patients receiving any anticoagulant with a severe thrombophilia, such as antithrombin deficiency and antiphospholipid antibody syndrome, the Panel suggests anticoagulation with either heparin or LMWH through surgery, rather than stopping anticoagulation before and after surgery ***(weak, low-quality evidence)***.

R32. In patients with high-risk mechanical prosthetic heart valves, such as cage-ball valves, receiving warfarin, the Panel recommends bridging with LMWH prior and subsequent to surgery, rather than discontinuing anticoagulation peri-operatively ***(strong, high-quality evidence)***. Anticoagulation in these patients involves stopping the warfarin five days prior, commencing LMWH four days prior, omitting LMWH on the day of surgery, and recommencing LMWH and warfarin after surgery.

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