Guidelines on Urological Infections

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1. INTRODUCTION

1.1 Aim

The current Guidelines aim to provide both urologists and physicians from other medical specialities with evidence-based guidance regarding the treatment and prophylaxis of urinary tract infections (UTIs). These Guidelines cover male and female UTIs, male genital infections and special fields such as UTIs in paediatric urology and risk factors, e.g. immunosuppression, renal insufficiency and diabetes mellitus. Much attention is given to peri-operative antibacterial prophylaxis (ABP), aiming to reduce the overuse of antimicrobial agents in conjunction with surgery. High quality clinical research using strict internationally recognised definitions and classifications, as presented in these Guidelines, are encouraged.

1.2 Publication history

The first version of the EAU Guidelines on Urological Infections were published in 2001 and in European Urology [1]. A second updated version followed in 2006. The EAU/ICUD textbook on Urogenital Infections [2], gathering world experts in the field, was published in 2010 and has become the book of reference for the present Guidelines. Several chapters were subsequently re-written and updated during 2011-2013 (e.g. classification of UTI, uncomplicated UTI, sepsis, bacterial prostatitis and antibiotic prophylaxis). Guidelines on specific conditions of the urogenital tracts have also been published elsewhere and used as references [3-5].

A modified classification of UTI was introduced successively and for the present 2015 Guidelines, the anatomical level and gradual degree of severity of infection presented in a synoptic view in Figure 1 is used as the basis for the structure of this chapter. A new chapter on asymptomatic bacteriuria (ABU) has been introduced (Chapter 3B), to underline the importance of avoiding antibacterial over-treatment of commensal colonisation. The medical risk factors for UTI have also been integrated within Chapter 3C on cystitis and pyelonephritis. The text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines so that all Guidelines follow a similar format. This document was peer-reviewed prior to publication.

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile device application, presenting the main findings of the Urological Infections Guidelines. These versions are abridged and therefore may require consultation with the full text version. All are available through the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.3 Panel composition

The Urological Infections Guidelines Panel consists of a group of urologists, specialised in the treatment of UTIs and male genital infections.

1.4 Background

Urinary tract infections are among the most prevailing infectious diseases with a substantial financial burden on society. In the US, UTIs are responsible for > 7 million physician visits annually [6]. Approximately 15% of all community-prescribed antibiotics in the US are dispensed for UTI [7] and data from some European countries suggest a similar rate [8]. In the US, UTIs account for > 100,000 hospital admissions annually, most often for pyelonephritis [6]. These data do not account for complicated UTI associated with urological patients, the prevalence of which is not well known. At least 40% of all hospital acquired infections are UTIs and the majority of cases are catheter associated [9]. Bacteriuria develops in up to 25% of patients who require a urinary catheter for one week or more with a daily risk of 5-7% [10, 11]. The recent Global Prevalence Infection in Urology (GPIU) studies have shown that 10-12% of patients hospitalised in urological wards have a healthcare-associated infection (HAI). The strains retrieved from these patients are even more resistant [12].

1.4.1 Bacterial resistance development

The present state of microbial resistance development is alarming [13]. The use of antibiotics in different European countries mirrors the global increase in resistant strains [14]. The presence of extended-spectrum β-lactamase (ESBL) producing bacteria showing resistance to most antibiotics, except for the carbapenem group, is steadily increasing in the population [15]. Even more alarming are the recent reports from all continents about the emergence and increased prevalence of different carbapenemase producing organisms making them resistant even to the carbapenem group of antibiotics.

Particularly troublesome is the increasing resistance to broad-spectrum antibiotics, in particular to fluoroquinolones and cephalosporins, due to an overconsumption of these two groups and the parallel development of co-resistance to other antibiotics (collateral damage) [16]. This development is a threat to patients undergoing urological surgery in general and men subjected to prostate biopsy in particular.

An urgent and strong grip on this threatening development is thus required. With only a few new

antibiotics expected in the coming 5 to 10 years, prudent use of available antibiotics is the only option to delay the development of resistance [14] and the urological community has a responsibility to participate in this combat. It is essential to consider the local microbial environment and resistance pattern as well as risk factors for harbouring resistant microbes in individual patients.

Bacterial resistance development is a threat: • To treatment of UTI. • To prophylaxis in urological surgery.
There is a direct correlation between the use of antibiotics and resistance development.
There is an urgent need for combating resistance development by a prudent use of available antibiotics.

*1.4.2 **Pathogenesis of UTIs***

Microorganisms can reach the urinary tract by haematogenous or lymphatic spread, but there is abundant clinical and experimental evidence showing that the ascent of microorganisms from the urethra is the most common pathway that leads to a UTI, especially organisms of enteric origin (e.g. *E. coli* and other Enterobacteriaceae). This provides a logical explanation for the greater frequency of UTIs in women than in men, and for the increased risk of infection following bladder catheterisation or instrumentation. A single insertion of a catheter into the urinary bladder in ambulatory patients results in urinary infection in 1-2% of cases. Indwelling catheters with open-drainage systems result in bacteriuria in almost 100% of cases within 3-4 days. The use of a closed-drainage system, including a valve to prevent retrograde flow, delays the onset of infection, but ultimately does not prevent it. It is thought that bacteria migrate within the mucopurulent space between the urethra and catheter, and that this leads to the development of bacteriuria in almost all patients within ~ 4 weeks.

Haematogenous infection of the urinary tract is restricted to a few relatively uncommon micro-organisms, such as *Staphylococcus aureus*, *Candida sp.*, *Salmonella sp*. and *Mycobacterium tuberculosis*, which cause primary infections elsewhere in the body. Candida albicans readily causes a clinical UTI via the haematogenous route, but this is also an infrequent cause of an ascending infection if an indwelling catheter is present, or following antibiotic therapy.

The concept of bacterial virulence or pathogenicity in the urinary tract infers that not all bacterial species are equally capable of inducing infection. The more compromised the natural defence mechanisms (e.g. obstruction, or bladder catheterisation), the fewer the virulence requirements of any bacterial strain to induce infection. This is supported by the well-documented in vitro observation that bacteria isolated from patients with a complicated UTI frequently fail to express virulence factors. The virulence concept also suggests that certain bacterial strains within a species are uniquely equipped with specialised virulence factors, e.g. different types of pili, which facilitate the ascent of bacteria from the faecal flora, introitus vaginae or periurethral area up the urethra into the bladder, or less frequently, allow the organisms to reach the kidneys to induce systemic inflammation.

*1.4.3 **Microbiological and other laboratory findings***

The number of bacteria is considered relevant for the diagnosis of a UTI. In 1960, Kass developed the concept of significant bacteriuria ($\geq 10^5$ cfu/mL) in the context of pyelonephritis in pregnancy [17]. Although this concept introduced quantitative microbiology into the diagnosis of infectious diseases, and is therefore still of general importance, it has recently become clear that there is no fixed bacterial count that is indicative of significant bacteriuria, which can be applied to all kinds of UTIs and in all circumstances [18]. As described in Appendix 4.1, the following bacterial counts are clinically relevant:

- $\geq 10^3$ cfu/mL of uropathogens in a mid-stream sample of urine (MSU) in acute uncomplicated cystitis in women.
- $\geq 10^4$ cfu/mL of uropathogens in an MSU in acute uncomplicated pyelonephritis in women.
- $\geq 10^5$ cfu/mL of uropathogens in an MSU in women, or $\geq 10^4$ cfu/mL uropathogens in an MSU in men, or in straight catheter urine in women, in a complicated UTI.

In a suprapubic bladder puncture specimen, any count of bacteria is relevant. The problem of counting low numbers, however, has to be considered. If an inoculum of 0.1 mL of urine is used and 10 identical colonies are necessary for statistical reasons of confidence, then in this setting, the lowest number that can be counted is 100 cfu/mL of uropathogens. Asymptomatic bacteriuria is diagnosed if two cultures of the same bacterial strain (in most cases the species only is available), taken ≥ 24 h apart, show bacteriuria of $\geq 10^5$ cfu/mL of uropathogens.

It is obvious that methods of urine collection and culture, as well as the quality of laboratory investigations, may vary. Two levels of standard must therefore be used for the management of patients. A basic standard level is necessary for routine assessment, whereas a higher standard level is

required for scientific assessment and in special clinical circumstances, e.g. fever of unknown origin in immunocompromised patients. In research, the need for a precise definition of sampling methods, such as the time that urine is kept in the bladder, must be recognised, and these parameters carefully recorded.

In clinical routine assessment, a number of basic criteria must be looked at before a diagnosis can be established, including:

- clinical symptoms;
- results of selected laboratory tests (blood, urine or expressed prostatic secretion [EPS]);
- evidence of the presence of microorganisms by culturing or other specific tests;

most of these investigations can today be performed in any laboratory.

It has to be considered, however, that microbiological methods and definitions applied must follow accepted standards with regard to specimen transport, pathogen identification, and antimicrobial susceptibility testing. These methods and microbiological definitions may vary between countries and institutions. One example is the breakpoints for classification of pathogen susceptibility. It is important to report not only the results, but also which methods and standards were applied, such as the European Committee for Antimicrobial Susceptibility Testing (EUCAST) [19, 20], or the National Committee for Clinical Laboratory Standards (NCCLS) [21]. Mixing results obtained by different methods, e.g. rates of bacterial resistance, can be problematic and requires careful interpretation. Histological investigation sometimes shows the presence of non-specific inflammation. Only in some cases, such findings (e.g. prostatitis in patients who have elevated levels of prostate-specific antigen [PSA]) might help determine the appropriate treatment, whereas in more specific inflammation, such as tuberculosis and actinomycosis, histology can be diagnostic. In general, however, histological findings usually contribute very little to the treatment decisions.

2. METHODS

The EAU/ICUD textbook on Urological Infections [2] mentioned in Chapter 1.2 was based as far as possible and appropriate on a structured literature search. One expert chaired each chapter, gathering several co-authors. Available systematic reviews, meta-analyses, and high quality review articles and controlled studies were preferably used in each chapter as references and the recommendations underwent vigorous consensus. The criteria for evidence and recommendations align with those used in the EAU Guidelines and included during subsequent updates in 2011-2013 of these Guidelines. Thereafter, the recommendations have been adjusted whenever necessary based on an annual assessment of newly published literature in the field.

The new ABU guideline (Chapter 3B) is based on a structured search for scientific articles using the term “asymptomatic bacteriuria”. The panel selected reviews, meta-analysis and randomised controlled trials (RCTs), assigned according to the different patients groups covered.

It must be emphasised that clinical guidelines present the best evidence available to the experts at the time of writing. Compliance to the guidelines is expected to result in a favourable outcome. However, guidelines can never replace clinical expertise when treatment decisions for individual patients are being taken. Guidelines help to focus decisions. Clinical decisions must also take into account patients’ personal values and preferences and their individual circumstances.

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [22]. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines.

3. THE GUIDELINE
3A CLASSIFICATION OF UTIs

3A.1 Introduction

The following Guidelines cover UTIs and male accessory gland infections (MAGI); both infections are closely associated in males. Chapters 3A-H cover UTIs and Chapters 3I-K cover MAGI. Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings. Practically, UTIs have been divided into uncomplicated and complicated UTIs, and sepsis. The following classification model is a working instrument useful for daily assessment and for clinical research.

A critical review of present classifications was undertaken for the EAU/ICUD Urogenital Infections initiative [23] see Appendix 4.1. The overall aim is to provide the clinician and researcher with a standardised tool and nomenclature for UTI. The present guidelines give a short summary of a tentative improved system of classification of UTI based on:

- anatomical level of infection;
- grade of severity of infection;
- underlying risk factors;
- microbiological findings.

The symptoms, signs and laboratory finding focus on the anatomical level and the degree of severity of the infection. The risk factor analysis contributes to define any additional therapeutic measure required (i.e. drainage).

*3A.1.1 **Anatomical level of infection***

The symptoms (see Appendix 4.1) focus on the anatomical level of infection, defined as:

- urethra: urethritis (UR);
- urinary bladder: cystitis (CY);
- kidney: pyelonephritis (PN);
- bloodstream: sepsis (US).

Figure 1 illustrates the basic diagnostic and treatment strategy for UTI. Urethritis, being poorly understood besides sexually transmitted conditions, is for the time being not included. Also MAGI, orchitis, epididymitis and prostatitis are not included.

Asymptomatic bacteriuria needs to be considered a special entity because it can have its source in both the lower and upper urinary tracts, and requires no treatment unless the patient is subjected to urological surgery or is pregnant.

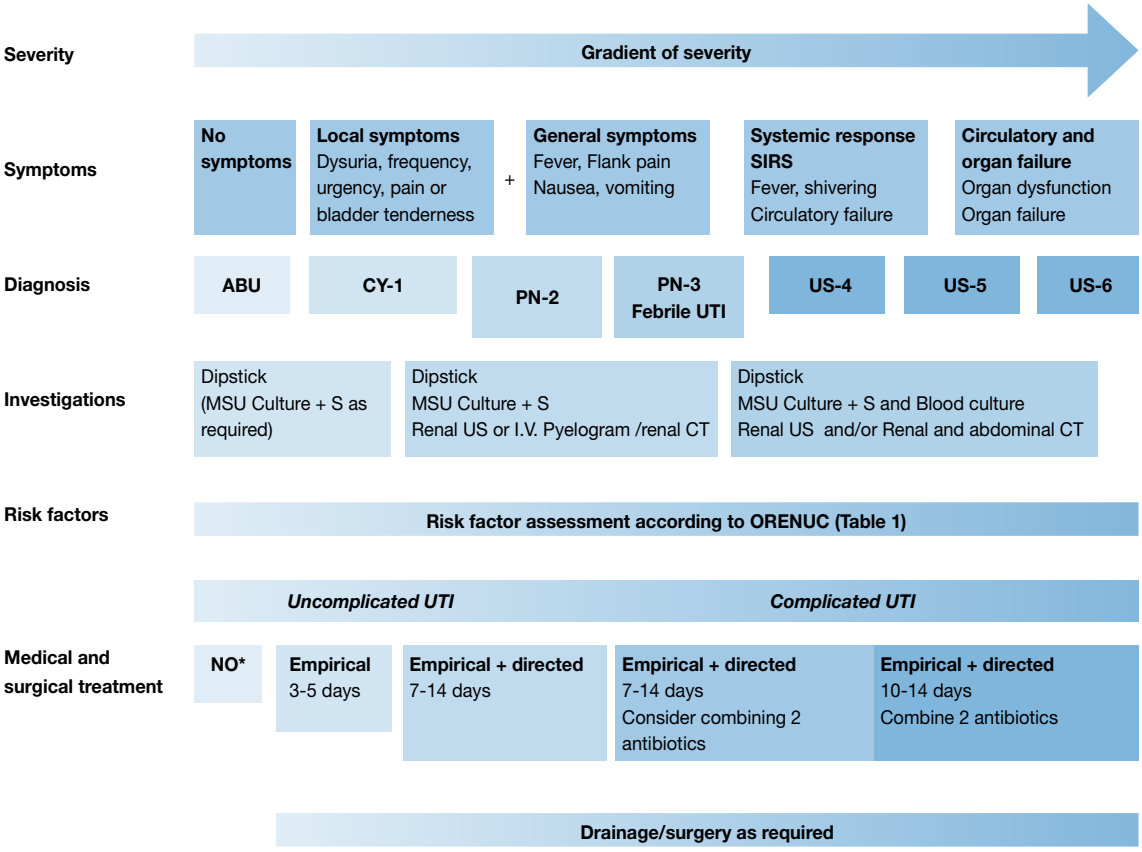
*3A.1.2 **Grade of severity***

The grade of severity is set on a scale of 1-6 that is related to the risk of fatal outcome (Figure 1).

3A.2 Pathogens

Urine culture will usually identify the causative pathogen ($\geq 10^4$ cfu/mL) and its susceptibility pattern. Both characteristics can be introduced in the final classification of the clinical stage of infection. The degree of susceptibility is defined as grade a (susceptible) to c (resistant). The list of most frequent pathogens is given in Appendix 4.2.

Figure 1: Synoptic view of the classification of UTI as proposed by the EAU Section of Infection in Urology (ESIU) [23] and including the basic priciples of diagnosis and treatment



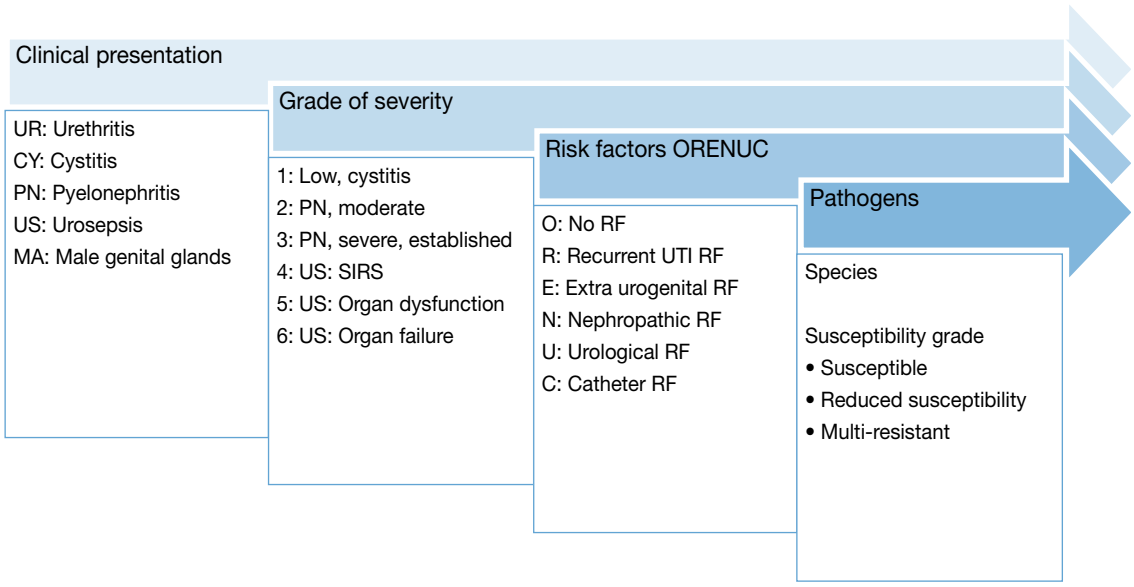
** Two presently accepted exceptions: during pregnancy and prior to urological surgery.*

Table 1: Host risk factors in UTI

Type	Category of risk factor	Examples of risk factors
O	N**O** known/associated RF	- Healthy premenopausal women
R	**R**ecurrent UTI RF, but no risk of severe outcome	- Sexual behaviour and contraceptive devices - Hormonal deficiency in post menopause - Secretory type of certain blood groups - Controlled diabetes mellitus
E	**E**xtra-urogenital RF, with risk of more severe outcome	- Pregnancy - Male gender - Badly controlled diabetes mellitus - Relevant immunosuppression* - Connective tissue diseases* - Prematurity, new-born
N	**N**ephropathic disease, with risk of more severe outcome	- Relevant renal insufficiency* - Polycystic nephropathy
U	**U**rological RF, with risk of more severe outcome, which can be resolved during therapy	- Ureteral obstruction (i.e. stone, stricture) - Transient short-term urinary tract catheter - Asymptomatic Bacteriuria** - Controlled neurogenic bladder dysfunction - Urological surgery
C	Permanent urinary **C**atheter and non-resolvable urological RF, with risk of more severe outcome	- Long-term urinary tract catheter treatment - Non-resolvable urinary obstruction - Badly controlled neurogenic bladder

*RF = risk factor; * = not well defined; ** = usually in combination with other RF (i.e. pregnancy, urological internvention).*

Figure 2: Additive parameters of UTI classification and severity assessment



3A.3 Classification systems

Figure 2 shows a summary of the additive parameters that make up an individual class of UTI.
By cumulating the different parameters, a UTI can be classified as follows (examples) [23]:

- CY-1R: *E. coli* (a): simple cystitis but recurrent with susceptibility to standard antibiotics.
- PN-3U: *K pneumonia* (b): severe pyelonephritis (with high fever and vomiting), with underlying urological disease (e.g. stones or obstruction) due to *Klebsiella sp*., with a moderate antibiotic resistance profile.
- US-5C: *Enterococcus sp*. (a): severe urosepsis with an antibiotic-sensitive *Enterococcus sp*. in a patient with an indwelling catheter.

3B ASYMPTOMATIC BACTERIURIA IN ADULTS

3B.1 Introduction

Urinary growth of bacteriae in an asymptomatic individual (ABU) is common, and corresponds to a commensal colonisation [24]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [25, 26]. The aim of these Guidelines is to support the clinician in deciding whether ABU should be treated or not.

3B.2 Methods

The Guidelines on ABU are based on a structured search for scientific articles using the term: “asymptomatic bacteriuria”. The panel selected reviews, meta-analyses and RCTs, assigned according to the different patient groups covered in the Guidelines.

3B.3 Epidemiology, aetiology and pathophysiology

ABU occurs in an estimated 1-5% of healthy premenopausal women. ABU increases to: 4-19% in otherwise healthy elderly women and men, 0.7-27% in diabetes patients, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and 23-89% in spinal cord injury patients [27]. ABU in younger men is uncommon, but when detected, a chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence or not of a risk factor (see Chapters 3A, C and D).

3B.4 Diagnostic evaluation

ABU is defined by a mid-stream sample of urine (MSU) showing bacterial growth $\geq 10^5$ cfu/ml in two consecutive samples in women [28] and in one single sample in men [29], in an individual without symptoms

from the urinary tract. In a single catheterised sample, bacterial growth may be as low as 10^2 cfu/ml to be considered representing true bacteriuria in both men and women [27, 30]. Diagnostic work-up should include measurement of residual urine while cystoscopy and/or imaging of the upper urinary tract is not mandatory if the medical history is otherwise without remarks (LE: 4; GR: A). If persistent growth of urease producing bacteria, i.e. *Proteus* mirabilis, is detected, stone formation in the urinary tract must be excluded [31]. In men, a DRE of the prostate has to be performed to rule out prostate diseases, including chronic bacterial prostatitis (Chapter 3I).

3B.5 Disease management

3B.5.1 ***Patients without identified risk factors***

ABU does not cause renal disease or damage [32]. RCTs in paediatric populations and women, demonstrate that ABU treatment increases the risk for a subsequent symptomatic UTI episode, as compared to non-treated controls [25, 26]. Consequently, screening and treatment of ABU is not recommended in patients (females and young males) without risk factors (LE: 1b; GR: A).

3B.5.2 ***Patients with ABU and recurrent UTI, otherwise healthy***

In women with recurrent symptomatic UTI and without identified risk factors, the protective effect of spontaneously developed ABU has been demonstrated [26]. Therefore, treatment of ABU in women with recurrent symptomatic UTI is not recommended (LE: 1b; GR: A). However, occasionally the eradication of a strain considered the causative agent of recurrent episodes of UTI, may be justified (LE: 4; GR: C). In men with recurrent symptomatic UTI and with ABU, chronic bacterial prostatitis must be considered and, if diagnosed, treated (Chapter 3I).

3B.5.3. ***Pregnant women***

ABU is common during pregnancy (2-10%) and correlates to an increased risk for symptomatic UTI and pyelonephritis [27]. Evidence for the association between ABU and preterm delivery/low birth weight is however weak [33]. Screening and treatment of ABU in pregnant women is recommended by many guidelines, but the evidence for an improved outcome is low and not supported [34]. Therefore no general recommendation can be made and in case of doubt, consultation of national recommendations for pregnant women is advised.

3B.5.4 ***Patients with identified risk-factors***

3B.5.4.1 ABU in postmenopausal women

Elderly women have an increased incidence of ABU, which should be managed as for pre-menopausal women (see 3B.5.2) [35].

3B.5.4.2 Diabetes mellitus

Diabetes mellitus, also well regulated, correlates with a higher frequency of ABU in women [36, 37]. Eradicating ABU has not been shown to reduce the risk of symptomatic UTI and infectious complications in diabetes patients, and untreated ABU does not correlate with diabetic nephropathy [38]. Screening and treatment of ABU in well-regulated diabetes mellitus is therefore not recommended (LE: 1b; GR: A). However, poorly regulated diabetes may be a risk factor for symptomatic UTI and infectious complications.

3B.5.4.3 Elderly institutionalised patients

The rate of ABU is high (15-50%) in elderly institutionalised patients [39]. Differential diagnosis to symptomatic UTI is difficult in multi-diseased and mentally deteriorated patients, and is probably a cause of unnecessary antibiotic treatment [40, 41]. It has been shown that treatment of ABU in this patient group is of no benefit [42]. Furthermore, before treatment is given the possible protective effect of spontaneously developed ABU (see 3.5.4.4.) should be taken into account. Therefore screening and treatment of ABU is not recommended in this patient group (LE: 1b; GR: A).

3B.5.4.4 Patients with dysfunctional and/or reconstructed lower urinary tracts

Patients with lower urinary tract dysfunction (LUTD), e.g. neurogenic bladder patients secondary to multiple sclerosis and spinal cord injury patients, and patients with incomplete bladder emptying, patients with neo-bladder, and ileo-cystoplasty, patients using clean intermittent catheterisation (CIC), and patients with ileal conduits, orthotopic bladder replacement and continent reservoirs, frequently become colonised [43, 44]. Studies have shown no benefit in ABU treatment in these patient groups [43, 44]. Furthermore, in LUTD patients who do not spontaneously develop ABU, deliberate colonisation with an ABU strain (*E. coli* 83972) has shown a protective effect against symptomatic recurrences [45, 46]. Screening and treatment of ABU in these patient groups is therefore not recommended (LE: 2b; GR: B). In case these patient groups develop recurrent symptomatic UTI (Chapter 3B.5.2), the potential protective effect of a spontaneously developed ABU against

lower UTI should be considered before any treatment (LE: 4; GR: B).

3B.5.4.5 Patients with catheters in the urinary tract
Patients with indwelling or supra-pubic catheters, and with nephrostomy tubes, invariably become carriers of ABU, with antibiotic treatment showing no benefit, which is also applicable for patients with ABU and internal ureteric stents [47] where treatment is not recommended see section 3F (LE: 4; GR: C).

3B.5.4.6 Patients with ABU subjected to catheter placements/exchanges
In patients subjected to uncomplicated placement/exchanges of indwelling catheters ABU is not considered a risk factor per se, and should not be screened or treated (LE: 4; GR: C). In patients subjected to placement/exchanges of nephrostomy tubes and internal stents, ABU is considered as a risk factor for infectious complications (contaminated procedure), and screening and treatment prior to the procedure is recommended (LE: 4; GR: C).

3B.5.4.7 Patients with renal transplants
Based on the result of a retrospective observational study, there are no short- or long-term benefits of antibiotic treatment of ABU in patients with renal transplants and with an uncomplicated medical history otherwise [48], therefore they should not be treated (LE: 3; GR: B). However, prospective randomised comparative studies are needed to confirm this [49].

3B.5.4.8 Immuno-comprised and severely diseased patients, patients with candiduria
These patient groups have to be considered individually and the benefit of screening and treatment of ABU should be assessed in each case (LE: 4; GR: C). Patients with asymptomatic candiduria may, but not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended in patients with an otherwise uncomplicated medical history [50] (LE: 1b; GR: A).

3B.5.5 ***Prior to surgery***
In diagnostic and therapeutic procedures not entering the urinary tract (clean procedures), ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary (LE: 4; GR: C). On the other hand, in procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor. In case of absence of bacteriuria, the procedure in the present guidelines is usually classified as clean-contaminated, while the presence of bacteriuria, obstruction and drainage catheters, define the procedure as contaminated. A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment should be given (LE: 3; GR: B). The recommendations for antibiotic prophylaxis in different urological procedures are given in Chapter 3N.

3B.5.6 ***Pharmacological management***
If the decision is taken to eradicate ABU the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (Table 3 and 4) or complicated (Table 7) UTI could be given, depending on gender, medical background and if complicating factors are present. Treatment should be tailored and not empirical. If ABU patients complain of odour and mild dysuria, methenamine hippurate 1g two to three times daily, and/or increased water intake, could be an option worth consideration (LE: 4; GR: C).

3B.6 Follow-up
If ABU is treated, a follow-up with subsequent urine culture should secure the treatment effect.

3C CYSTITIS AND PYELONEPHRITIS IN ADULTS

3C.1 Introduction
This chapter is based also on the EAU/ICUD publication on urogenital infections, Chapter 3 on uncomplicated UTI (uUTI), Chapter 4 on prevention of recurrent UTI in adults, and partially Chapter 7 on patients with nephropathies and immunodeficiency [2].

Acute, uncomplicated UTIs in adults include sporadic or recurrent, community-acquired episodes of acute cystitis and acute pyelonephritis in otherwise healthy individuals, comprising the host risk factors O and R, and partially E according to the ORENUC classification (see Table 1). These UTIs are seen mostly in otherwise healthy women without relevant structural and functional abnormalities within the urinary tract, kidney diseases, or comorbidity that could lead to more serious outcomes and therefore require additional

attention [51, 52]. Only a small number of men will suffer from uUTI.

3C.2 Epidemiology, aetiology and pathophysiology

Almost half of all women will experience at least one episode of UTI during their lifetime. Nearly 1 in 3 women will have had at least one episode of UTI by the age of 24 years [53].

Table 2: The most important age related known and possible risk factors for UTI in women [39, 54, 55]

Young and premenopausal women	Postmenopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
A mother with a history of UTI	Cystocoele
History of UTI during childhood	Increased post-void urine volume
	Blood group antigen secretory status
	Urine catheterisation and functional status
	deterioration in elderly institutionalised women

Only a small number of 15-50 year-old men suffer from acute uncomplicated cystitis [56]. As reviewed by Fünfstück et al. [57], UTI (cystitis and pyelonephritis) occurs more frequently in patients with diabetes mellitus, which may represent an independent risk factor. It is, however, difficult to determine the impact of renal insufficiency on the epidemiology of UTI because of the wide variety of underlying diseases [58].

The place of immunosuppression per se in the development of UTI remains also unresolved [59]. In male patients with HIV and AIDS a close relationship between CD4 counts and the risk of bacteriuria was found, particularly in patients whose counts are < 200 cells/mL [60]. About 40% of those with bacteriuria, however, were asymptomatic and there is no evidence that treatment of ABU in this group leads to improved outcome [61].

The spectrum of aetiological agents is similar in uncomplicated upper and lower UTIs, with *E. coli* the causative pathogen in 70-95% of cases and Staphylococcus saprophyticus in 5-10%. Occasionally, other Enterobacteriaceae, such as *Proteus* mirabilis and *Klebsiella sp*., are isolated [62] (LE: 2a).

3C.3 Acute episode of uncomplicated cystitis (lower UTI) in adults

*3C.3.1 **Diagnostic evaluation***

3C.3.1.1 Clinical diagnosis

The diagnosis of acute uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation, in those women who have no other risk factors for complicated UTIs [52, 63] (LE: 2a, GR: B). In elderly women genitourinary symptoms are not necessarily related to UTI [55].

In otherwise healthy diabetic patients with stable glycaemic metabolism, a sporadic or even recurrent cystitis can also be considered uncomplicated. However, in the long-term patients with diabetes may develop a neuropathic bladder with voiding disturbances which may be present as a relevant complicating factor [57].

In otherwise healthy patients with mild and moderate renal insufficiency without other relevant structural and functional abnormalities within the urinary tract and the kidneys, a sporadic or recurrent cystitis can also be considered uncomplicated because no more serious outcome needs to be considered.

3C.3.1.2 Differential diagnosis

Symptomatic UTI should be differentiated from asymptomatic bacteriuria, which is considered not an infection but rather a commensal colonisation, which usually should not be treated and therefore not screened for, except if it is considered a risk factor in special situations see Section 3B.

3C.3.1.3 Laboratory diagnosis

Urine dipstick testing, as opposed to urinary microscopy, is a reasonable alternative to culture for diagnosis of acute uncomplicated cystitis [64, 65] (LE: 2a, GR: B).

Urine cultures are recommended in the following situations:

- Suspected acute pyelonephritis;
- Symptoms that do not resolve or recur within 2-4 weeks after the completion of treatment;
- Women who present with atypical symptoms [66, 67];
- Pregnant women, and

- Males with suspected UTI (LE: 4, GR: B).

A colony count of $\geq 10^3$ cfu/mL of uropathogens is microbiologically diagnostic in women who present with symptoms of acute uncomplicated cystitis [68] (LE: 3, GR: B).

Women who present with atypical symptoms of either acute uncomplicated cystitis or acute uncomplicated pyelonephritis, as well as those who fail to respond to appropriate antimicrobial therapy should be considered for additional diagnostic studies (LE: 4, GR: B).

Urological evaluation including rectal examination should always be carried out in men to rule out relevant complicating factors (LE: 4, GR: A).

*3C.3.2 **Disease management***

Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo [69] (LE: 1a, GR: A). The choice of antibiotic therapy should be guided by [52]:

- spectrum and susceptibility patterns of the aetiological uropathogens;
- efficacy for the particular indication in clinical studies;
- tolerability and adverse reactions;
- adverse ecological effects;
- cost;
- availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg tid for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available [70-72] (LE: 1a, GR: A) (Table 3). These regimens are recommended for women, but not for men. Most ESBL-producing *E. coli* are still susceptible to fosfomycin. However, in Spain a parallel increase in community use of fosfomycin and resistance to fosfomycin in ESBL-producing *E. coli* has been observed [73].

Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [74, 75] (LE: 1b, GR: B). Despite still lower resistance rates in some areas, fluoroquinolones are not considered first choice because of adverse effects including negative ecological effects and selection of resistance (Table 3).

Aminopenicillins are no more suitable for empirical therapy because of the worldwide high *E. coli* resistance. Aminopenicillins in combination with a betalactamase inhibitor such as ampicillin/sulbactam or amoxicillin/slavulanic acid and oral cephalosporins are in general not so effective as short-term therapy and are not recommended for empirical therapy because of ecological collateral damage, but can be used in selected cases [76, 77].

Short courses of antimicrobial therapy can also be considered for the treatment of cystitis in pregnancy [78] (LE: 1a, GR: A), but not all antibiotics are suitable during pregnancy. In general penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of G6P deficiency and during end of pregnancy), trimethoprim not in the first and sulphonamides not in the last trimenon, can be considered.
In men a treatment duration of at least 7 days is recommended, preferably with TMP-SMX or a fluoroquinolone if in accordance with the susceptibility testing (LE: 4; GR: B).

In patients with renal insufficiency the choice of antimicrobials may be influenced by the decreased renal excretion. Most antibiotics, however, have a wide therapeutic index. No adjustment of dose is necessary until GFR < 20 mL/min, except antibiotics with nephrotoxic potential, e.g. aminoglycosides. Combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin and tetracyclines are contraindicated, but not doxycycline.

Table 3: Recommended antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy women

Antibiotics	Daily dose	Duration of therapy	Comments
First choice			
Fosfomycin trometamol	3 g SD	1 day	
Nitrofurantoin macrocrystal	100 mg bid	5 days	avoid in G6PD deficiency
Pivmecillinam	400 mg tid	3 days	
Alternatives			
Ciprofloxacin	250 mg bid	3 days	not during pregnancy
Levofloxacin	250 mg qd	3 days	not during pregnancy
Ofloxacin	200 mg bid	3 days	not during pregnancy
Cephalosporin (e.g. cefadroxil)	500 mg bid	3 days	Or comparable (see Appendix 4.5)
If local resistance pattern is known (E. coli resistance < 20%)			
TMP	200 mg bid	5 days	TMP not in the first trimenon of pregnancy
TMP- SMX	160/800 mg bid	3 days	SMX not in the last trimenon of pregnancy

SD = single dose; G6PD = glucose-6-phosphate dehydrogenase; TMP = trimethoprim; SMX = sulphamethoxazole.

3C.3.3 ***Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [27] (LE: 2b, GR: B), except in pregnant women, if asymptomatic bacteriuria is an issue of therapy (see Chapter 3B.5.3). In women whose symptoms do not resolve by the end of treatment, and in those whose symptoms resolve but recur within 2 weeks, urine culture and antimicrobial susceptibility tests should be performed (LE: 4, GR: B). For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a 7-day regimen using another agent should be considered (LE: 4, GR: C).

3C.4 Acute uncomplicated pyelonephritis in adults

3C.4.1 ***Diagnostic evaluation***

3C.4.1.1 Clinical diagnosis

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness, and it can occur in the absence of symptoms of cystitis [79].

Pregnant women with acute pyelonephritis need special attention, because this kind of infection may have not only an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn with more frequent preterm labour and preterm birth [80].

Most men with febrile UTI have a concomitant infection of the prostate as measured by transient increases of PSA and prostate volume [81]. Thus, urological evaluation should be carried out routinely in men with febrile UTI, pyelonephritis, or recurrent UTI, or whenever a complicating factor is suspected (LE: 4, GR: A).

In diabetic patients with acute pyelonephritis metabolic abnormalities, e.g. hypo- and hyperglycaemia, hyperosmolar dehydration, or ketoacidosis, need to closely be followed [57]. Diabetic patients may also develop progression of renal parenchymal infection sometimes caused by gas-forming organisms, with a high mortality (emphysematous pyelonephritis), characterised histologically by acute pyogenic infiltration with micro-abscesses and the development of acute renal failure [82].

The origin of the organisms may be haematogenous. Intrarenal abscesses may rupture, leading to a perinephric collection and a psoas abscess, which occasionally may be indolent. Papillary necrosis is common in diabetics, particularly in association with acute pyelonephritis, resulting in renal parenchymal scarring, although it is difficult to exclude obstruction by the sloughed papillae as the cause of the nephropathy.

The risk of chronic renal disease and renal insufficiency caused by pyelonephritis is low. Underlying lesions including vesicoureteral reflux, analgesic abuse, nephrolithiasis and obstruction of the urinary tract have to be observed. However, acute bacterial infection, including pyelonephritis, can dramatically influence the progression of a chronic renal disease and vice versa chronic renal failure can alter the severity of an infection [58].

3C.4.1.2 Differential diagnosis.

It is most important to differentiate by appropriate imaging very early between an acute uncomplicated and

complicated, mostly obstructive form of pyelonephritis, because the latter can very quickly lead to urosepsis.

3C.4.1.3 Laboratory diagnosis

Urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis [83] (LE: 4, GR: C). Colony counts $\geq 10^4$ cfu/mL of uropathogens are considered to be indicative of clinically relevant bacteriuria [84] (LE: 2b, GR: C).

3C.4.1.4 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary obstruction or renal stone disease (LE: 4, GR: C). Additional investigations, such as an unenhanced helical computed tomography (CT), excretory urography, or dimercaptosuccinic acid (DMSA) scanning, should be considered if the patient remains febrile after 72 h of treatment (LE: 4, GR: C). For diagnostis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus (LE: 4, GR: B).

3C.4.2 ***Disease management***

As a result of the lack of suitable surveillance studies, the spectrum and susceptibility patterns of uropathogens that cause uncomplicated cystitis can be used as a guide for empirical therapy [62] (LE: 4, GR: B). However, S. saprophyticus is less frequent in acute pyelonephritis as compared to acute cystitis (LE: 4, GR: B).

3C.4.2.1 Mild and moderate cases

In mild and moderate cases of acute uncomplicated pyelonephritis (see Table 4), oral therapy of 10-14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still < 10% [85] (LE: 1b, GR: A). If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days [86, 87] (LE: 1b, GR: B). However, increasing numbers of fluoroquinolone-resistant *E. coli* in the community have already been found in some parts of the world, thus restricting the empirical use of fluoroquinolones, and fluoroquinolones are contraindicated during pregnancy.

A third-generation oral cephalosporin, such as cefpodoxime proxetil or ceftibuten, could be an alternative [88, 89] (LE: 1b, GR: B). However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin.

As a result of increasing *E. coli* resistance rates >10%, cotrimoxazole is not suitable for empirical therapy in most areas, but it can be used after sensitivity has been confirmed through susceptibility testing [90] (LE: 1b, GR: B).

Co-amoxiclav is not recommended as a drug of first choice for empirical oral therapy of acute pyelonephritis (LE: 4, GR: B). It is recommended when susceptibility testing shows a susceptible Gram-positive organism (LE: 4, GR: C).

In communities with high rates of fluoroquinolone-resistant and ESBL-producing *E. coli* (> 10%), initial empirical therapy with an aminoglycoside or carbapenem has to be considered until susceptibility testing demonstrates that oral drugs can also be used (LE: 4, GR: B).

Table 4: Recommended initial empiric oral antimicrobial therapy in mild and moderate acute uncomplicated pyelonephritis

Oral Therapy in mild and moderate uncomplicated pyelonephritis			
Antibiotics	Daily dose	Duration of therapy	Reference
Ciprofloxacin	500-750 mg bid	7-10 days	[85]
Levofloxacin	500 mg qd	7-10 days	[91]
Levofloxacin	750 mg qd	5 days	[86, 87]
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones):			
Cefpodoxime proxetil	200 mg bid	10 days	[89]
Ceftibuten	400 mg qd	10 days	[88]
Only if the pathogen is known to be susceptible (not for initial empirical therapy):			
Trimethoprim-sulphamethoxazole	160/800 mg bid	14 days	[84]
Co-amoxiclav[1,2]	0.5/0.125 g tid	14 days	

Note: fluoroquinolones are contraindicated during pregnancy.
[1]not studied as monotherapy for acute uncomplicated pyelonephritis.
[2]mainly for Gram-positive pathogens.

3C.4.2.2 Severe cases

Patients with severe pyelonephritis who cannot take oral medication because of systemic symptoms such as nausea and vomiting, have to be treated initially with one of the following parenteral antibiotics (Table 5).

Hospital admission should be considered if complicating factors cannot be ruled out by available diagnostic procedures and/or the patient has clinical signs and symptoms of sepsis (LE: 4, GR: B).

After improvement, the patient can be switched to an oral regimen using one of the antibacterials mentioned in Table 4, if active against the infecting organism, to complete the 1-2-week course of therapy (LE: 1b, GR: B).

Table 5: Recommended initial empirical parenteral antimicrobial therapy in severe acute uncomplicated pyelonephritis

Initial parenteral therapy in severe uncomplicated pyelonephritis		
After improvement, the patient can be switched to an oral regimen using one of the agents listed in Table 4 (if active against the infecting organism) to complete the 1-2-week course of therapy. Therefore, only daily dose and no duration of therapy are indicated.		
Antibiotics	**Daily dose**	**Reference**
Ciprofloxacin	400 mg bid	[85]
Levofloxacin[1]	250-500 mg qd	[91]
Levofloxacin	750 mg qd	[86]
Alternatives:		
Cefotaxime[2]	2 g tid	
Ceftriaxone[1,4]	1-2 g qd	[92]
Ceftazidime[2]	1-2 g tid	[93]
Cefepime[1,4]	1-2 g bid	[94]
Co-amoxiclav[2,3]	1.5 g tid	
Piperacillin/tazobactam[1,4]	2.5-4.5 g tid	[95]
Gentamicin[2]	5 mg/kg qd	
Amikacin[2]	15 mg/kg qd	
Ertapenem[4]	1 g qd	[92]
Imipenem/cilastatin[4]	0.5/0.5 g tid	[95]
Meropenem[4]	1 g tid	[93]
Doripenem[4]	0.5 g tid	[96]

Note: fluoroquinolones are contraindicated during pregnancy.
[1]lower dose studied, but higher dose recommended by experts.
[2]not studied as monotherapy in acute uncomplicated pyelonephritis.
[3]mainly for Gram-positive pathogens.
[4]same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).

In pregnant women with pyelonephritis outpatient management with appropriate antibiotics may also be considered, provided symptoms are mild and close follow-up is feasible [97, 98] (LE: 1b, GR: A). In more severe cases of pyelonephritis, hospitalisation and supportive care are usually required. After clinical improvement parenteral therapy can also be switched to oral therapy for a total treatment duration of 7-10 days (LE: 4, GR: B).

In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of 2 weeks is recommended preferably with a fluoroquinolone since prostatic involvement is frequent [99] (LE: 2a, GR: B).

3C.4.3 ***Follow-up***

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C), except in pregnant women, if asymptomatic bacteriuria is a treatment issue see Section 3B.5.3.

In patients whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal US, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

In patients with no urological abnormality, it should be assumed that the infecting organism is not susceptible to the agent originally used, and an alternative tailored treatment should be considered based on culture results (LE: 4, GR: B).

For patients who relapse with the same pathogen, the diagnosis of uncomplicated pyelonephritis should be reconsidered. Appropriate diagnostic steps are necessary to rule out any complicating factors (LE: 4, GR: C).

3C.5 Recurrent uncomplicated UTIs in adult women

3C.5.1 ***Diagnostic evaluation***

Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts [100] (LE: 2a). Common risk factors are given in Table 2.

Recurrent UTIs need to be diagnosed by urine culture (LE: 4, GR: A). Imaging of the upper urinary tract and cystoscopy are not routinely recommended for evaluation of women with recurrent UTIs [101] (LE: 1b, GR: B) but should be performed without delay in atypical cases. Also, residual urine should be excluded (LE: 4, GR: B).

Recurrent UTIs in men are not included here because this may be a sign of exacerbation from chronic bacterial prostatitis (see Chapter 3I). Also not included here are recurrent UTI due to complicating urological factors, such as urinary catheters, nephrolithiasis and neuropathic bladder voiding disturbances, among others.

3C.5.2 ***Disease management and follow-up***

Prevention of rUTI includes i) counselling and behavioural modifications, i.e. avoidance of risk factors, ii) non-antimicrobial measures and iii) antimicrobial prophylaxis, which should be attempted also in this order. Urological risk factors need to be looked for and eliminated as far as possible. Significant residual urine should be treated optimally, which also includes clean intermittent catheterisation (CIC) when valued necessary.

3C.5.2.1 Risk factors and behavioural modifications

A number of measures such as fluid intake and personal hygiene behaviours (e.g. reduced fluid intake, habitual and post-coitial delayed urination, wiping from back to front after defection, douching and wearing occlusive underwear) have been suggested to increase the risk of UTI. However, studies that have explored these risk factors have consistently documented the lack of association with recurrent UTI.

In young healthy women, sexual intercourse is the risk factor most highly associated with rUTI. Others include spermicide use, having a new sex partner, having a mother with history of UTI, and having UTI during childhood.

The most common risk factors in postmenopausal women are given in Table 2. There is growing evidence that UTIs in children and adults are associated with genetic mutations that affect the innate immune system [54].

3C.5.2.2 Non-antimicrobial prophylaxis

There are many non-antimicrobial measures recommended for recurrent UTI but only a few result from well-designed studies and are therefore able to make evidence-based recommendations [102, 103].

Hormonal replacement

In postmenopausal women local, vaginal oestrogen replacement, but not oral oestrogen, showed a trend

towards preventing UTI recurrences, but vaginal irritation occurred in 6 - 20% of women [103, 104] (LE: 1b, GR: C).

Immunoactive prophylaxis

OM-89 (Uro-Vaxom®) is sufficiently well documented and has been shown to be more effective than placebo in several randomised trials with a good safety profile. Therefore, it can be recommended for immunoprophylaxis in female patients with recurrent uncomplicated UTI [103, 105, 106] (LE: 1a, GR: B). Efficacy in other groups of patients and relative to antimicrobial prophylaxis remains to be established.

The vaginal vaccine Urovac® slightly reduced UTI recurrence and primary immunisation followed by booster immunisation increased time to re-infection [103] (LE: 1a, GR: C).

For parenteral immunotherapeutic products on the market, larger phase III studies are still missing. In smaller phase II studies, StroVac® and Solco-Urovac® have been shown to be effective when administered with a booster cycle of the same agents (LE: 1a, GR: C).

For other immunotherapeutic products, no controlled studies are available. Therefore, no recommendations are possible.

Prophylaxis with probiotics (Lactobacillus sp)

Accessibility of clinically proven probiotics for UTI prophylaxis is currently not universal. Only the Lactobacillus strains specifically tested in studies should be considered for prophylaxis.

When commercially available, it is reasonable to consider the use of intravaginal probiotics that contain L. rhamnosus GR-1 and L. reuteri RC-14 for the prevention of recurrent UTI [107], and these products can be used once or twice weekly (LE: 4, GR: C). Vaginal application of Lactobacillus crispatus reduced the rate of recurrent UTI in pre-menopausal women in one study, and can also be used if available [108] (LE: 1b, GR: B).

Daily use of the oral product with strains GR-1 and RC-14 is worth testing given that it can restore the vaginal lactobacilli, compete with urogenital pathogens, and prevent bacterial vaginosis, a condition that increases the risk of UTI [102]. However, oral lactobacilli prophylaxis did not decrease UTI recurrence [103], therefore no recommendations are possible.

In summary, pooled data from meta-analyses of available RCTs show no convincing benefit of lactobacillus products as prophylaxis of recurrent UTI. However differences in effectiveness between available preparations suggest further trials are needed before any recommendation for use can be made. Recommendation: Do not use outside of investigational trials.

Prophylaxis with cranberry

Previous limited studies have suggested that cranberry (Vaccinium macrocarpon) is useful in reducing the rate of lower UTIs in women [109, 110]. A recent meta-analysis including 24 studies and comprising 4,473 participants showed however that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or for any of the following sub-groups: children with recurrent UTIs, older people, women with recurrent UTIs, pregnant women, cancer patients, or people with neuropathic bladder or spinal injury [111]. Due to these contradictory results, no recommendation of the daily consumption of cranberry products can be made.

Prophylaxis with d-mannose

In a recent randomised placebo-controlled non-blinded clinical trial, it was shown that a daily dose of 2g d-mannose was significantly superior to placebo and as effective as 50 mg nitrofurantoin in preventing recurrent UTI [112]. This is indicative but not sufficient for a recommendation. D-mannose should at the present time only be used within the frame of high quality clinical investigations.

Endovesical instillation

Endovesical instillation of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment in the therapy of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of recurrent UTI. A recent review of 27 clinical studies concluded that large-scale trials are urgently needed to underline the benefit of this type of therapy [113]. Therefore, no general recommendation is possible at this stage.

3C.5.2.3 Antimicrobial prophylaxis

Antimicrobial prophylaxis can be given continuously (daily, weekly) for longer periods of time (3-6 months), or as a single post-coital dose. Continuous or post-coital antimicrobial prophylaxis [114] for prevention of recurrent UTI should be considered only after counselling and behavioural modification has been attempted, and when non-antimicrobial measures have been unsuccessful (LE: 4, GR: B).

In appropriate women with recurrent uncomplicated cystitis, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [115] (LE: 2b, GR: A). The choice of antibiotics is the same as for sporadic acute uncomplicated UTI (Table 3).

Postcoital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [116] (LE: 2b, GR: B).

Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs include e.g. nitrofurantoin (macrocrystal) 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every 10 days, and during pregnancy e.g. cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [100].

In general, the choice of antibiotics should be based upon the identification and susceptibility pattern of the organism causing the UTI, the patient's history of drug allergies and the ecological collateral effects including bacterial selection of resistance by the chosen antimicrobial. Using these principles, several issues need to be considered:

- Ecological collateral effects mean that oral fluoroquinolones and cephalosporins are no longer recommended routinely, except in specific clinical situations.
- The worldwide increase of *E. coli* resistance against trimethoprim casts doubts on trimethoprim with or without a sulphonamide to be an effective prophylactic agent still.
- There are recent warnings by governmental agencies for the long-term prophylactic use of nitrofurantoin because of the rare but severe pulmonary and hepatic adverse effects [117].

Altogether this underlines the need for reconsidering long-term antibiotic prophylaxis in recurrent UTI and assess in each individual case effective alternative preventive measures.

3D COMPLICATED UTIs WITH UROLOGICAL AND NEPHROLOGICAL RISK FACTORS IN ADULTS

3D.1 Introduction

This chapter is based also on the EAU/ICUD publication on urogenital infections, Chapter 7 on UTI in nephropathies, transplant patients and immunosuppression, and on Chapter 8 on UTI in patients with underlying urological abnormalities [2].

A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease, which increase the risk of a more serious outcome than expected from UTI in individuals without identified risk factor (Chapter 3C) or of failing therapy. Examples of risk factors corresponding mainly to the category N,U, and C of the ORENUC classification are listed in Table 1.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than in uncomplicated UTIs, and bacteria are more likely to be resistant to antimicrobials, especially in a treatment-related complicated UTI.

Enterobacteriaceae are the predominant pathogens, with *E. coli* being the most common. However, non-fermenters (e.g. Pseudomonas aeruginosa) and Gram-positive cocci (e.g. staphylococci and enterococci) may also play an important role, depending on the underlying conditions.

Treatment strategy depends on the severity of the illness and encompasses three goals: management of the urological abnormality, antimicrobial therapy, and supportive care when needed. Hospitalisation is often required. To avoid the emergence of resistant strains, therapy should be guided by urine culture whenever possible.

It is reasonable to measure the treatment effect after completion of surgical correction of a urological abnormality or medical correction of a risk factor and associated UTI, with a urine culture 1-2 weeks after completion of therapy and thereafter according to the clinical needs or surveillance purposes.

3D.2 Classification systems

Host-related risk factors for UTI in general, and complicated UTI in particular, are listed in Table 6. Complicated UTI can arise in a heterogeneous group of patients. However, neither patient age nor sex per se are part of the definition of a complicated UTI. With regard to prognosis and clinical studies, it is advisable to stratify complicated UTIs due to urological disorders into at least two groups [118]:

- Patients in whom the complicating factors could be eliminated by therapy, e.g. stone extraction, removal of an indwelling catheter corresponding to host risk factor U according to the ORENUC system (see Table 1).

- Patients in whom the complicating factor could not be or is not removed satisfactorily during therapy, e.g. permanent indwelling catheter, stone residues after treatment or neurogenic bladder corresponding to host risk factor C according to the ORENUC system (see Table 1).

Table 6: Factors that suggest a potential complicated UTI

The presence of an indwelling catheter, stent or splint (urethral, ureteral, renal) or the use of intermittent bladder catheterisation.
Post-void residual urine of > 100 mL.
An obstructive uropathy of any aetiology (upper and lower urinary tracts), e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumour.
Vesicoureteric reflux or other functional abnormalities.
Urinary tract modifications/deviation, such as an ileal loop or pouch.
Chemical or radiation injuries of the uroepithelium.
Peri- and postoperative UTI, including renal transplantation.

3D.3 Diagnostic evaluation

3D.3.1 ***Clinical presentation***

A complicated UTI, in contrast to asymptomatic bacteriuria, also needs to be associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may not be typical, e.g. in neuropathic bladder disturbances, catheter-associated UTI. Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a catheter-associated postoperative UTI, which might disappear spontaneously as soon as the catheter is removed. It also has to be recognised that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as benign prostatic hyperplasia (BPH) or transurethral resection of the prostate (TURP).

Apart from urological abnormalities, concomitant medical conditions, such as diabetes mellitus (10%) and renal failure, which can be related to urological abnormalities [119], are often present in a complicated UTI.

3D.3.2 ***Urine cultures***

Significant bacteriuria in a complicated UTI is defined by counts of $\geq 10^5$ cfu/mL and $\geq 10^4$ cfu/mL, in the mid-stream urine (MSU) of women and men, respectively [84, 120]. If a straight catheter urine sample is taken, $\geq 10^4$ cfu/mL can be considered relevant. The requirement for pyuria is ≥ 10 white blood cells (WBC) per high-power field (x400) in the resuspended sediment of a centrifuged aliquot of urine or per mm^3 in unspun urine. A dipstick method can also be used for routine assessment, including a leukocyte esterase test, haemoglobin and probably a nitrite reaction.

3D.3.3 ***Microbiology (spectrum and antibiotic resistance)***

Patients with a complicated UTI, both community and hospital-acquired, tend to show a diversity of microorganisms with a higher prevalence of resistance against antimicrobials, and higher rates of treatment failure if the underlying abnormality cannot be corrected.

However, the presence of a resistant strain on its own is not enough to define a complicated UTI. Urinary abnormality (anatomical or functional) or the presence of an underlying disease predisposing to a UTI is also necessary.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than with an uncomplicated UTI and the bacteria are more likely to be antibiotic-resistant (especially in a treatment-related complicated UTI) than those isolated in an uncomplicated UTI. *E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas* and *Serratia sp*. and enterococci are the usual strains found in cultures. Enterobacteriaceae predominate (60-75%) [121-123], with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another.

3D.3.4 ***Special types of complicated UTIs***

Urinary stones: In the subset of complicated UTIs related to urinary stones, the frequency of *E. coli* and enterococci infection seem less important pathogens. In contrast, a greater portion of *Proteus* and *Pseudomonas sp*. [124] is found.

Of the urease-producing organisms, *Proteus*, *Providencia* and *Morganella sp*., and *Corynebacterium urealyticum* are predominant, but *Klebsiella*, *Pseudomonas* and *Serratia sp*. and staphylococci are also urease producers to a certain extent.

Among patients with staghorn calculus disease, 88% were found to have a UTI at the time of diagnosis, with 82% of patients infected with urease-producing organisms [125]. The enzyme, urease, splits urea into carbon dioxide and ammonia. The resultant increase in ammonia in the urine injures the glycosaminoglycan layer, which in turn increases bacterial adherence [126] and enhances the formation of struvite crystals. These aggregate to form renal stones and incrustations on urinary catheters [127].

The pathogenic potential of coagulase-negative staphylococci and non-group D streptococci is controversial [63, 128]. Under certain circumstances, such as the presence of a stone or foreign bodies, staphylococci can be relevant pathogens. Otherwise, staphylococci are not so common in complicated UTIs (0-11%), according to published reports [122, 129].

Nephrectomy should be performed only as a last resort, because even residual renal function may be of vital importance (GR: B).

Urinary catheters: In catheter-associated UTIs, the distribution of microorganisms is similar [92], and biofilm has to be considered. Antimicrobial therapy may only be effective in the early stages of the infection [129]. For more details see Chapter 3F on catheter-associated UTIs.

Adult polycystic kidney disease (APCKD): UTI is a prominent complication of ADPKD, with symptomatic UTI being the presenting feature in 23-42% of patients, who are usually female [130]. It may be difficult to obtain a positive culture on standard laboratory media, but pyuria is common, particularly in the later stages of disease progression. Acute pyelonephritis is common and may originate from pyogenic infection in the cysts [131] (LE: 3). Puncture/aspiration of infected material from an infected cyst must be considered both for microbiological diagnosis and therapy (drainage). Polycystic disease is not to be confused with acquired renal cystic disease of the end-stage kidney, which has no predisposition to UTI.

3D.3.5 ***Special types of renal infections***

Focal bacterial nephritis: This is restricted to one or several renal segments and usually resolves with appropriate medical treatment. In rare situations, especially in association with an obstruction, it may liquefy and form a renal abscess requiring drainage.

Renal abscess: They can rupture into the urinary tract or penetrate through the renal capsule to become a perinephric abscess.

Perinephric abscess: The clinical symptoms are chills, fever, back or abdominal pain, CVA tenderness, flank mass and redness, protection of the upper lumbar and paraspinal muscles. In bed-ridden patients, however, perinephric abscesses can present with few symptoms. Respiratory insufficiency, haemodynamic instability and paralytic ileus may predominate.

Emphesematous pyelonephritis: This is caused by gas-forming *E. coli*, *K. pneumoniae, E. cloacae* fermenting glucose. The contralateral kidney is often also affected. Papillary necrosis, intrarenal vascular thrombus, and renal infarction are often seen in pathology.

Xanthogranulomatous pyelonephritis: This is characterised by a chronic purulent, fatty inflammation of the renal parenchyma, the pyelon and the hilar tissue.

3D.3.6 ***Complicated UTI after renal transplantation***

UTI is the most common infectious complication following kidney transplantation [132]. In a large database the cumulative incidence of UTI during the first six months after renal transplantation was 17% for both genders and at three years 60% for women and 47% for men [133]. Donor type (living vs. deceased) has conflicting evidence for UTI risk.

Symptomatic UTI after transplant has a wide clinical spectrum including acute cystitis, transplant pyelonephritis, and pyelonephritis of the native kidney. Risk factors include more intensive immunosuppression, extremes of age, diabetes mellitus, prolonged time on dialysis, abnormal or reconstructed lower urinary tract and prolonged use of urinary catheters and stents.

Typical signs and symptoms of UTI may be mimicked by other common post-transplant conditions including catheter induced bladder spasm, stent irritation, low volume defunctionalised bladder, polyuria due to early loss of urinary concentrating ability, urinary retention and fever/graft tenderness from acute rejection. Furthermore, common UTI features may not be evident. Immunosuppression can suppress fever, primarily through blockade of IL-1 and TNF. WBC counts may not be elevated due to bone marrow suppression. The transplanted kidney is denervated and may not be tender even in the face of pyelonephritis.

Typical uropathogens are commonly involved but UTI's may also be caused by commensal and

fastidious bacteria, fungus, mycobacteria and viruses. Some studies suggest post-transplant UTI has a negative impact on graft survival and function, although causality has not been established [132, 133].

3D.4 Disease management

Treatment strategy depends on the severity of the illness. Appropriate antimicrobial therapy and the management of the urological abnormality are mandatory. If needed, supportive care is given. Hospitalisation is often necessary depending on the severity of the illness.

*3D.4.1 **Choice of antibiotics***

Empirical treatment of a symptomatic complicated UTI requires knowledge of the spectrum of possible pathogens and local antibiotic resistance patterns, as well as assessment of the severity of the underlying urological abnormality (including the evaluation of renal function).

Bacteraemia is usually reported too late to influence the choice of antibiotics. However, suspicion of bacteraemia must influence the empirical treatment. The severity of the associated illness and the underlying urological condition are still of utmost importance for prognosis.

Many therapeutic trials have been published on the use of specific antimicrobial therapies in complicated UTIs. Unfortunately, most reports are of limited use for the practical management of the patient in a day-to-day situation because of limitations such as:

- poor characterisation of the patient populations;
- unclear evaluation of the severity of the illness;
- nosocomial and community-acquired infections are not accurately distinguished;
- urological outcome is seldom taken into consideration.

Intense use of any antimicrobial, especially when used on an empirical basis in this group of patients with a high likelihood of recurrent infection, will lead to the emergence of resistant microorganisms in subsequent infections. Whenever possible, empirical therapy should be replaced by a therapy adjusted for the specific infective organisms identified in the urine culture. Therefore, a urine specimen for culture must be obtained before initiation of therapy, and the selection of an antimicrobial agent should be re-evaluated once culture results are available [123]. To date, it has not been shown that any agent or class of agents is superior in cases in which the infective organism is susceptible to the drug administered.

In patients with renal failure, whether related to a urological abnormality or not, appropriate dose adjustments have to be made after initiated treatment, usually by means of drug concentration monitoring.

If empirical treatment is necessary, the antibacterial spectrum of the antibiotic agent should include the most relevant pathogens (GR: A). A fluoroquinolone with mainly renal excretion, a Group 3a cephalosporin, or an aminoglycoside are recommended alternatives (LE: 1b, GR: B). In case of failure of initial therapy, or in case of clinically severe infection, a broader-spectrum antibiotic should be chosen that is also active against pseudomonas [134] (LE: 1b, GR: B), e.g. a Group 3b cephalosporin, an acylaminopenicillin (piperacillin) plus a BLI, or a carbapenem, with or without combination with an aminoglycoside (LE: 1b, GR: B). Local resistance pattern needs to be considered, which may result in different recommendations. The antibacterial treatment options are summarised in Table 7 and Appendix 4.3 (Recommendations for antimicrobial therapy in urology).

Patients can generally be treated as outpatients. In more severe cases (e.g. hospitalised patients), antibiotics have to be given parenterally. After a few days of parenteral therapy and clinical improvement, patients can be switched to oral treatment. Therapy has to be reconsidered when the infective strains have been identified and their susceptibilities are known. The successful treatment of a complicated UTI always combines effective antimicrobial therapy, optimal management of the underlying urological abnormalities or other diseases, and sufficient life-supporting measures.

*3D.4.2 **Duration of antibiotic therapy***

Treatment for 7-14 days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality [84]. Sometimes, a prolongation for up to 21 days, according to the clinical situation, is necessary [120].

Table 7: Antimicrobial treatment options for empirical therapy

Antibiotics recommended for initial empirical treatment, if local resistance pattern is still < 20%
Fluoroquinolone
Aminopenicillin plus a BLI
Cephalosporin (Groups 3a)
Aminoglycoside
Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases
Fluoroquinolone (if not used for initial therapy)
Piperacillin plus BLI
Cephalosporin (Group 3b)
Carbapenem
Antibiotics not recommended for empirical treatment
Aminopenicillins, e.g. amoxicillin, ampicillin
Trimethoprim-sulphamethoxazole (only if susceptibility of pathogen is known)
Fosfomycin trometamol

BLI = β-lactam inhibitor

*3D.4.3 **Specific treatment considerations***

3D.4.3.1 Adult Polycystic kidney disease

In patients with APCKD, acute pyelonephritis by infected cysts may occur, presenting as recurrent pyelonephritis or even sepsis. Treatment requires a long course of high-dose systemic, preferably (if appropriate) fluoroquinolones, followed by suppressive therapy. Drainage may be required (see 3D.3.4). After transplantation, overall graft and patient survival rates do not differ between ADPKD and control groups [135] (LE: 2a). However, despite close monitoring, UTI and septicaemic episodes are still a significant cause of morbidity, such that bilateral nephrectomy may be the only option.

3D.4.3.2 Special types of complicated UTIs

Urinary stones: If a nidus of a stone or an infection remains, stone growth will occur. Complete removal of the stones and adequate antimicrobial therapy are both needed. Eradication of the infection will probably eliminate the growth of struvite calculi [136]. Long-term antimicrobial therapy should be considered if complete removal of the stone cannot be achieved [137].

Indwelling catheters: Current data do not support the treatment of ABU, either during short-term (< 30 days) or long-term catheterisation, because it will promote the emergence of resistant strains [138, 139]. In short-term catheterisation, antibiotics may delay the onset of bacteriuria, but do not reduce complications [140]. See Chapter 3F.

A symptomatic complicated UTI associated with an indwelling catheter is treated with an agent with as narrow a spectrum as possible, based on culture and sensitivity results. The optimal duration is not well established. Treatment durations that are too short as well as too long may cause the emergence of resistant strains. A 5 to 7-day course could be a reasonable compromise.

Spinal cord injury: In case of persistent UTIs and suspicion of urinary retention, a full urodynamic assessment to appraise bladder function is to be carried out. Priority is to ensure proper drainage of the bladder, preferably by clean intermittent catheterisation (CIC), to protect the urinary tract [141, 142].

It is generally accepted that ABU in patients with spinal cord injury should not be treated, even in cases of CIC, because it could be shown that deliberately induced *E. coli* ABU in these patients could prevent recurrences [45, 46]. For symptomatic episodes of infection in patients with spinal cord injury, only a few studies have investigated the most appropriate agent and duration of therapy. Currently, 7-10 days of therapy is most commonly used. There is no superiority of one agent or class of antimicrobials. Treatment or prophylaxis of asymptomatic bacteriuria in spinal cord patients does not decrease the frequency of subsequent symptomatic infections.

3D.4.3.3 Special types of renal infections

The special types of renal infections with abscess formation are not seen frequently. Conservative broad spectrum, antimicrobial therapy may be successful at the beginning of the infection or for abscesses of 3 cm or less (relative size) (see also 3D.3.5). Larger abscesses will usually need to be drained. In rare instances, only nephrectomy can cure the patient.

3D.4.3.4 UTI in renal transplantation

The need to correct uropathy or to remove a potential focus of infection in an end-stage disease kidney is more pressing in patients enlisted for renal transplantation. Even so, the results of nephrectomy for a scarred or hydronephrotic kidney may be disappointing.

There is a paucity of prospective controlled data that can guide UTI prophylaxis or therapy in terms of agent or duration, although most programs will routinely use prophylaxis for at least 6 months (GR: B). Post transplant UTI can be reduced by early removal or urinary foreign bodies, such as indwelling urinary catheter, ureteral stent (GR: C).

Bacteriocidal antibiotics should be preferred to bacteriostatic ones, which might be insufficient to cure the infection since the immune system cannot eradicate the dormant bacteria. Predisposing factors should be corrected if possible (e.g. optimal diabetic control, removal or change of stents and catheters, minimise immunosuppression based upon drug levels and clinical course).

Interactions exist between antibiotics used to treat post-transplant UTI and immunosuppressant drugs. Ciprofloxacin may raise calcineurin inhibitor (CNI) levels, but levofloxacin and ofloxacin usually do not [143]. Erthryomycin and antifungal agents inhibit cytochrome P450 and increase CNI levels. Rifampin, imipenim and cephalosporins can reduce CNI levels. Nephrotoxic antibiotics (e.g. aminoglycosides, amphotericin) may have synergistic effects with CNIs, increasing renal damage.

UTI can co-exist with common post-transplant viral illnesses (e.g. cytomegalovirus). Transplant pyelonephritis may cause elevated serum creatinine, however reduced renal function should not be simply attributed to the infection without ruling out other causes (e.g. obstruction, rejection, drug toxicity). Ultimately, lack of response should prompt a biopsy to rule out rejection or other renal conditions (e.g. primary disease recurrence).

Asymptomatic bacteriuria post kidney transplant does not require therapy beyond standard prophylaxis (GR: C) [132].

3D.5 Follow-up

The greater likelihood of the involvement of resistant microorganisms in complicated UTIs is another feature of these infectious diseases. This is not a priori related to the urinary abnormality, but is related more to the fact that patients with a complicated UTI tend to have recurrent infection [123]. For these reasons, before and after the completion of the antimicrobial treatment, urine cultures must be obtained for the identification of the microorganisms and the evaluation of susceptibility testing.

3E SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

3E.1 Introduction

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a complicated UTI. The systemic inflammatory response syndrome, known as SIRS (fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia, tachypnoea), is recognised as the first event in a cascade to multi-organ failure (Figure 1). Mortality is considerably increased when severe sepsis or septic shock are present, although the prognosis of urosepsis is globally better than that of sepsis from other infectious sites.

The treatment of urosepsis calls for the combination of adequate life-supporting care, appropriate and prompt antibiotic therapy, adjunctive measures (e.g. sympathomimetic amines, hydrocortisone, blood glucose control) and the optimal management of urinary tract disorders (LE: 1a, GR: A). The drainage of any obstruction in the urinary tract is essential as first-line treatment (LE: 1b, GR: A). Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists (LE: 2a, GR: B).

Urosepsis is seen in both community-acquired and healthcare associated infections. Most nosocomial urosepsis can be avoided by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urethral catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily asepsis techniques to avoid cross-infection (LE: 2a, GR: B).

Urinary tract infections can manifest as bacteriuria with limited clinical symptoms, sepsis or severe sepsis, depending on localised or systemic extension. Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia). Severe sepsis is defined by the presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.

3E.2 Epidemiology, aetiology and pathophysiology

Urinary tract infections can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localised and potential systemic extension. It is important to note that a patient can move from an almost harmless state to severe sepsis in very short time. Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia). Severe sepsis is defined by the presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.

Mortality associated to severe sepsis are reported in various rates depending on the organ source [144] with urinary tract sepsis generally having a lower mortality than that from other sources [145]. Sepsis is more common in men than in women [146]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [144], but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000) [147]. Although sepsis due to fungal organisms from some sites has increased and Gram-positive bacteria have become the predominant pathogen overall, Gram-negative bacteria remain predominant in urosepsis.

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include: elderly patients; diabetics; immunosuppressed patients, such as transplant recipients; patients receiving cancer chemotherapy or corticosteroids; and patients with AIDS. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract. Moreover, it is now recognised that SIRS may be present without infection (e.g. pancreatitis, burns, or non-septic shock) [148].

3E.3 Classification systems

For therapeutic purposes, the diagnostic criteria of sepsis should identify patients at an early stage of the syndrome, which should prompt urologists and intensive care specialists to search for and treat infection, apply appropriate therapy, and monitor for organ failure and other complications.

3E.4 Diagnostic evaluation

The clinical evidence of UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. The following definitions apply (Table 8):

- Sepsis is a systemic response to infection. The symptoms of SIRS which were initially considered to be ‘mandatory’ for the diagnosis of sepsis [148], are now considered to be alerting symptoms [149]. Many other clinical or biological symptoms must be considered.
- Severe sepsis is associated with organ dysfunction.
- Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation.
- Refractory septic shock is defined by an absence of response to therapy.

Table 8: Clinical diagnostic criteria of sepsis and septic shock [148, 149]

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient.
Systematic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following conditions: - Temperature > 38°C or < 36°C - Heart rate > 90 bpm - Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg (< 4.3 kPa) - WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms
Sepsis	Activation of the inflammatory process due to infection.
Hypotension	Systolic blood pressure < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes of hypotension.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or acute alteration of mental status.
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Refractory septic shock	Septic shock that lasts for > 1 h and does not respond to fluid administration or pharmacological intervention.

3E.4.1 ***Physiology and biochemical markers***

Microorganisms reach the urinary tract by way of the ascending, haematogenous, or lymphatic routes. For urosepsis to be established, the pathogens have to reach the bloodstream. The risk of bacteraemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis, and is facilitated by obstruction of the urinary tract. *E. coli* remains the most prevalent microorganism. In several countries, some bacterial strains can be resistant to quinolones or third-generation cephalosporins. Some microorganisms are multiresistant, such as methicillin-resistant Staphylococcus aureus (MRSA), P. aeruginosa and *Serratia sp*. and therefore difficult to treat. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection. A fatal outcome is described in 20-40% of all patients.

3E.4.1.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis syndrome. They are peptides that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. When they become bound to specific receptors on other cells, cytokines change their behaviour in the inflammatory response. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Other cytokines that are associated with sepsis are interleukins (ILs) (IL-1, -6, -8) and tumour necrosis factor (TNF)-α. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood [145].

3E.4.1.2 Procalcitonin is a potential marker of sepsis

Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise to > 100 ng/mL. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. Procalcitonin monitoring may be useful in patients likely to develop a SIRS of infectious origin and to differentiate from a severe inflammatory status [150, 151] but can presently not be recommended as a diagnostic tool.

3E.5 Disease management

3E.5.1 ***Prevention***

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for a combination of treatment of the cause (obstruction of the urinary tract), adequate life-support care, and appropriate antibiotic therapy [145]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3E.5.1.1 Preventive measures of proven or probable efficacy

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections [152, 153]:

- Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. It is well known that long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting [154]. Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective, disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

3E.5.1.2 Appropriate perioperative antimicrobial prophylaxis

For appropriate perioperative antimicrobial prophylaxis see Chapter 3N. The potential side-effects of antibiotics must be considered before their administration in a prophylactic regimen.

3E.5.1.3 Ineffective or counterproductive measures

- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.
- Use of urinary catheters with antimicrobial coatings [155]*.
- Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase the risk of infection with resistant bacteria [152, 156].
- Routine administration of antimicrobial drugs to catheterised patients, which reduces the incidence of bacteriuria only for a few days and increases the risk of infection with multi-resistant bacteria [152, 156]. Its use may be reserved for immunosuppressed patients.

*Catheters coated or impregnated with antimicrobials may have efficacy in reduction of bacteriuria but this does not seem to translate to clinical benefit in terms of occurrence of symptomatic infection.

3E.5.2 *Treatment*

Figure 3: Clinical algorithm for the management of urosepsis

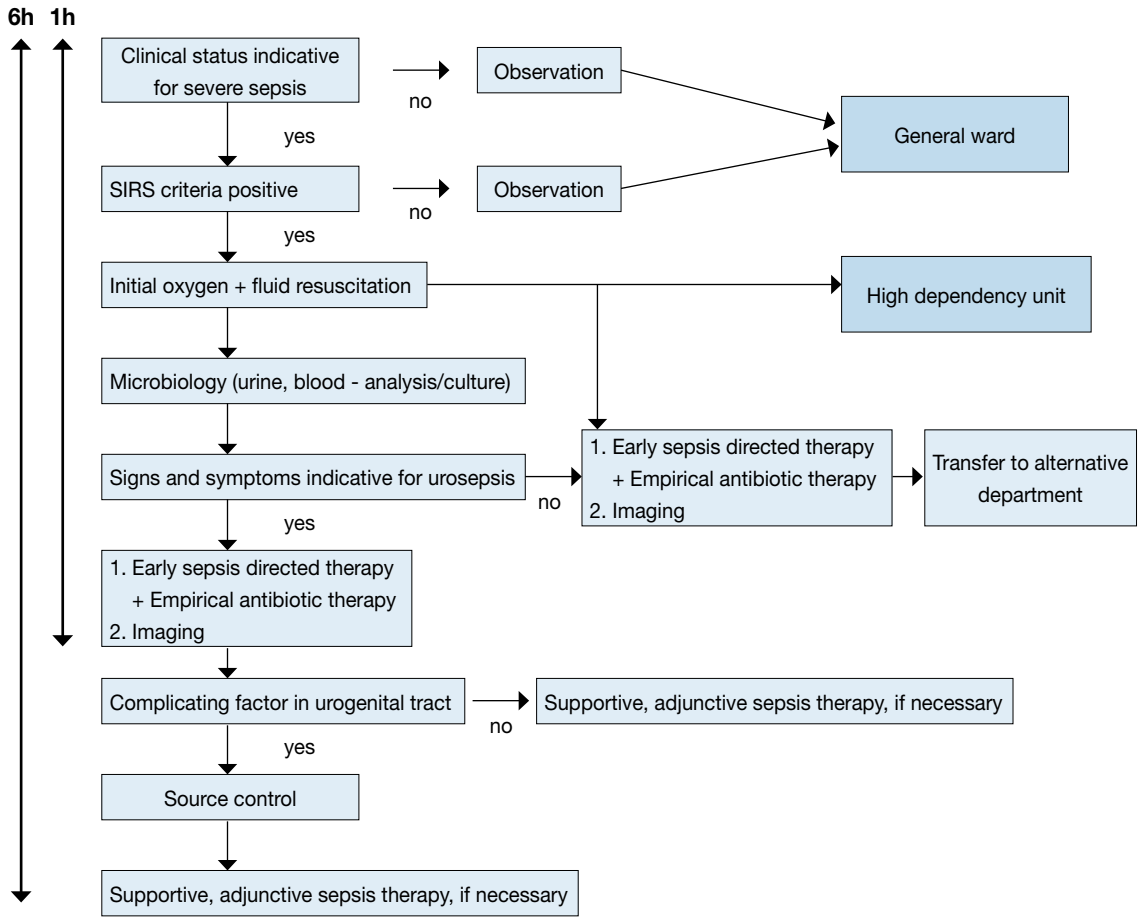


Table 9: Early sepsis therapy

Early sepsis therapy	
Central venous pressure (CVP)	8-12 mmHg
Mean arterial pressure (MAP)	65-90 mmHg
Central venous oxygen (CVO_2)	≥ 70%
Haematocrit (HKT)	> 30 %
Urine output	> 40 mL/h

Table 10: Levels of therapy in sepsis

Levels of therapy in sepsis	
Causal therapy	1. Antimicrobial treatment 2. Source control
Supportive therapy	1. Haemodynamic stabilisation 2. Airways, respiration
Adjunctive therapy	1. Glucocorticosteroids 2. Intensified insulin therapy

3E.5.2.1 Relief of obstruction

Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, should lead to resolution of symptoms and recovery. These are key components of the strategy. This condition is an absolute emergency.

3E.5.2.2 Antimicrobial therapy

Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the

basis of culture results. The dosage of the antibiotic substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure. Antimicrobials must be administered no later than 1 h after clinical assumption of sepsis (Figure 3). The antibacterial treatment options are summarised in Appendix 4.3 and 4.4.

3E.5.2.3 Adjunctive measures

The management of fluid and electrolyte balance is a crucial aspect of patient care in sepsis syndrome; particularly when the clinical course is complicated by shock [156, 157]. The use of human albumin is debatable. Early therapy aimed at restoring clinical indicators of vital organ above specific thresholds (goal-directed therapy) has been shown to reduce mortality [158]. Volaemic expansion and vasopressor therapy have a considerable impact on the outcome. Early intervention with appropriate measures to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilisation of arterial pressure, and providing sufficient oxygen transport capacity are highly effective.

Hydrocortisone (with a debate on dosage) is useful in patients with relative insufficiency in the pituitary gland-adrenal cortex axis (adrenocorticotropin test) [159].

Tight blood glucose control by administration of insulin doses up to 50 U/h is associated with a reduction in mortality [160].

The best strategy has been summarised and graded according to a careful evidence-based methodology in the recently published 'Surviving Sepsis Guidelines' [161].

In conclusion, sepsis syndrome in urology remains a severe situation with an appreciable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next few years [161]. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patient survival. The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using ABP and therapy in a prudent and well-accepted manner.

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3F CATHETER-ASSOCIATED UTIs

3F.1 Introduction

Based on the EAU Guidelines published in 2007 (ISBN-13:978-90-70244-59-0), the following text presents the findings of a comprehensive update produced as a collaborative effort by the ESIU (a full EAU section office), the Urological Association of Asia, the Asian Association of UTI/STD, the Western Pacific Society for Chemotherapy, the Federation of European Societies for Chemotherapy and Infection, and the International Society of Chemotherapy for Infection and Cancer. This text was recently published as "The European and Asian guidelines on management and prevention of catheter-associated urinary tract infections" [47]. Since the complete document is available online, only the abstract and a summary of the recommendations are presented here.

3F.2 Methods

The extensive literature regarding the development, therapy and prevention of catheter-associated UTIs (CAUTIs) was surveyed. Systematic searching involved: meta-analyses of RCTs available in Medline, the Cochrane Central Register of Controlled Trials, and also other relevant publications, rating them on the basis of their quality. Studies were identified through a PubMed search. The recommendations of the studies, rated according to a modification of the US Department of Health and Human Services (1992), give a close-to-evidence-based guideline for all medical disciplines, with special emphasis on urology, in which catheter care is an important issue.

3F.3 Classification systems

The survey found that the urinary tract is the commonest source of nosocomial infection, particularly when the bladder is catheterised (LE: 2a). Most CAUTIs are derived from the patient's own colonic flora (LE: 2b) and the catheter predisposes to UTI in several ways. The most important risk factor for the development of catheter-associated bacteriuria is the duration of catheterisation (LE: 2a). Most episodes of short-term catheter-

associated bacteriuria are asymptomatic and are caused by a single organism (LE: 2a). Further organisms tend to be acquired by patients who are catheterised for > 30 days.

3F.4 Diagnostic evaluation

The clinician should be aware of two priorities: the catheter system should remain closed and the duration of catheterisation should be minimal (GR: A). The use of nurse-based or electronic reminder systems to remove unnecessary catheters can decrease the duration of catheterisation and the risk of CAUTI (LE: 2a). The drainage bag should be always kept below the level of the bladder and the connecting tube (GR: B). In case of short-term catheterisation, routine prophylaxis with systemic antibiotics is not recommended (GR: B). There are sparse data about ABP in patients on long-term catheterisation, therefore, no recommendation can be made (GR: C). For patients using intermittent catheterisation, routine ABP is not recommended (GR: B). Antibiotic irrigation of the catheter and bladder is of no advantage (GR: A). Healthcare workers should be constantly aware of the risk of cross-infection between catheterised patients. They should observe protocols on hand washing and the need to use disposable gloves (GR: A).

3F.5 Disease management

A minority of patients can be managed with the use of the non-return (flip) valve catheters, thus avoiding the closed drainage bag. Such patients may exchange the convenience of on-demand drainage with an increased risk of infection. Patients with urethral catheters in place for > 10 years should be screened annually for bladder cancer (GR: C). Clinicians should always consider alternatives to indwelling urethral catheters that are less prone to causing symptomatic infection. In appropriate patients, suprapubic catheters, condom drainage systems and intermittent catheterisation are each preferable to indwelling urethral catheterisation (GR: B). While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended (GR: A), except for some special cases. Routine urine culture in an asymptomatic catheterised patient is also not recommended (GR: C) because treatment is in general not necessary. Antibiotic treatment is recommended only for symptomatic infection (GR: B). After initiation of empirical treatment, usually with broad-spectrum antibiotics based on local susceptibility patterns (GR: C), the choice of antibiotics might need to be adjusted according to urine culture results (GR: B). Long-term antibiotic suppressive therapy is not effective (GR: A).

The summary of recommendations in the present Guidelines is based on this extensive review [47] updated data from chapter 9 of Urological Infections [2] and a recent large scale study on catheters [155].

3F.6 Summary of recommendations

Recommendations		**GR**
General aspects		
1.	Written catheter care protocols are necessary.	B
2.	Health care workers should observe protocols on hand hygiene and the need to use disposable gloves between catheterised patients.	A
Catheter insertion and choice of catheter		
3.	An indwelling catheter should be introduced under antiseptic conditions.	B
4.	Urethral trauma should be minimised by the use of adequate lubricant and the smallest possible catheter calibre.	B
5.	Antibiotic-impregnated catheters may decrease the frequency of asymptomatic bacteriuria when used for a few days. There is, however, no evidence that they decrease symptomatic infection. Therefore, they cannot be recommended routinely.	B
6.	Silver alloy catheters have been shown in some studies to significantly reduce the incidence of asymptomatic bacteriuria, but only when used for < 1 week. There was weak evidence or contradictory results regarding the reduction of symptomatic UTI. More large scale clinical research is needed and no clear recommendation can be given.	B
Prevention		
7.	The catheter drainage system should remain closed.	A
8.	The duration of catheterisation should be minimal.	A
9.	Topical antiseptics or antibiotics applied to the catheter, urethra or meatus are not recommended.	A
10.	Benefits from prophylactic antibiotics and antiseptic substances have never been established, therefore, they are not recommended.	A

11.	Removal of the indwelling catheter after non-urological operation before midnight might be beneficial.	B
12.	Long-term indwelling catheters should be changed at intervals adapted to the individual patient, but must be changed before blockage is likely to occur. However, there is no evidence for the exact intervals of changing catheters.	B
13.	Chronic antibiotic suppressive therapy is not recommended.	A
14.	The drainage bag should always be kept below the level of the bladder and the connecting tube.	B
Diagnostics		
15.	Routine urine culture in asymptomatic catheterised patients is not recommended.	B
16.	Urine, and in septic patients, also blood for culture must be taken before any antimicrobial therapy is started.	C
17.	Febrile episodes are only found in < 10% of catheterised patients living in a long-term facility. It is therefore extremely important to rule out other sources of fever.	A
Treatment		
18.	While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended, except in certain circumstances, especially before traumatic urinary tract interventions.	A
19.	In case of asymptomatic candiduria, neither systemic nor local antifungal therapy is indicated, but removal of the catheter or stent should be considered.	A/C
20.	Antimicrobial treatment is recommended only for symptomatic infection.	B
21.	In case of symptomatic CAUTI, it might be reasonable to replace or remove the catheter before starting antimicrobial therapy if the indwelling catheter has been in place for > 7 days.	B
22.	For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns.	C
23.	After culture results are available, antibiotic therapy should be adjusted according to pathogen sensitivity.	B
24.	In case of candiduria associated with urinary symptoms, or if candiduria is the sign of systemic infection, systemic therapy with antifungals is indicated.	B
25.	Bacteriuria after catheter removal in elderly patients does usually not require any treatment unless symptomatic.	C
Alternative drainage systems		
26.	There is limited evidence that postoperative intermittent catheterisation reduces the risk of bacteriuria compared with indwelling catheters. No recommendation can be made.	C
27.	In appropriate patients, a suprapubic, condom drainage system or intermittent catheter is preferable to an indwelling urethral catheter.	B
28.	There is little evidence to suggest that antibiotic prophylaxis decreases bacteriuria in patients using intermittent catheterisation, therefore, it is not recommended.	B
Long-term follow up		
29.	Patients with urethral catheters in place for > 10 years should be screened for bladder cancer.	C

3G UTIs IN CHILDREN

3G.1 Introduction

In children, UTIs are a frequent health problem, with the incidence only a little lower than that of upper respiratory and digestive infections. Incidence varies depending on age and sex. In the first year of life, mostly the first 3 months, UTI is more common in boys (3.7%) than in girls (2%), after which the incidence changes to 3% in girls and 1.1% in boys. Paediatric UTI is the most common cause of fever of unknown origin in boys aged < 3 years. The clinical presentation of UTI in infants and young children can vary from fever to gastrointestinal and lower or upper urinary tract symptoms.

Investigation should be undertaken after two episodes of UTI in girls and one in boys (GR: B). The objective is to rule out the unusual occurrence of obstruction, vesicoureteric reflux (VUR) and dysfunctional voiding, e.g. as caused by a neuropathic disorder.

Chronic pyelonephritic renal scarring develops very early in life due to the combination of a UTI, intrarenal reflux and VUR. It sometimes arises in utero due to dysplasia. Although rare, renal scarring may lead to severe long-term complications such as hypertension and chronic renal failure.

VUR is treated with long-term prophylactic antibiotics (GR: B). Surgical re-implantation or endoscopic treatment is reserved for the small number of children with breakthrough infection (GR: B).

For treatment of UTI in children, short courses are not advised and therefore treatment is continued for 5-7 days and longer (GR: A). If the child is severely ill with vomiting and dehydration, hospital admission is required and parenteral antibiotics are given initially (GR: A). For further information please refer to the EAU Paediatric Urology Guidelines.

3G.2 Epidemiology, aetiology and pathophysiology

The urinary tract is a common source of infection in children and infants. It represents the most common bacterial infection in children < 2 years of age [162] (LE: 2a). The outcome of a UTI is usually benign, but in early infancy, it can progress to renal scarring, especially when associated with congenital anomalies of the urinary tract. Delayed sequelae related to renal scarring include hypertension, proteinuria, renal damage and even chronic renal failure, which requires dialysis treatment in a significant number of adults [163] (LE: 2a).

The risk of UTI during the first decade of life is 1% in males and 3% in females [6]. It has been suggested that 5% of schoolgirls and up to 0.5% of schoolboys undergo at least one episode of UTI during their school life. The incidence is different for children < 3 months of age, when it is more common in boys. The incidence of ABU is 0.7-3.4% in neonates, 0.7-1.3% in infants < 3 months of age, and 0.2-0.8% in preschool boys and girls [6]. The incidence of symptomatic bacteriuria is 0.14% in neonates, with a further increase to 0.7% in boys and 2.8% in girls aged < 6 months. The overall recurrence rate for the neonatal period has been reported to be 25% [6, 164].

The common pathogenic sources are Gram-negative, mainly enteric, bacteria. Of these, *E. coli* is responsible for 90% of UTI episodes [165]. Gram-positive bacteria (particularly enterococci and staphylococci) represent 5-7% of cases. Hospital-acquired infections show a wider pattern of aggressive bacteria, such as *Klebsiella*, *Serratia* and *Pseudomonas sp*. Groups A and B streptococci are relatively common in new-born infants [166]. There is an increasing trend towards the isolation of *S. saprophyticus* in UTIs in children, although the role of this bacterium is still debatable [167].

The urinary tract is a sterile space with an impermeable lining. Retrograde ascent is the most common mechanism of infection. Nosocomial infection and involvement as part of a systemic infection are less common [168].

Obstruction and dysfunction are among the most common causes of urinary infection. Phimosis predisposes to UTI [169, 170] (LE: 2a). Enterobacteria derived from intestinal flora colonise the preputial sac, glandular surface and the distal urethra. Among these bacteria are strains of *E. coli* that express P fimbriae, which adhere to the inner layer of the preputial skin and to uroepithelial cells [171].

A wide variety of congenital urinary tract abnormalities can cause UTIs through obstruction, e.g. urethral valves, ureteropelvic junction obstruction or non-obstructive urinary stasis (e.g. prune belly syndrome, or VUR). More mundane but significant causes of UTIs include labial adhesion and chronic constipation [167].

Dysfunctional voiding in an otherwise normal child may result in infrequent bladder emptying aided by delaying manoeuvres, e.g. crossing legs, sitting on heels [172]. Neuropathic bladder dysfunction (e.g. spina bifida, or sphincter dyssynergia) may lead to post-void residual urine and secondary VUR [164].

The link between renal damage and UTIs is controversial. The mechanism in obstructive nephropathy is self-evident, but more subtle changes occur when there is VUR. Almost certainly, the necessary components include VUR, intrarenal reflux and UTI. These must all work together in early childhood when the growing kidney is likely to be susceptible to parenchymal infection. Later on in childhood, the presence of bacteriuria seems irrelevant to the progression of existing scars or the very unusual formation of new scars. Another confounding factor is that many so-called scars are dysplastic renal tissue which develop in utero [173].

Symptoms are non-specific, and vary with the age of the child and the severity of the disease. Epididymoorchitis is extremely unusual. With scrotal pain and inflammation, testicular torsion has to be considered.

A UTI in neonates may be non-specific and with no localisation. In small children, a UTI may present with gastrointestinal signs, such as vomiting and diarrhoea. In the first weeks of life, 13.6% of patients with fever have a UTI [174]. Rarely, septic shock is the presentation. Signs of UTI may be vague in small children, but later on, when they are older than 2 years, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain may appear with or without fever.

3G.3 Classification systems

UTIs may be classified as a first episode or recurrent, or according to severity (simple or severe).
Recurrent UTI may be subclassified into three groups [168]:

- *Unresolved infection*: subtherapeutic level of antimicrobial, non-compliance with treatment, malabsorption, resistant pathogens.

- *Bacterial persistence*: may be due to a nidus for persistent infection in the urinary tract. Surgical correction or medical treatment for urinary dysfunction may be needed.
- *Reinfection*: each episode is a new infection acquired from periurethral, perineal or rectal flora.

From the clinical point of view, severe and simple forms of UTIs should be differentiated because to some extent the severity of symptoms dictates the degree of urgency with which investigation and treatment are to be undertaken (Table 10).

Table 10: Clinical classification of UTIs in children

Severe UTI	Simple UTI
Fever > 39°C	Mild pyrexia
Persistent vomiting	Good fluid intake
Serious dehydration	Slight dehydration
Poor treatment compliance	Good treatment compliance

Severe UTI: Severe UTI is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

Simple UTI: A child with a simple UTI may have only mild pyrexia, but is able to take fluids and oral medication. The child is only slightly or not dehydrated and has a good expected level of compliance. When a low level of compliance is expected, such a child should be managed as one with a severe UTI.

3G.4 Diagnostic evaluation

3G.4.1 ***Physical examination***

It is mandatory to look for phimosis, labial adhesion, signs of pyelonephritis, epididymo-orchitis, and stigmata of spina bifida, e.g. hairy patch on the sacral skin. The absence of fever does not exclude the presence of an infective process.

3G.4.2 ***Laboratory tests***

The definitive diagnosis of infection in children requires a positive urine culture [168, 175]. Urine must be obtained under bacteriologically reliable conditions when undertaking a urine specimen culture [176]. A positive urine culture is defined as the presence of > 100,000 cfu/mL of one pathogen. The urine specimen may be difficult to obtain in a child < 4 years old, and different methods are advised because there is a high risk of contamination [177, 178].

3G.4.2.1 Collection of the urine

Suprapubic bladder aspiration: This is the most sensitive method, even though urine may be obtained in 23-99% of cases [168, 177].

Bladder catheterisation: This is also a very sensitive method, even though there is the risk of introduction of nosocomial pathogens [168, 179].

Plastic bag attached to the genitalia: Prospective studies have shown a high incidence of false-positive results, ranging from 85 - 99% [168, 177]. It is helpful when the culture is negative [168, 177] and has a PPV of 15% [176]. To obtain a urine sample in the best condition in children < 2 years of age (girls and uncircumcised boys without sphincteric control), it is better to use suprapubic bladder aspiration or bladder catheterisation. In older children with sphincteric control, MSU collection is possible and reliable [177].

3G.4.2.2 Quantification of bacteriuria

The final concentration of bacteria in urine is directly related to the method of collection, diuresis, and method of storage and transport of the specimen [175]. The classical definition of significant bacteriuria of > 10^5 cfu/mL is still used and depends on the clinical environment [175, 178].

The presence of pyuria (> 5 leukocytes per field) and bacteriuria in a fresh urine sample reinforce the clinical diagnosis of UTI [178].

In boys, when the urine is obtained by bladder catheterisation, the urine culture is considered positive with > 10^4 cfu/mL. Even though Hoberman [180] has identified a microorganism in 65% of cases with colony counts between 10,000 and 50,000 cfu/mL, there was a mixed growth pattern suggesting contamination. In these cases, it is better to repeat the culture or to evaluate the presence of other signs, such

as pyuria, nitrites or other biochemical markers [175]. The collection of MSU or in a collecting bag of $\geq 10^5$ cfu/mL is considered positive [176] (Table 11).

Table 11: Criteria for UTI in children

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	≥ 1,000-50,000 cfu/mL	≥ 10^4 cfu/mL with symptoms ≥10^5 cfu/mL without symptoms

3G.4.2.3 Other biochemical markers

The presence of other biochemical markers in a urine sample are useful to establish the diagnosis of UTI [168]. The most frequent markers are nitrite and leukocyte esterase usually combined in a dipstick test.

Nitrite: This is the degradation product of nitrate in bacterial metabolism, particularly in Gram-negative bacteria. When an infection is caused by Gram-positive bacteria, the test may be negative [168, 176]. Limitations of the nitrite test include:

- not all uropathogens reduce nitrate to nitrite, e.g. P. aeruginosa, or enterococci;
- even nitrite-producing pathogens may show a negative test result, due to the short transit time in the bladder in cases of high diuresis and urine dilution, e.g. neonates;
- the nitrite test has a sensitivity of only 45-60%, but a very good specificity of 85-98% [168, 178, 181].

Leukocyte esterase: This is produced by the activity of leukocytes. The test for leukocyte esterase has a sensitivity of 48-86% and a specificity of 17-93% [168, 178, 180, 181].

A combination of nitrite and leukocyte esterase testing improves sensitivity and specificity, but carries the risk of false-positive results [181].

The dipstick test has become useful to exclude rapidly and reliably the presence of a UTI, provided both nitrite and leukocyte esterase tests are negative. If the tests are positive, it is better to confirm the results in combination with the clinical symptoms and other tests [178, 181].

Bacteriuria without pyuria may be found:

- in bacterial contamination;
- in colonisation (ABU);
- when collecting a specimen before the onset of an inflammatory reaction.

In such cases, it is advisable to repeat the urinalysis after 24 h to clarify the situation. Even in febrile children with a positive urine culture, the absence of pyuria may cast doubt on the diagnosis of UTI. Instead, ABU with a concomitant septic focus responsible for the febrile syndrome has to be considered.

Bacteriuria without pyuria is found in 0.5% of specimens. This figure corresponds well with the estimated rate of ABU in childhood [180, 182] (LE: 2a).

Pyuria without bacteriuria may be due to:

- incomplete antimicrobial treatment of UTI;
- urolithiasis and foreign bodies;
- infections caused by M. tuberculosis and other fastidious bacteria, e.g. *C. trachomatis*.

Thus, either bacteriuria or pyuria may not be considered reliable parameters to diagnose or exclude UTI. Their assessment can be influenced by other factors, such as the degree of hydration, method of specimen collection, mode of centrifugation, volume in which sediment is resuspended and subjective interpretation of results [183]. However, according to Landau et al. [184], pyuria in febrile children is indicative of acute pyelonephritis.

For all of these reasons, in neonates and children < 6 months of age, either pyuria, bacteriuria or the nitrite test, separately, have minimal predictive value for UTI [185, 186] (LE: 3). In contrast, the PPV of significant Gram staining with pyuria is 85% [180] (LE: 2b). In older children, pyuria with a positive nitrite test is more reliable for the diagnosis of UTI, with a PPV of 98%.

Combining bacteriuria and pyuria in febrile children, the findings of ≥ 10 WBC/mm^3 and ≥ 50,000 cfu/mL in a specimen collected by catheterisation are significant for a UTI, and discriminate between infection and contamination [180, 185].

C-reactive protein: Although non-specific in febrile children with bacteriuria, C-reactive protein seems to be useful in distinguishing between acute pyelonephritis and other causes of bacteriuria. It is considered

significant at a concentration > 20 µg/mL.

Urinary N-acetyl-b-glucosaminidase: This is a marker of tubular damage. It is increased in febrile UTI and may become a reliable diagnostic marker for UTIs, although it is also elevated in VUR [187].

IL-6: The clinical use of urinary concentrations of IL-6 in UTIs [188] is still at the research stage.

3G.4.3 ***Imaging of the urinary tract***

A gold standard imaging technique has to be cost-effective, painless, safe, and have minimal or no radiation, as well as have the ability to detect any significant structural anomaly. Current techniques do not fulfil all such requirements.

3G.4.3.1 Ultrasound

Ultrasound (US) has become very useful in children because of its safety, speed and high accuracy in identifying the anatomy and size of the renal parenchyma and collecting system [189]. It is subjective and therefore operator-dependent, and gives no information on renal function. However, scars can be identified, although not as well as with Tc-99m DMSA scanning [189, 190] (LE: 2a). This technique has been shown to be very sensitive and excretory urography must be reserved only for when images need to be morphologically clarified [191] (LE: 2a).

3G.4.3.2 Radionuclide studies

Tc-99m DMSA is a radiopharmaceutical that is bound to the basement membrane of proximal renal tubular cells; half of the dose remains in the renal cortex after 6 h. This technique is helpful in determining functional renal mass and ensures an accurate diagnosis of cortical scarring by showing areas of hypoactivity, which indicates lack of function. A UTI interferes with the uptake of this radiotracer by the proximal renal tubular cells, and may show areas of focal defect in the renal parenchyma. A star-shaped defect in the renal parenchyma may indicate an acute episode of pyelonephritis. A focal defect in the renal cortex usually indicates a chronic lesion or a renal scar [192-194] (LE: 2a).

Focal scarring or a smooth uniform loss of renal substance as demonstrated by Tc-99m DMSA is generally regarded as being associated with VUR (reflux nephropathy) [195, 196]. However, Rushton et al. [197] have stated that significant renal scarring may develop, regardless of the existence or absence of VUR. Ransley and Risdon [198] have reported that Tc-99m DMSA shows a specificity of 100% and sensitivity of 80% for renal scarring.

The use of Tc-99m DMSA scanning can be helpful in the early diagnosis of acute pyelonephritis. About 50-85% of children show positive findings in the first week. Minimal parenchymal defects, when characterised by a slight area of hypoactivity, can resolve with antimicrobial therapy [199, 200]. However, defects lasting > 5 months are considered to be renal scarring [201] (LE: 2a).

Tc-99m DMSA scans are considered more sensitive than excretory urography and US in the detection of renal scars [202-205]. It remains questionable whether radionuclide scans can substitute echography as a first-line diagnostic approach in children with a UTI [206, 207].

3G.4.3.3 Cystourethrography

Conventional voiding cystourethrography (VCU): This is the most widely used radiological exploration for the study of the LUT and especially of VUR. It is considered mandatory in the evaluation of UTIs in children < 1 year of age. Its main drawbacks are the risk of infection, the need for retrogrades filling of the bladder, and the possible deleterious effect of radiation on children [208]. In recent years, tailored low-dose fluoroscopic VCU has been used for the evaluation of VUR in girls to minimise radiological exposure [209]. VCU is mandatory in the assessment of febrile childhood UTI, even in the presence of normal US. Up to 23% of these patients may reveal VUR [210].

Radionuclide cystography (indirect): This investigation is performed by prolonging the period of scanning after the injection of Tc-99m diethylene triamine pentaacetate (DTPA) or mercaptoacetyltriglycine (MAG-3) as part of dynamic renography. It represents an attractive alternative to conventional cystography, especially when following patients with reflux, because of its lower dose of radiation. Disadvantages are poor image resolution and difficulty in detecting LUT abnormalities [211, 212].

Cystosonography: Contrast-material-enhanced voiding US has been introduced for the diagnoses of VUR without irradiation [207, 212]. Further studies are necessary to determine the role of this new imaging modality in UTI.

3G.4.3.4 Additional imaging

Excretory urography remains a valuable tool in the evaluation of the urinary tract in children, but its use in UTIs is debatable unless preliminary imaging has demonstrated abnormalities that require further investigation. The major disadvantages in infants are the risks of side-effects from exposure to contrast media and radiation [213]. However, the role of excretory urography is declining with the increasing technical superiority of CT [214] and MRI. However, the indications for their use is still limited in UTI.

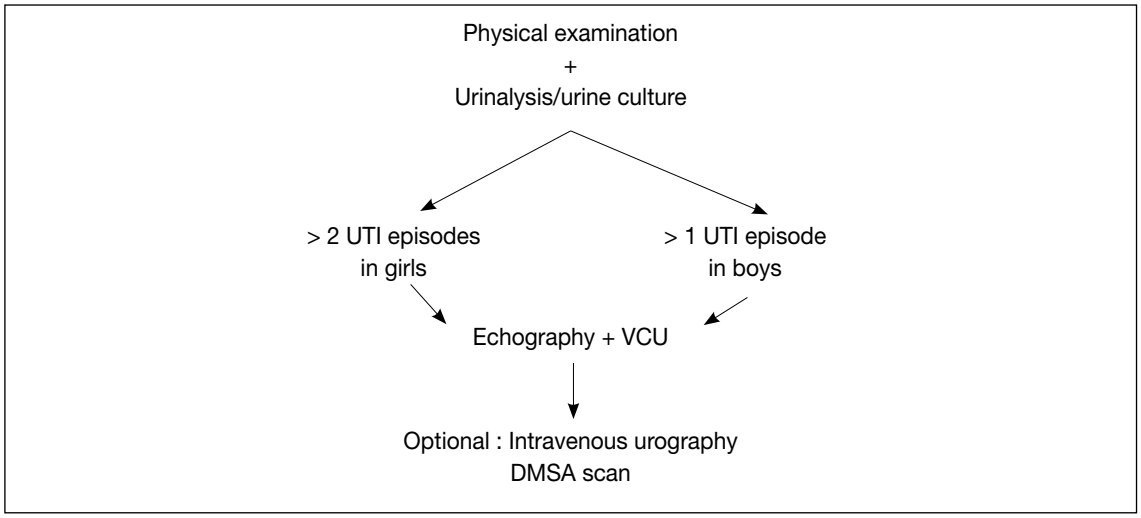
3G.4.3.5 Urodynamic evaluation

When voiding dysfunction is suspected, e.g. incontinence, residual urine, increased bladder wall thickness, urodynamic evaluation with uroflowmetry, (video) cystometry, including pressure flow studies, and electromyography should be considered.

3G.4.4 ***Schedule of investigation***

Screening of infants for ABU is unlikely to prevent pyelonephritic scar formation, as these usually develop very early in infancy. Only a minority of children with a UTI have an underlying urological disorder, but when present, such a disorder can cause considerable morbidity. Thus, after a maximum of two UTI episodes in a girl and one in a boy, investigations should be undertaken (Figure 4), but not in the case of ABU [210-213, 215, 216]. The need for DTPA/MAG-3 scanning is determined by the US findings, particularly if there is suspicion of an obstructive lesion.

Figure 4: Schedule of investigation of a UTI in a child



DMSA = dimercaptosuccinic acid; UTI = urinary tract infection; VCU = voiding cystourethrography.

3G.5 Disease management

Treatment has four main goals:

- elimination of symptoms and eradication of bacteriuria in the acute episode;
- prevention of renal scarring;
- prevention of a recurrent UTI;
- correction of associated urological lesions.

3G.5.1 ***Severe UTIs***

A severe UTI requires adequate parenteral fluid replacement and appropriate antimicrobial treatment, preferably with cephalosporins (third generation). If a Gram-positive UTI is suspected by Gram stain, it is useful to administer aminoglycosides in combination with ampicillin or amoxycillin/clavulanate [217] (LE: 2a). Antimicrobial treatment has to be initiated on an empirical basis, but should be adjusted according to culture results as soon as possible. In patients with an allergy to cephalosporins, aztreonam or gentamicin may be used. When aminoglycosides are necessary, serum levels should be monitored for dose adjustment. Chloramphenicol, sulphonamides, tetracyclines, rifampicin, amphotericin B and quinolones should be avoided. The use of ceftriaxone must also be avoided due to its undesired side effect of jaundice.

A wide variety of antimicrobials can be used in older children, with the exception of tetracyclines (because of tooth staining). Fluorinated quinolones may produce cartilage toxicity [218], but if necessary, may be used as second-line therapy in the treatment of serious infections, because musculoskeletal adverse events are of moderate intensity and transient [219, 220]. For a safety period of 24-36 h, parenteral therapy should be

administered. When the child becomes afebrile and is able to take fluids, he/she may be given an oral agent to complete the 10-14 days of treatment, which may be continued on an outpatient basis. This provides some advantages, such as less psychological impact on the child and more comfort for the whole family.

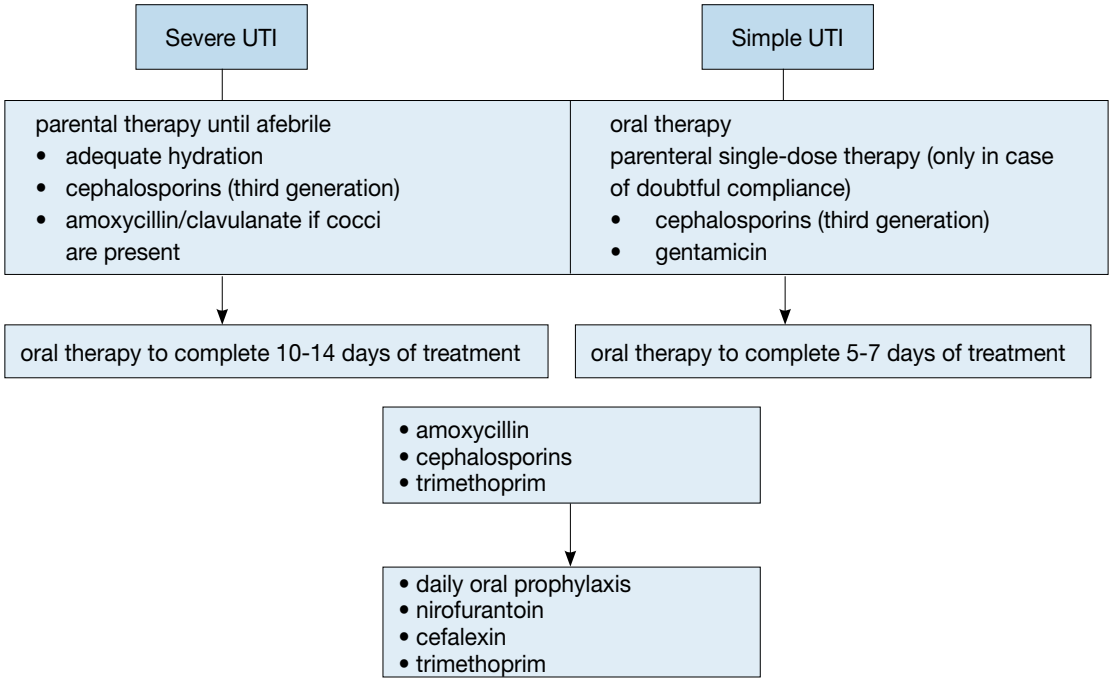
It is also less expensive, well tolerated and eventually prevents opportunistic infections [180]. The preferred oral antimicrobials are: trimethoprim (TMP), co-trimoxazole (TMP plus sulphamethoxazole), an oral cephalosporin, or amoxycillin/clavulanate. However, the indications for TMP are declining in areas with increasing resistance.

In children < 3 years of age, who have difficulty taking oral medications, parenteral treatment for 7-10 days seems advisable, with similar results to those with oral treatment [221].

If there are significant abnormalities in the urinary tract (e.g. VUR, or obstruction), appropriate urological intervention should be considered. If renal scarring is detected, the patient will need careful follow-up by a paediatrician in anticipation of sequelae such as hypertension, renal function impairment, and recurrent UTI.

An overview of the treatment of febrile UTIs in children is given in Figure 5 and the dosing of antimicrobial agents is outlined in Table 12 [222].

Figure 5: Treatment of febrile UTIs in children



3G.5.2 ***Simple UTIs***

A simple UTI is considered to be a low-risk infection in children. Oral empirical treatment with TMP, an oral cephalosporin or amoxycillin/clavulanate is recommended, according to the local resistance pattern. The duration of treatment in uncomplicated UTIs treated orally should be 5-7 days [223, 224] (LE: 1b). A single parenteral dose may be used in cases of doubtful compliance and with a normal urinary tract [225] (LE: 2a). If the response is poor or complications develop, the child must be admitted to hospital for parenteral treatment [226].

3G.5.3 ***Prophylaxis***

If there is an increased risk of pyelonephritis, e.g. VUR, and recurrent UTI, low-dose ABP is recommended [227, 228] (LE: 2a). It may also be used after an acute episode of UTI until the diagnostic work-up is completed. The most effective antimicrobial agents are: nitrofurantoin, TMP, cephalexin and cefaclor [227].

Acknowledgement

With our grateful thanks, the chapter on UTIs in children was updated also by Jorge Caffaratti Sfulcini, Paediatric Urology, Fundació Puigvert, Barcelona, Spain, as co-author.

Table 12: Dosing of antimicrobial agents in children aged 3 months to 12 years*

Antimicrobial agent	Application	Age	Total dose per day	No. of doses per day
Ampicillin	Intravenous	3-12 months	100-300 mg/kg BW	3
Ampicillin	Intravenous	1-12 years	60-150 (-300) mg/kg BW	3
Amoxycillin	Oral	3 months to 12 years	50-100 mg/kg BW	2-3
Amoxycillin/clavulanate	Intravenous	3 months to 12 years	60-100 mg/kg BW	3
Amoxycillin/clavulanate	Oral	3 months to 12 years	37.5-75 mg/kg BW	2-3
Cephalexin				
Treatment	Oral	3 months to 12 years	50-100 mg/kg BW	3
Prophylaxis	Oral	1-12 years	10 mg/kg BW	1-2
Cefaclor				
Treatment	Oral	3 months to 12 years	50-100 mg/kg BW	3
Prophylaxis	Oral	1-12 years	10 mg/kg BW	1-2
Cefixime	Oral	3 months to 12 years	8-12 mg/kg BW	1-2
Cetriaxone	Intravenous	3 months to 12 years	50-100 mg/kg BW	1
Aztreonam	Intravenous	3 months to 12 years	(50)-100 mg/kg BW	3
Gentamicin	Intravenous	3-12 months	5-7.5 mg/kg BW	1-3
Gentamicin	Intravenous	1-2 years	5 mg/kg BW	1-3
Trimethoprim				
Treatment	Oral	1-12 years	6 mg/kg BW	2
Prophylaxis	Oral	1-12 years	1-2 mg/kg BW	1
Nitrofurantoin				
Treatment	Oral	1-12 years	3-5 mg/kg BW	2
Prophylaxis	Oral	1-12 years	1 mg/kg BW	1-2

*BW = body weight. * Adapted from [222].*

3H URETHRITIS

3H.1 Introduction

Inflammation of the urethra presents usually with symptoms of the LUT and must be distinguished from other infections of the LUT. For the purpose of these Guidelines, urethritis due to microbiological invasion and requiring antibiotic treatment is reviewed.

3H.2 Methods

These recommendations are based on a review of several European national guidelines updates and in line with the CDC on STD [229-232].

3H.3 Epidemiology, aetiology and pathogenesis

From a therapeutic and clinical point of view, gonorrhoeal urethritis (GU) has to be differentiated from non-gonococcal urethritis (NGU). In Central Europe, NGU is much more frequent than GU. NGU is common, but up to about 50% of cases have no defined aetiology [233]. There is a correlation between promiscuity and low socioeconomic status and the frequency of infections due to *Neisseria gonorrhoeae* and *C. trachomatis*. Infection is spread by sexual contact.

Pathogens include *N. gonorrhoeae* (NG), *C. trachomatis* (CT), *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV), and *Ureaplasma urealyticum* (UU). The frequency of the different species varies between patient populations [233-238]. In a US study NGU with diagnosed aetiology were: CT in 22.3%, MG in 12.5%, TV in 2.5%, and UU in 24.0%, with multiple pathogens detected in 9.5% and no aetiology in [233]. *Mycoplasma hominis* probably does not cause urethritis. In most cases, however, *Mycoplasma* or *Ureaplasma spp.* are by asymptomatic colonisation of the urogenital tract.

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae

and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women. Recent evidence has suggested that *Mycoplasma genitalium* can also cause cervicitis and pelvic inflammatory disease in women [239] (LE: 3).

Mucopurulent or purulent discharge, alguria, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

3H.4 Diagnostic evaluation

A Gram stain of a urethral discharge or a urethral smear that shows more than five leukocytes per high power field (× 1,000) and eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis [240] (LE: 3, GR: B). The Gram stain is a rapid diagnostic test for evaluating urethritis. Laboratories should use validated nucleic acid amplification tests (NAATs) to detect chlamydia and gonorrhoea which are better than any of the other tests available for the diagnosis of chlamydial and gonococcal infections with respect to overall sensitivity, specificity, and ease of specimen transport [241]. N. gonorrhoeae and chlamydia cultures are mainly to evaluate treatment failures and monitor developing resistance to current treatment.

In all patients with urethritis, and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. If an amplification system is used for identifying the pathogens, the first voiding urine specimen can be taken instead of a urethral smear. Trichomonas sp. can usually be identified microscopically.

3H.5 Disease management

*3H.5.1 **Treatment of gonococcal urethritis***

Table 13: Recommendations of antimicrobials for the treatment of gonorrhoea

As first choice treatment
• ceftriaxone, 1 g intramuscularly (with local anaesthetic) or intravenously as a single dose plus • azithromycin, 1.0-1.5 g (3 tablets a 0.5 g) orally as a single dose
• If i.m. injection contraindicated and i.v. administration not possible: cefixime 800 mg p.o. (instead of ceftriaxone)
Alternative regimens, only if susceptibility is established
• cefixime, 400 mg p.o.as single dose; or • azithromycin 1.0-1.5 g p.o. as single dose.

As a result of the continuous spread of fluoroquinolone-resistant N. gonorrhoeae, this class of antibiotics is no longer recommended for the treatment of gonorrhoea, but could be used in case of proven susceptibility and in accordance with national guidelines. There is also an increase of resistance against cephalosporins in some areas, therefore knowledge of local susceptibility patterns is mandatory for the correct treatment of gonorrhoeal urethritis. Gonorrhoeae is frequently accompanied by chlamydial infection, therefore an active antichlamydial therapy should always be added.

*3H.5.2 **Treatment of chlamydial urethritis***

Standard: azithromycin 1.0-1.5 g p.o. as single dose
Alternative: doxycycline 100 mg bid p.o. for 7 days

*3H.5.3 **Treatment of Mycoplasma genitalium urethritis***

Standard: azithromycin 0.5 g p.o. day 1, 250 mg p.o. day 2-5
Alternative: moxifloxacin 400 mg q.d. for 5 days*
*because of reported failures, some experts recommend 10 to 14 days

*3H.5.4 **Treatment of Ureaplasma urealyticum urethritis***

Standard: doxycycline 100 mg bid p.o. for 7 days
Alternative: azithromycin 1.0-1.5 g p.o. as single dose or clarithromycin 500 mg bid for 7 days
(resistance against macrolides is possible)

3H.5.5 ***Treatment of Trichomonas vaginalis urethritis***
Standard: metronidazole 2 g p.o. as single dose
In case of persistence: 4 g daily for 3-5 days

3H.5.6 ***Treatment of non-gonococcal urethritis (NGU)****
Standard: doxycycline 100 mg bid p.o. for 7-10 days
Alternative: azithromycin 0.5 g p.o. day 1, 250 mg p.o. day 2-5
*if no agent could be identified

Doxycycline and azithromycin are considered to be equally effective in the treatment of chlamydial infections, however, infections with *M. genitalium* may respond better to azithromycin [242]. Erythromycin is less effective and causes more side effects. In pregnant women, fluoroquinolones and doxycycline are contraindicated, therefore, besides erythromycin and azithromycin, a regimen with amoxicillin 500 mg three times daily for 7 days is also recommended.

If therapy fails, one should consider treating infections by *T. vaginalis* and/or *M. genitalium* with a combination of metronidazole (2 g orally as single dose) and erythromycin (500 mg orally four times daily for 7 days). As in other STDs, the treatment of sexual partners is necessary.

3H.6 Follow-up

Patients should be followed-up for control of eradication or if symptoms persist or recur after completion of therapy. Patients should be instructed to abstain from sexual intercourse for 7 days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and tracing source should be done according to national routines and in cooperation with specialists in venereology whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV.

3I BACTERIAL PROSTATITIS

3I.1 Introduction

Bacterial prostatitis is a disease entity diagnosed clinically and by evidence of inflammation and infection localised to the prostate. According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, when symptoms persist for at least 3 months. It is recommended that European urologists use the classification suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis with confirmed or suspected infection is distinguished from chronic pelvic pain syndrome (CPPS).

Acute bacterial prostatitis can be a serious infection. Parenteral administration of high doses of a bactericidal antibiotic is usually required, which may include a broad-spectrum penicillin, a third-generation cephalosporin, or a fluoroquinolone. All of these agents can be combined with an aminoglycoside for initial therapy. Treatment is required until there is defervescence and normalisation of infection parameters (LE: 3, GR: B). In less severe cases, a fluoroquinolone may be given orally for 10 days (LE: 3, GR: B).

In chronic bacterial prostatitis, and if infection is strongly suspected in CPPS, preferably a fluoroquinolone should be given for at least 4 weeks. In case of fluoroquinolone resistance or adverse reactions, trimethoprim can be given orally for a period of 4-12 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics only continued if pre-treatment cultures are positive and/or the patient has reported positive effects from the treatment. A total treatment period of 4-6 weeks is recommended (LE: 3, GR: B). Patients with CPPS are treated empirically with numerous medical and physical modalities. The management of pain and other related symptoms are covered in the EAU Guidelines on Chronic Pelvic Pain [243].

3I.2 Epidemiology, aetiology and pathogenesis

Traditionally, the term prostatitis has included both acute and chronic bacterial prostatitis, in which an infective origin is accepted, and the term prostatitis syndrome or, more recently, CPPS, in which no infective agent can be found and whose origin is multifactorial and in most cases obscure.

Prostatitis and CPPS are diagnosed by symptoms and evidence of inflammation and infection localised to the prostate [244]. A causative pathogen, however, is detected by routine methods in only 5-10% of cases [245], and for whom antimicrobial therapy therefore has a rational basis. The remainder of patients are treated empirically with numerous medical and physical modalities. However, recent improvement

in classification and application of modern methods, including molecular biology, should allow proper systematisation of treatment [246-248].

This chapter reviews documented or suspected bacterial infections of the prostate (type I and II in Table 14).

3I.3 Diagnostic evaluation

3I.3.1 ***History and symptoms***

According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, the latter being defined by symptoms that persist for at least 3 months [246-248]. The predominant symptoms are pain at various locations and LUTS (Tables 15 and 16) [249-251]. Chronic bacterial prostatitis is the most frequent cause of recurrent UTI in men [252].

Table 14: Classification of prostatitis and CPPS according to NIDDK/NIH [246-248]

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis - CPPS
IIIA	Inflammatory CPPS (white cells in semen/EPS/VB3)
IIIB	Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine 3 (urine following prostatic massage).

Table 15: Localisation of pain in patients with prostatitis like symptoms*

Site of pain	Percentage of patients
Prostate/perineum	46%
Scrotum and/or testes	39%
Penis	6%
Urinary bladder	6%
Lower back	2%

**Adapted from Zermann et al. [251].*

Table 16: LUTS in patients with prostatitis like symptoms*

Frequent need to urinate
Difficulty urinating, e.g. weak stream and straining
Pain on urination, or that increases with urination

**Adapted from Alexander et al. [250].*

3I.3.1.1 Symptom questionnaires

Symptoms appear to have a strong basis for use as a classification parameter in bacterial prostatitis as well as in CPPS [253]. Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms [253, 254]. They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH (USA) [255].

Although the CPSI has been validated, to date, its benefit in clinical studies is still uncertain. The questionnaire contains four questions regarding pain or discomfort, two regarding urination, and three related to QoL (see online only material 4.6).

3I.3.2 ***Clinical findings***

In acute prostatitis, the prostate may be swollen and tender on digital rectal examination (DRE). Prostatic massage is contraindicated. Otherwise, the prostate is usually normal on palpation. An essential consideration in the clinical evaluation is to exclude prostatic abscess.

In case of lasting symptoms (“chronic prostatitis” symptoms) CPPS as well as other urogenital and ano-rectal disorders must be taken into consideration.

Symptoms of chronic prostatitis or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should be investigated for urogenital tuberculosis.

*3I.3.3 **Urine cultures and expressed prostatic secretion***

The most important investigation in the evaluation of the patient with acute prostatitis is MSU culture. If the patient presents with clinical signs suggestive of blood-stream infection, a blood culture should be taken using local protocol. In chronic bacterial prostatitis, quantitative bacteriological localisation cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey [244] are important investigations (see online only material 4.7).

The Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in acute bacterial prostatitis (Table 17) [256]. In chronic bacterial prostatitis, the spectrum of strains is wider. The significance of intracellular bacteria, such as *C. trachomatis*, is uncertain [257]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis, Candida sp*. and rare pathogens, such as *Coccidioides immitis, Blastomyces dermatitidis*, and *Histoplasma capsulatum* [258]. In case of suspected prostate tuberculosis, the urine should be investigated for Mycobacterium spp by PCR technique.

Table 17: Most common pathogens in prostatitis

Aetiologically recognised pathogens*
E. coli
Klebsiella sp.
Prot. mirabilis
Enterococcus faecalis
P. aeruginosa
Organisms of debatable significance
Staphylococci
Streptococci
Corynebacterium sp.
C. trachomatis
U. urealyticum
Myc. hominis

**Adapted from Weidner et al. [245] and Schneider et al. [256].*

*3I.3.4 **Prostate biopsy***

Perineal biopsies cannot be recommended as routine work-up and should be reserved only for research purposes. Transrectal prostate biopsy is not advisable in bacterial prostatitis (LE: 4, GR: C).

*3I.3.5 **Other tests***

Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles but is unreliable and cannot be used as a diagnostic tool in prostatitis [259].

*3I.3.6. **Additional investigations***

3I.3.6.1 Ejaculate analysis

An analysis of the ejaculate is not recommended for microbiological investigation due to the low sensitivity and specificity compared to the 2- or 3-glass tests. Ejaculate analysis is however frequently involved as part of the investigation of a generalised male accessory gland infection (MAGI) and it provides information about sperm quality. The EAU Panel believes that guidelines on prostatitis should not contain a set of differential diagnostic examinations. An experienced urologist should decide which investigations are relevant for each individual patient. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3I.3.6.2 Prostate specific antigen (PSA)

Prostate specific antigen is often increased in acute bacterial prostatitis and other urogenital infections. If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalise after antimicrobial treatment for 4 weeks in about 50% of patients [260]. A delay of at least 3 months should be allowed before it can be assumed that a stable level of PSA has been reached. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [261].

3I.4 Disease management

3I.4.1 ***Antibiotics***

Antibiotics are life-saving in acute bacterial prostatitis and recommended in chronic bacterial prostatitis.

Acute bacterial prostatitis is a serious infection with fever, intense local pain, and general symptoms. Parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone, should be administered. For initial therapy, any of these antibiotics may be combined with an aminoglycoside. After defervescence and normalisation of infection parameters, oral therapy can be substituted and continued for a total of 2-4 weeks [262].

The recommended antibiotics in chronic bacterial prostatitis, together with their advantages and disadvantages, are listed in Table 18 [263]. Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties [263] (LE: 2b, GR: B), their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including P. aeruginosa. In addition, levofloxacin is active against Gram-positive and atypical pathogens, such as *C. trachomatis* and genital mycoplasmas (LE: 2b, GR: B).

The duration of antibiotic treatment is based on experience and expert opinion and is supported by many clinical studies [264]. In chronic bacterial prostatitis antibiotics should be given for 4-6 weeks after initial diagnosis. Relatively high doses are needed and oral therapy is preferred [263, 264] (LE: 3, GR: B). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given [263, 265] (LE: 2b, GR: B).

Table 18: Antibiotics in chronic bacterial prostatitis*

Antibiotic	Advantages	Disadvantages	Recommendation
Fluoroquinolones	Favourable pharmacokinetics	Depending on the substance	Recommend
	Excellent penetration into the prostate	Drug interaction	
	Good bioavailability	Phototoxicity	
	Equivalent oral and parenteral pharmacokinetics (depending on the substance)	Central nervous system adverse events	
	Good activity against typical and atypical pathogens and *P. aeruginosa*		
	In general, good safety profile		
Trimethoprim	Good penetration into prostate	No activity against *Pseudomonas*, some enterococci and some Enterobacteriaceae	Consider
	Oral and parenteral forms available		
	Relatively cheap		
	Monitoring unnecessary		
	Active against most relevant pathogens		
Tetracyclines	Cheap	No activity against P. *Aeruginosa*	Reserve for special indications
	Oral and parenteral forms available	Unreliable activity against coagulase-negative staphylococci, *E. coli*, other Enterobacteriaceae, and enterococci	
	Good activity against *Chlamydia* and *Mycoplasma*	Contraindicated in renal and liver failure	
		Risk of skin sensitisation	
Macrolides	Reasonably active against Gram-positive bacteria	Minimal supporting data from clinical trials	Reserve for special indications
	Active against Chlamydia	Unreliable activity against Gram-negative bacteria	
	Good penetration into prostate		
	Relatively non-toxic		

**Adapted from Bjerklund Johansen et al. [263].*

*3I.4.2 **Intraprostatic injection of antibiotics***

This treatment has not been evaluated in controlled trials and should not be considered [266, 267].

*3I.4.3 **Drainage and surgery***

Approximately 10% of men with acute prostatitis will experience urinary retention [268] which can be managed by suprapubic, intermittent or indwelling catheterisation. Suprapubic cystostomy placement is generally recommended. The use of catheterisation without evidence of retention may increase the risk of progression to chronic prostatitis [269]. Alpha-blocker treatment has also been recommended, but clinical evidence of benefit is poor.

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [270]. The size may matter. In one study conservative treatment was successful if the abscess cavities were < 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage [271]. Surgery should be avoided in the treatment of bacterial prostatitis.

3J EPIDIDYMITIS AND ORCHITIS

3J.1 Introduction

Epididymitis and orchitis are classified as acute or chronic processes according to the onset and clinical course. The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis.

Epididymitis is almost always unilateral and relatively acute in onset. In young males it is associated with sexual activity and infection of the consort (LE: 3). The majority of cases in sexually active males aged < 35 years are due to sexually transmitted organisms, whereas in elderly patients, it is usually due to common urinary pathogens (LE: 3). Epididymitis causes pain and swelling, which begins in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information.

The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria (LE: 3). A urethral swab and MSU should be obtained for microbiological investigation before antimicrobial therapy (GR: C). Antimicrobials should be selected on the empirical basis that in young, sexually active men, *C. trachomatis* is usually causative, and that in older men, the most common uropathogens are involved. Fluoroquinolones with activity against *C. trachomatis* (e.g. ofloxacin and levofloxacin), should be the drugs of first choice. If *C. trachomatis* has been detected, treatment could also be continued with doxycycline, 200 mg/day, for a total of at least 2 weeks. Macrolides may be used as alternative agents (GR: C). Supportive therapy includes bed rest, up-positioning of the testes and anti-inflammatory therapy. In case of *C. trachomatis* epididymitis, the sexual partner should also be treated (GR: C). Abscess forming epididymitis or orchitis needs surgical treatment. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

3J.2 Epidemiology, aetiology and pathophysiology

There are no new data available concerning the incidence and prevalence of epididymitis. According to older data, acute epididymitis has been a major cause for admission to hospitals of military personnel [272] (LE: 3). Acute epididymitis in young men is associated with sexual activity and infection of the consort [273] (LE: 3).

The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. The incidence depends upon the vaccination status of the population [274]. Primary chronic orchitis is a granulomatous disease, and a rare condition with uncertain aetiology that has been reported in about 100 cases in the literature [275].

Complications in epididymo-orchitis include abscess formation, testicular infarction, testicular atrophy, development of chronic epididymal induration and infertility [272].

Epididymitis caused by sexually transmitted organisms occurs mainly in sexually active males aged < 35 years [272, 276] (LE: 3). The majority of cases of epididymitis are due to common urinary pathogens, which are also the most common cause of bacteriuria [272, 276] (LE: 3). Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection.

Typically, in epididymitis due to common bacteria and sexually transmitted organisms, the infection is spread from the urethra or bladder. In non-specific granulomatous orchitis, autoimmune phenomena are assumed to trigger chronic inflammation [275, 277]. Paediatric orchitis and mumps orchitis are of

haematogenous origin [277].

Epididymo-orchitis is also seen in systemic infections such as tuberculosis, lues, brucellosis and cryptococcus disease.

3J.3 Classification systems

Epididymitis (inflammation of the epididymis) causes pain and swelling which is almost always unilateral and relatively acute in onset. In some cases, the testes are involved in the inflammatory process (epididymo-orchitis). On the other hand, inflammatory processes of the testicle, especially virally induced orchitis, often involve the epididymis.

Orchitis and epididymitis are classified as acute or chronic processes according to the onset and clinical course. Chronic disease with induration develops in 15% of acute epididymitis cases. In the case of testicular involvement, chronic inflammation may result in testicular atrophy and the destruction of spermatogenesis [258, 272].

3J.4 Diagnostic evaluation

In acute epididymitis, the inflammation and swelling usually begin in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. All men with epididymitis that is caused by sexually transmitted organisms have a history of sexual exposure, and the organisms can lie dormant for months before the onset of symptoms. If the patient is examined immediately after undergoing urinalysis, urethritis and urethral discharge may be missed because WBC and bacteria have been washed out of the urethra during urination.

The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria. The presence of intracellular Gram-negative diplococci on the smear correlates with infection with N. gonorrhoeae. The presence of only WBC on a urethral smear indicates the presence of non-gonorrhoeal urethritis. *C. trachomatis* is isolated in approximately two-thirds of these patients [272, 276] (LE: 3).

Ejaculate analysis according to WHO criteria including leukocyte analysis indicates persistent inflammatory activity. In many cases, transient decreased sperm counts and forward motility can be found. Azoospermia due to complete obstruction of both epididymides is a rare complication. If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis. In about 20% of mumps orchitis cases, the disease occurs bilaterally in post-pubertal men with a risk of testicular atrophy and azoospermia [273] (LE: 3).

*3J.4.1 **Differential diagnosis***

It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information, including the age of the patient, history of urethritis, clinical evaluation and Doppler (duplex) scanning of testicular blood flow.

3J.5 Disease management

Only a few studies have measured the penetration of antimicrobial agents into the epididymis and testes in humans. Of these, the fluoroquinolones have shown favourable properties [278, 279] (LE: 2a).

Antimicrobials should be selected on the empirical basis that in young, sexually active men, *C. trachomatis* is usually causative, and that in older men, with BPH or other micturition disturbances, the most common uropathogens are involved. Studies that have compared microbiological results from puncture of the epididymis and from urethral swabs as well as urine have shown very good correlation. Therefore, before antimicrobial therapy, a urethral swab and MSU should be obtained for microbiological investigation (GR: C).

Again, fluoroquinolones, preferably those with activity against *C. trachomatis* (e.g. ofloxacin and levofloxacin), should be the drugs of first choice, because of their broad antibacterial spectra and their favourable penetration into the tissues of the urogenital tract. If *C. trachomatis* has been detected as an aetiological agent, treatment could also be continued with doxycycline, 200 mg/day, for at least 2 weeks. Macrolides may be used as alternative agents (GR: C).

Supportive therapy includes bed rest, up-positioning of the testes and antiphlogistic therapy. In young men, epididymitis can lead to permanent occlusion of the epididymal ducts and thus to infertility, therefore, one should consider antiphlogistic therapy with methylprednisolone, 40 mg/day, and reduce the dose by half every second day (GR: C).

In case of *C. trachomatis* epididymitis, the sexual partner should also be treated (GR: C). If uropathogens are found as causative agents, a thorough search for micturition disturbances should be carried out to prevent relapse (GR: C). Abscess-forming epididymitis or orchitis also needs surgical treatment. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

3K FOURNIER'S GANGRENE

3K.1 Introduction

- Full, repeated surgical debridement should commence within 24 h of presentation (LE: 3: GR: B).
- Treatment with broad-spectrum antibiotics should be started on presentation, with subsequent refinement according to culture and clinical response (LE: 3: GR: B).
- Adjunctive treatment such as pooled immunoglobulin and hyperbaric oxygen are not recommended, except in the context of clinical trials (LE: 3: GR: C).

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway. Evidence regarding investigation and treatment is predominantly from case series and expert opinion (LE: 3/4).

3K.2 Diagnostic evaluation

Fournier's gangrene remains rare but its incidence is increasing with an ageing population and higher prevalence of diabetes, and emergence of multi-resistant pathogens. Typically there is painful swelling of the scrotum or perineum with severe sepsis. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease. Risk factors include immuno-compromised patients, most commonly diabetes or malnutrition, or a recent history of catheterisation, instrumentation or perineal surgery. In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment. A high index of suspicion and careful examination, particularly of obese patients, is required.

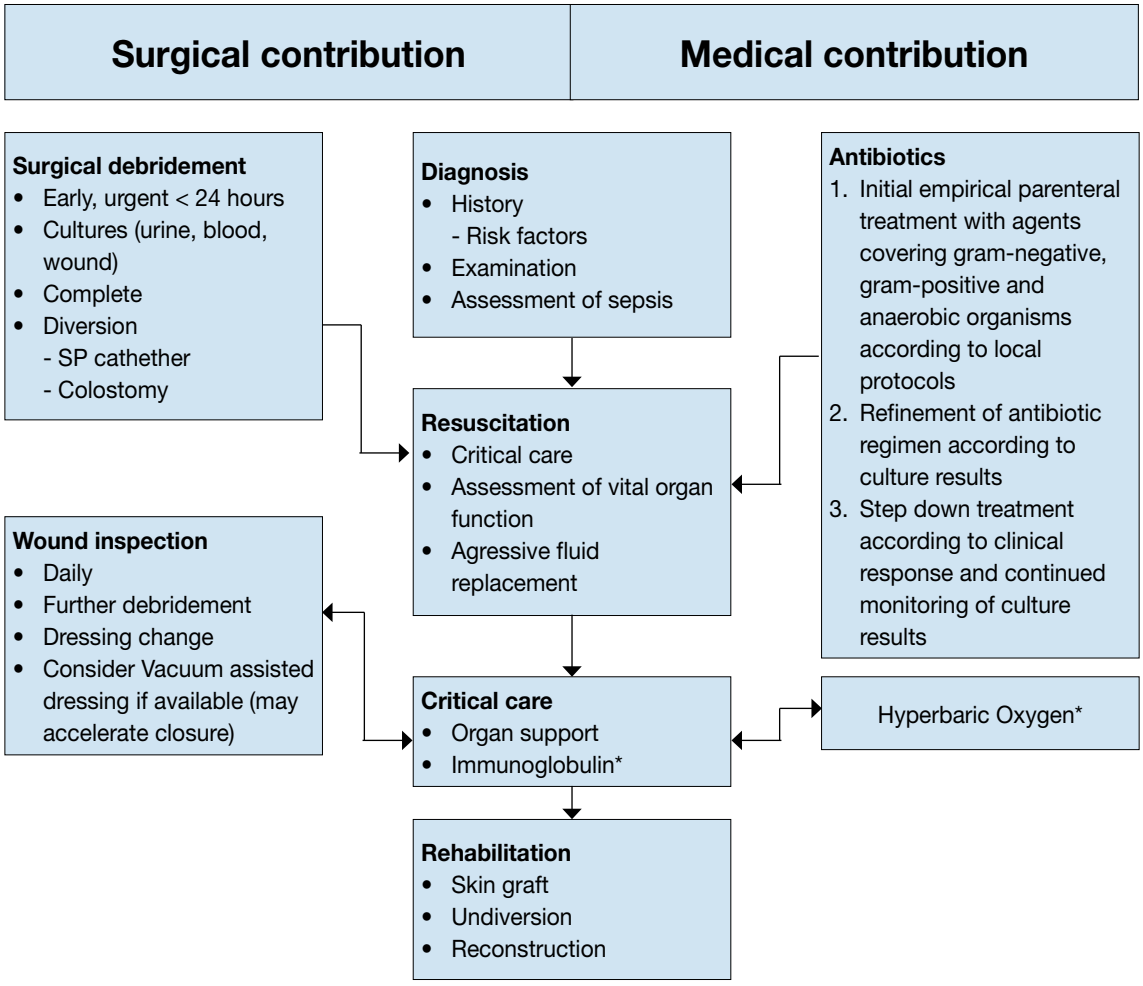
*3K.2.1 **Microbiology***

Fournier's gangrene is typically a type 1 necrotising fasciitis that is polymicrobial in origin, including S. aureus, Streptococcus sp., *Klebsiella sp.*, *E. coli* and anaerobs; involvement of Clostridium sp. is now less common. These organisms secrete endotoxins causing tissue necrosis and severe cardiovascular impairment. Subsequent inflammatory reaction by the host contributes to multi-organ failure and death if untreated.

3K.3 Disease management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement is necessary to save the patient's life (LE: 3, GR: B). Disease specific severity scoring systems do not appear superior to generic critical illness scores and are therefore not recommended for routine use (LE: 3, GR: C). Computed tomography or MRI can help define para-rectal involvement, suggesting the need for colostomy (LE: 3, GR: C). Consensus from case series suggests that surgical debridement should be early (< 24 h) and complete, because delayed and/or inadequate surgery results in higher mortality (LE: 3, GR: B). Concurrent parenteral antibiotic treatment should be given that covers all causative organisms and can penetrate inflammatory tissue (LE: 3, GR: B). This can then be refined following surgical cultures. The benefit of pooled immunoglobulin therapy and hyperbaric oxygen remains uncertain and should not be used routinely (LE:3, GR: C). With aggressive early surgical and medical management, survival rates are > 70% depending upon patient group and availability of critical care (LE: 3). Following resolution, reconstruction using skin grafts is required [280-283].

Figure 6: Care pathway



**Use of immunoglobulin and hyperbaric oxygen therapy is of uncertain benefit.*

3L SEXUALLY TRANSMITTED INFECTIONS

The classical bacteria that cause venereal diseases, e.g. gonorrhoea, syphilis, chancroid and inguinal granuloma, only account for a small proportion of all known sexually transmitted diseases (STDs) today. Other bacteria and viruses as well as yeasts, protozoa and epizoa must also be regarded as causative organisms of STD. Taken together, all STDs are caused by > 30 relevant pathogens. However, not all pathogens that can be sexually transmitted manifest genital diseases, and not all genital infections are exclusively sexually transmitted. At present, the reader is referred to the 2010 CDC STD Treatment Guidelines and later update [229].

The human immunodeficiency virus (HIV) causes a disease of the immune system leading to a vast panorama of complications and complex medical conditions also called acquired immunodeficiency syndrome (AIDS). The urogenital tract is rarely involved. The topic is beyond the scope of these Guidelines.

3M SPECIFIC INFECTIONS

Urogenital tuberculosis and bilharziasis are two infections that may affect the urogenital tract. Although not endemic in Europe, cases of urogenital tuberculosis are occasionally diagnosed in all communities. In a world of globalisation, travellers are regularly confronted with situations in which they may be infected. Guidelines on the diagnosis and management of these two infections have been published elsewhere [3, 4, 279, 284].

3M.1 Urogenital tuberculosis

Nearly one third of the world's population is estimated to be infected with M. tuberculosis. Moreover, tuberculosis is the most common opportunistic infection in AIDS patients. Urogenital tuberculosis is not very common but it is considered a severe form of extra-pulmonary tuberculosis. The diagnosis of urogenital tuberculosis is made based on culture studies by isolation of the causative organism; however, biopsy material on conventional solid media may occasionally be required. Drugs are the first-line therapy in urogenital tuberculosis. Treatment regimens of six months are effective in most patients. Although chemotherapy is the mainstay of treatment, surgery in the form of ablation or reconstruction may be unavoidable. Both radical and reconstructive surgery should be carried out in the first two months of intensive chemotherapy. The management should be done by, or in direct cooperation with, a specialist in the field of tuberculosis [4, 279, 284].

3M.2 Urogenital schistosomiasis

More than 200 million people worldwide are affected by bilharziasis, which is caused by Schistosoma haematobium. For travellers, precautions are most important. For the population in endemic areas, an integrated approach including health education is necessary. Effective pharmacological treatment is available [3].

3N PERIOPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

3N.1 Introduction

The aim of antimicrobial prophylaxis in urological surgery is to decrease the load of microorganisms in the surgical field at the time of surgery in order to prevent infective complications resulting from diagnostic and therapeutic procedures. However, evidence for the best choice of antibiotics and prophylactic regimens is limited (Table 19).

Before surgery, it is essential to categorise the patients in relation to:

- The general health status according to American Society of Anaesthesiology (ASA) score P1-P5;
- The presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight;
- The presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;
- The type of surgery and surgical field contamination burden;
- The expected level of surgical invasiveness, duration and technical aspects.

Only transrectal core prostate biopsy (LE: 1b, GR: A) and TUR-P (LE: 1a, GR: A) are well documented. There is no evidence for any benefits of antibiotic prophylaxis (ABP) in standard non-complicated endoscopic procedures and shockwave lithotripsy (SWL), although it is recommended in complicated procedures and patients with identified risk factors.

No ABP is recommended for clean operations, whereas a single or 1-day dose is recommended in clean-contaminated (urinary tract entered, breach of mucosal layer). The approach in contaminated operations varies with the type of procedure, the level of surgical site contamination and level of difficulty.

A urine culture is recommended prior to surgical interventions and the presence of bacteriuria controlled by directed pre-operative treatment of the detected pathogen (LE: 1b, GR A).

Antibiotic prophylaxis should be given as a single dose or a short course orally or parenterally. The administration route depends on the type of intervention and patient characteristics. Oral administration requires drugs that have good bioavailability. In the case of continuous close urinary drainage, prolongation of perioperative ABP is not recommended.

Many antibiotics are suitable for perioperative ABP, e.g. co-trimoxazole, second-generation cephalosporins, fluoroquinolones, aminopenicillins plus a beta-lactam inhibitor, and aminoglycosides. Broader-spectrum antibiotics including fluoroquinolones and carbapenem antibiotic group should however not be used or only cautiously in very selected cases. This applies also to the use of vancomycin.

The use of antimicrobials should be based on knowledge of the local pathogen profile and antibiotic susceptibility pattern. Best practice includes surveillance and an audit of infectious complications.

Table 19: Summary of level of evidence (LE) and grade of recommendation (GR) for peri-operative antibacterial prophylaxis in standard urological procedures
(for practical management refer to Tables 22-24 and text)

Procedure	LE	GR	Remarks	ABP
Diagnostic procedures				
Cystoscopy	1b	A	Low frequency of infections. Consider individual risk factors for UTI (i.e. BU, history of febrile UTI)	No
Urodynamic study	1a	A	Low frequency of infections. Consider individual risk factors for UTI (as for cystoscopy)	No
Trans-rectal core biopsy of prostate	1b	A	High risk of infection Assess carefully risk factors including risk of carrying resistant bacterial strains (i.e. fluoroquinolone resistance)	Yes
Diagnostic ureteroscopy	4	C	No available studies	Optional
Common endourological/endoscopic therapeutic procedures (examples)				
Fulguration of small bladder tumours	2b	C	As for cystoscopy	No
TUR-BT	2b	C	Poor data. No concern given to burden of tumour, i.e. size, multiplicity, necrosis	Optional See text
TUR-P	1a	A	High risk of febrile infection and sepsis. Control of BU/UTI and other risk factors prior to surgery	Yes
SWL (standard, no bacteriuria, no catheters, otherwise healthy)	1a	A	Low frequency of infections	No
SWL with risk factors for infection	1a	A	Increased risk of infection. Control of BU and risk factors	Yes
Ureteroscopy for stone management	2b	B (A)	Low frequency of infections but variable with stone position (i.e. proximal impacted stone). Control of BU and risk factors	Optional, related to difficulty/ level
Percutaneous and retrograde intra-renal stone management	1b	A	High risk of febrile infection and sepsis	Yes
Common open and/or laparoscopic surgery (examples)				
Clean operations (no opening/entering of the urinary tract)				
Nephrectomy	3	C	SSI/WI poorly documented Secondary post-operative catheter-related BU/UTI	No
Planned scrotal surgery, vasectomy, surgery for varicocele	3	C	Conflicting data	No
Prosthetic implants	3	B	Limited documentation	Yes
Clean-contaminated (opening/entering of the urinary tract)				
Nephroureterectomy	3	B	Poor documentation Control of BU and other risk factors prior to surgery. Secondary post-operative catheter-related BU/UTI	Yes
Total (radical) prostatectomy	2a			
Uretero-pelvic junction repair	4	C		
Partial bladder resection	3			
Clean-contaminated/contaminated (opening of bowel, urine deviation)				
Cystectomy with urine deviation	2a	B	High risk of infection	Yes

ABP = antibiotic prophylaxis; BU = bacteriuria; SSI/WI = surgical site infection/wound infection; SWL = extracorporeal shockwave lithotripsy; TUR-BT = transurethral resection of the bladder tumour; TUR-P = transurethral resection of the prostate.

This section aims to clarify the current knowledge and to propose practical recommendations based on a few

existing systematic reviews [285, 286], available clinical studies, expert opinion and professional consensus. This section considers the recommendations of societies, such as the Paul Ehrlich Society for Chemotherapy, the corresponding working groups of the German Society of Urology [287], French Association of Urology [288], the Swedish Council on Health Technology Assessment [289], the Scottish Intercollegiate Guidelines Network [290] and an international consensus working group [2].

The EAU Guidelines Panel on urological infections has further presented a tentative classification of the urological procedures in relation to the level of contamination of the surgical site in order to facilitate the decision on ABP in the absence of evidence [291].

The Global Prevalence Infection in Urology studies (GPIU) have found that approximately 10% of urological patients had a healthcare-associated UTI [12]. Moreover, a review showed large discrepancies in the use of ABP in all types of procedures and between countries, and low compliance to the guidelines [292]. The marked increase in bacterial resistance development underscores the need for a stringent antibiotic policy throughout Europe and compliance to the recommendations [293].

3N.1.1 ***Goals of perioperative antibacterial prophylaxis***

Antibiotic prophylaxis and therapy are two different issues. ABP aims to prevent healthcare-associated infections that result from diagnostic and therapeutic procedures. ABP is only one of several measures to prevent infections and can never compensate for poor hygiene and operative technique. In contrast, antibiotic therapy is the treatment of a clinically suspected or microbiologically proven infection.

The United States based CDC has presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications [294]. These definitions have also been used in the GPIU point prevalence studies [12]. Revision of definitions and recommendations are under consideration, see chapter 2 in [2]. Table 20 illustrates the different types of infectious complications encountered in urological surgery.

Table 20: Main types of healthcare-associated infections (HAI) encountered in urological practice

Site of infection	Minor	Major
Surgical wound Incision/surgical site infection (SSI)	Superficial wound infection	Deep wound infection Wound rupture (abdominal dehiscence) Deep abdominal or surgical site abscess
UTI or organ-specific infection Include Catheter Associated UTI (CAUTI)	Asymptomatic bacteriuria (bacterial colonisation) Symptomatic lower UTI (cystitis)	Febrile UTI Pyelonephritis Renal abscess Peri-renal abscess
Blood stream	Bacteraemia without signs of systemic response	Sepsis with signs of systemic response (SIRS)
MAGI	Epididymitis (Orchitis)	Acute bacterial prostatitis (type I)
Other sites		Septic embolism Pneumonia Secondary bone infection

The endpoints of perioperative prophylaxis in urology are the infectious complications presented in Table 20 when directly related to surgery. This might be extended to ABU and even minor wound infections. Asymptomatic bacteriuria after TURP or other endourological procedures can disappear spontaneously and is usually of no clinical significance.

3N.2 Risk factors

Risk factors (Tables 21 and 1) are underestimated in most trials. However, they are important in the pre-operative assessment of the patient [291]. They are related to:

- The general health of the patient as defined by ASA score P1-P5;
- The presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight;
- The presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;

- The type of surgery and surgical field contamination;
- The expected level of surgical invasiveness, duration and technical aspects.

The traditional classification of surgical procedures according to Cruse and Foord [295] into clean, clean-contaminated, contaminated, and infected/dirty operations applies to open surgery but not to endourological interventions. The present Guidelines consider the procedures entering the urinary tract and the breaching of the mucosa as clean-contaminated procedures because urine culture is not always a predictor of bacterial presence, and that the lower genitourinary tract is colonised by microflora, even in the presence of sterile urine [291, 296]. The presence of bacteriuria in an otherwise asymptomatic patient, revealed by a pre-operative culture, is indication of a contamination level (Table 23).

Table 21: Generally accepted risk factors for infectious complications

General risk factors	Special risk factors associated with an increased bacterial load
Older age	Long preoperative hospital stay or recent hospitalisation
Deficient nutritional status	History of recurrent urogenital infections
Impaired immune response	Surgery involving bowel segment
Diabetes mellitus	Colonisation with microorganisms
Smoking	Long-term drainage
Extreme weight	Urinary obstruction
Coexisting infection at a remote site	Urinary stone
Lack of control of risk factors	

The risk of infection varies with the type of intervention. The wide spectrum of interventions and recent advances in minimal invasive surgery further complicates the provision of clear-cut recommendations. Furthermore, the bacterial load, the duration and difficulty of the operation, the surgeon's skill, and perioperative bleeding may also influence the risk of infection [294-296]. For elective urological surgery, general and urinary tract specific risk factors must be controlled (i.e. bacteriuria, obstruction).

3N.3 Principles of antibiotic prophylaxis

Antibiotic prophylaxis aims at protecting the patient but not at the expense of promoting resistance. However, there is good evidence that intelligent use of prophylaxis can lower the overall consumption of antibiotics [297, 298]. It is essential to individualise the choice of ABP according to each patient's cumulative risk factors [299]. Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection [300-302].

*3N.3.1 **Timing***

There is a given time frame during which ABP should be administered. Although the following guidelines are based on research into skin wounds [303] and clean-contaminated and contaminated bowel surgery, there is good reason to believe that the same findings apply to urological surgery. The optimal time for ABP is 1-2 h before instrumentation. Some studies on bowel surgery indicate similar results up to 3 h after the start of an intervention [304, 305].

For practical purposes, oral peri-operative ABP should be given approximately 1 hour before the intervention while intravenous ABP should be given about 30 minutes prior to incision, e.g. at the induction of anaesthesia. These timings allow the antibiotic to reach a peak concentration at the time of highest risk during the procedure, and an effective concentration shortly afterwards [306, 307].

*3N.3.2 **Route of administration***

Oral administration is as effective as the intravenous route for antibiotics with sufficient bioavailability. This is recommended for most interventions when the patient can easily take the drug 1 h before intervention. In other cases, intravenous administration is recommended. Local irrigation of the operating field with antibiotics is not recommended.

*3N.3.3 **Duration of the regimen***

For most procedures, duration of ABP has not yet been adequately addressed and rarely can a defined regimen be recommended. In principle, the duration of perioperative prophylaxis should be minimised, ideally to a single perioperative antibiotic dose. The prophylaxis should be prolonged only where there are significant risk factors (see Section 3N.2).

3N.3.4 ***Choice of antibiotics***

No clear-cut recommendations can be given, as there are considerable variations in Europe regarding both bacterial spectra and susceptibility to different antibiotics. Antimicrobial resistance is usually higher in the Mediterranean region as compared with Northern European countries; resistance is correlated with an up to four-fold difference in sales of antibiotics [308]. Thus, knowledge of the local pathogen profile, susceptibility and virulence is mandatory in establishing local antibiotic guidelines. It is also essential to define the predominant pathogens for each type of procedure. When choosing an antimicrobial agent, it is necessary to consider the procedure-specific risk factors, contamination load, target organ, and the role of local inflammation.

In general, many antibiotics are suitable for perioperative antibacterial prophylaxis, e.g. co-trimoxazole, second-generation cephalosporins, aminopenicillins plus a BLI, aminoglycosides and fluoroquinolones. Broader-spectrum antibiotics such as fluoroquinolones, third generation cephalosporins and the carbapenem group should be used sparingly and reserved for treatment. This applies also to the use of vancomycin.

3N.3.5 ***Prophylactic regimens in defined procedures***

All procedures are not alike. There is a large variation in invasiveness and risk for identically named interventions. The present Guidelines suggested a distribution of the different common diagnostic and therapeutic urological procedures in relation to the categories of surgical site contamination after adaptation to the urological context [291, 295]. The recommendations for ABP in standard urological surgery are summarised in Tables 22 and 23 [309-311].

3N.4 Antimicrobial prophylaxis by procedure

3N.4.1 ***Diagnostic procedures***

3N.4.1.1 Transrectal prostate biopsy

Antimicrobial prophylaxis in core biopsy of the prostate is strongly recommended (LE: 1b, GR: A). However, the choice of regimens remains debatable. Most regimens used are effective, and recent studies have suggested that 1-day and even single doses are sufficient in low-risk patients [312-327] (LE: 1b, GR: A). The increase in fluoroquinolone resistance in the faecal flora has raised the question of appropriateness of the current recommendations [328, 329]. There is no clear-cut evidence-based alternative. In a recent review, it was recommended that men at risk for harbouring fluoroquinolone resistant strains should receive an alternate targeted regiment based on rectal swab finding [330]. Also several forms of bowel preparation are under investigation, although none has yet been shown to significantly impact on infection rates [330]. Each urologist must weigh the need for a prostate biopsy in relation to the risk, assess the individual risks factors including the risk of harbouring a resistant bacteria (e.g. ESBL) and consider the need for a rectal swab before the instrumentation [331].

3N.4.1.2 Cystoscopy

The frequency of infectious complications after cystoscopy, standard urodynamic studies and diagnostic simple ureteroscopy in otherwise healthy individuals is low [285, 332, 333]. In view of the very large number of cystoscopic examinations, the low infectious risk and the potential adverse effect on bacterial sensitivity, ABP is not recommended (LE: 1a, GR: A). However, bacteriuria, indwelling catheters, neurogenic LUTD and a history of urogenital infection are risk factors that must be considered [334-347] (LE: 1b, GR: A).

3N.4.2 ***Endourological treatment procedures (urinary tract entered)***

3N.4.2.1 TUR-BT

There is little evidence for any benefit of ABP in TURB. The studies do not distinguish between simple fulguration (= cystoscopy) and large or multiple tumours, the presence of necrotic material or not. Therefore, the present Guidelines recommend a differentiation of type of tumour (Table 23) and the choice of ABP accordingly [285, 298, 348, 349] (LE: 2b, GR: C).

3N.4.2.2 TUR-P

Transurethral resection of the prostate is the best studied urological intervention. At least two meta-analyses of a large number of prospective, randomised and controlled studies, including several thousand patients, showed a marked benefit of ABP with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively [285, 298, 348, 349] (LE: 1a, GR: A).

3N.4.2.3 Ureteroscopy

Well-conducted prospective controlled trials on ureteroscopy are lacking. It is reasonable, however, to distinguish low-risk procedures, such as simple diagnostic and distal stone treatment in otherwise healthy

individuals, from higher-risk procedures, such as treatment of proximal impacted stones with obstruction. These Guidelines recommend therefore a differentiation in degree of severity, stone anatomic position and patient related risk factors (Table 23), which is supported by a large database on URS [350].

3N.4.2.4 Percutaneous nephrolithotripsy

The risk of infection in PNL is high and use of ABP has been shown to significantly reduce the risk of infectious complications [351-359] (LE: 1b, GR: A). A single dose has shown to be sufficient [360]. Retrograde intra-renal stone treatment could be expected to have a similar risk profile [350].

3N.4.2.5 Shock-wave lithotripsy

No standard prophylaxis is recommended. However, control of bacteriuria and prophylaxis is recommended in cases of internal stent and treatment, due to the increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, or infectious stones) [361-370] (LE: 1a-1b, GR: A) (Table 23).

Most antibiotic groups have been evaluated, such as fluoroquinolones, BLIs, including cephalosporins, and co-trimoxazole, but comparative studies are limited. It is recommended to direct the choice of an antibiotic on findings at urine culture.

*3N.4.3 **Laparoscopic surgery***

There has been a lack of sufficiently powered studies in laparoscopic urological surgery. However, it seems reasonable to manage laparoscopic surgical procedures in the same manner as the corresponding open procedures (LE: 4, GR: C).

*3N.4.4 **Open or laparoscopic urological operations without opening of the urinary or genital tracts (clean procedures)***

No standard ABP is recommended in clean operations [371-375] (LE: 3, GR: C).

*3N.4.5 **Open or laparoscopic urological operations with opening of the urinary tract (clean-contaminated procedures)***

In cases of opening the urinary tract, a single perioperative parenteral dose of antibiotics is recommended (LE: 3, GR: C). This is valuable for standard procedures such as total (radical) prostatectomy [376-379]. In open enucleation of prostatic adenoma, the risk of postoperative infection is particularly high [380] (LE: 2b, GR: B).

*3N.4.6 **Open urological operations with bowel segment (clean-contaminated or contaminated procedures)***

Antibiotic prophylaxis is recommended, as for clean-contaminated operations in general surgery. Single or 1-day dosage is recommended, although prolonged operation and other morbidity risk factors might support the use of a prolonged regimen, which should be < 72 h. The choice of antibiotic should focus on aerobic and anaerobic pathogens. Evidence is based on colorectal surgery (LE: 1a, GR: A), but experience is limited as for specific urological interventions [381-384] (LE: 2a, GR: B).

*3N.4.7 **Postoperative drainage of the urinary tract***

When continuous urinary drainage is left in place after surgery, prolongation of perioperative antibacterial prophylaxis is not recommended, unless a complicated infection that requires treatment is suspected. Asymptomatic bacteriuria (bacterial colonisation) should only be treated after removal of the drainage tube if considered as necessary (LE: 3, GR: B).

*3N.4.8 **Implantation of prosthetic devices***

When infectious complications occur in implant surgery, they are usually problematic and often result in removal of the prosthetic device. Diabetes mellitus is considered a specific risk factor for infection. Skin-related staphylococci are responsible for most infections. The antibiotics used must be chosen to target these strains [385-388] (LE: 2a, GR: B).

Table 22: Surgical wound classes modified from [295] and adapted to urological surgery.

Classification of urological procedures in relation to the different levels of surgical field contamination. The risk of wound infection or SSI expressed in percent (within brackets in left column) is that of classical wound infections without ABP and not bacteriuria or clinical UTI in urological surgery (modified from pg. 674-75 [2]). In this table some examples of open and laparoscopic procedures are given and the ABP basic principle.

Level of surgical site contamination	Description	Open or laparoscopic urological surgery (examples of procedures)	Principle of antibiotic prophylaxis (timing see 3N.3.1)
Clean (I) (1-4%)	Uninfected surgical site Urogenital tract not entered No evidence of inflammation No break in technique	Simple nephrectomy Planned scrotal surgery Vasectomy Varicocoele	No
Clean-contaminated (IIA) (Not well studied)	**Urogenital tract** (UT) entered with no or little (controlled) spillage. No break in technique	Pelvic-ureteric junction repair Nephron-sparing tumour resection Total prostatectomy Bladder surgery, partial cystectomy	Single dose prior to (oral) or at surgery (i.v.)
Clean-contaminated (bowel) (IIB) (4-10%)	**Gastrointestinal tract** (GIT) entered with no or little (controlled spillage. No break in technique	Urine diversion (small intestine) Orthotopic bladder replacement; ileal conduit	Single dose prior to (oral) or at surgery (i.v.)
Contaminated (IIIA) (10-15%)	**UT** and/or **GIT** entered, spillage of GI content; inflammatory tissue Presence of bacteriuria (UT) Major break in technique; Open, fresh accidental wounds	Urine diversion (large intestine) Spillage (small and large intestine) Concomitant GI disease Trauma surgery	Control of bacteriuria prior to surgery Single dose at Surgery Consider prolonged regime
Dirty (IV) (15-40%)	Pre-existing infection; viscera perforation Old traumatic wound	Drainage of abscess Large dirty trauma surgery	Treatment in accordance with pathogen's sensitivity

GIT = gastrointestinal tract; UT = urogenital tract.

Table 23: Classification of the different diagnostic and therapeutic endoscopic urological procedures in relation to the level of surgical field contamination.
Bacteriuria is a key factor to separate between clean-contaminated and contaminated surgical environment (modified from pg. 674-75 [2]).

Level of surgical field contamination	Bacteriuria	Diagnostic procedures	TUR-BT and TUR-P	URS PNL	SWL	Principle of antibiotic prophylaxis (timing see 3N.3.1)
Clean (I)*	No	Cystoscopy Urodynamic study	Fulguration of small bladder tumours (similar cystoscopy)	Diagnostic URS (simple) No history of UTI	Standard kidney or ureter stone, (no obstruction, no history of UTI)	No
Clean-contaminated (UT) (IIA)	No	Trans-perineal prostate biopsy	TUR-BT large tumour (no history of UTI), TUR-P (no identified RF) Controlled BU	Diagnostic URS (simple) Uncomplicated stone (no obstruction, no stent, not "impacted") History of UTI	Standard kidney or ureter, moderate obstruction and/or history of UTI	Single dose prior to (oral) or at surgery (i.v.)

Contaminated (UT=IIIA)	Yes	Trans-perineal prostate biopsy (history of UTI) Trans-rectal prostate biopsy	TUR-BT necrosis tumour Bacteriuria TUR-P in men with indwelling catheter or bacteriuria	Complicated stone (Moderate obstruction, "impacted")	Complex stone Obstruction Nephrostomy tube or JJ-stent present	Control of bacteriuria prior to surgery (3-5 days) Single dose at surgery. Consider prolonged regimen
Infected/Dirty (IV)	Yes	Prostate biopsy in men with catheter or UTI	Clinical UTI Drainage as required Emergency TUR-BT, TUR-P			Antibiotic Treatment according to sensitivity pattern

** Although the urinary tract/bladder is entered, the standard procedure, smooth and atraumatic, is considered in this model as clean in patients without bacteriuria and or history of infection after these procedures.*
RF = risk factor; SWL = extracorporeal shockwave lithotripsy; TUR-BT = transurethral resection of the bladder tumour; TUR-P = transurethral resection of the prostate.

Table 24: Recommendations for perioperative antibiotic prophylaxis per type of procedure considering expected pathogens and individual risk factors (see 3N.3)

Procedure	Pathogens (expected)	Prophylaxis	Remarks	Choice of antimicrobial agents (when appropriate)
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes[1]	All patients Targeted alternative[2]	Single dose effective in low-risk patients Consider prolonged course in high-risk patients (i.e. history of UGI)	Fluoroquinolones TMP ± SMX Targeted alternative[2] Metronidazole?[1]
Cystoscopy Cystoscopy + fulguration Urodynamic study	Enterobacteriaceae Enterococci Staphylococci	No	Consider in high-risk patients (i.e. history UTI after procedure)	TMP ± SMX Cephalosporin group 2 Nitrofurantoin
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	Consider in high-risk patients	
Endourological surgery and SWL				
SWL	Enterobacteriaceae Enterococci	No		TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI[a]
SWL with stent or nephrostomy tube	Enterobacteriaceae Enterococci	All patients	Risk patients	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI[a]
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	Consider in risk patients	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI Fluoroquinolones
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	Short course length to be determined Intravenous suggested at operation	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI Fluoroquinolones

TUR-P	Enterobacteriaceae Enterococci	All patients	Low-risk patients and small-size prostate probably do not require prophylaxis	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI
TUR-BT (For detail grading see Table 23)	Enterobacteriaceae Enterococci	No standard in minor procedures	Consider in high-risk patients, larger resection and in necrotic tumours	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI
Open or laparoscopic urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens	No	Consider in high-risk patients Short postoperative catheter requires no treatment	
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	Single perioperative course	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI
Clean-contaminated/ contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	As for colonic surgery	Cephalosporin group 2 or 3 Metronidazole
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients		Cephalosporin group 2 or 3 Penicillin (penicillinase stable)

[1]The role of anaerobes in core biopsy of the prostate is not established and there is no evidence for metronidazole; [2]Increasing fluoroquinolone resistance has to be assessed. [a] = gram-negative bacteria excluding Pseudomonas aeruginosa.

BLI = beta-lactamase inhibitor; SMX = sulphamethoxazole; TMP = trimethoprim; TUR-BT = transurethral resection of the bladder tumour; TUR-P = transurethral resection of the prostate.

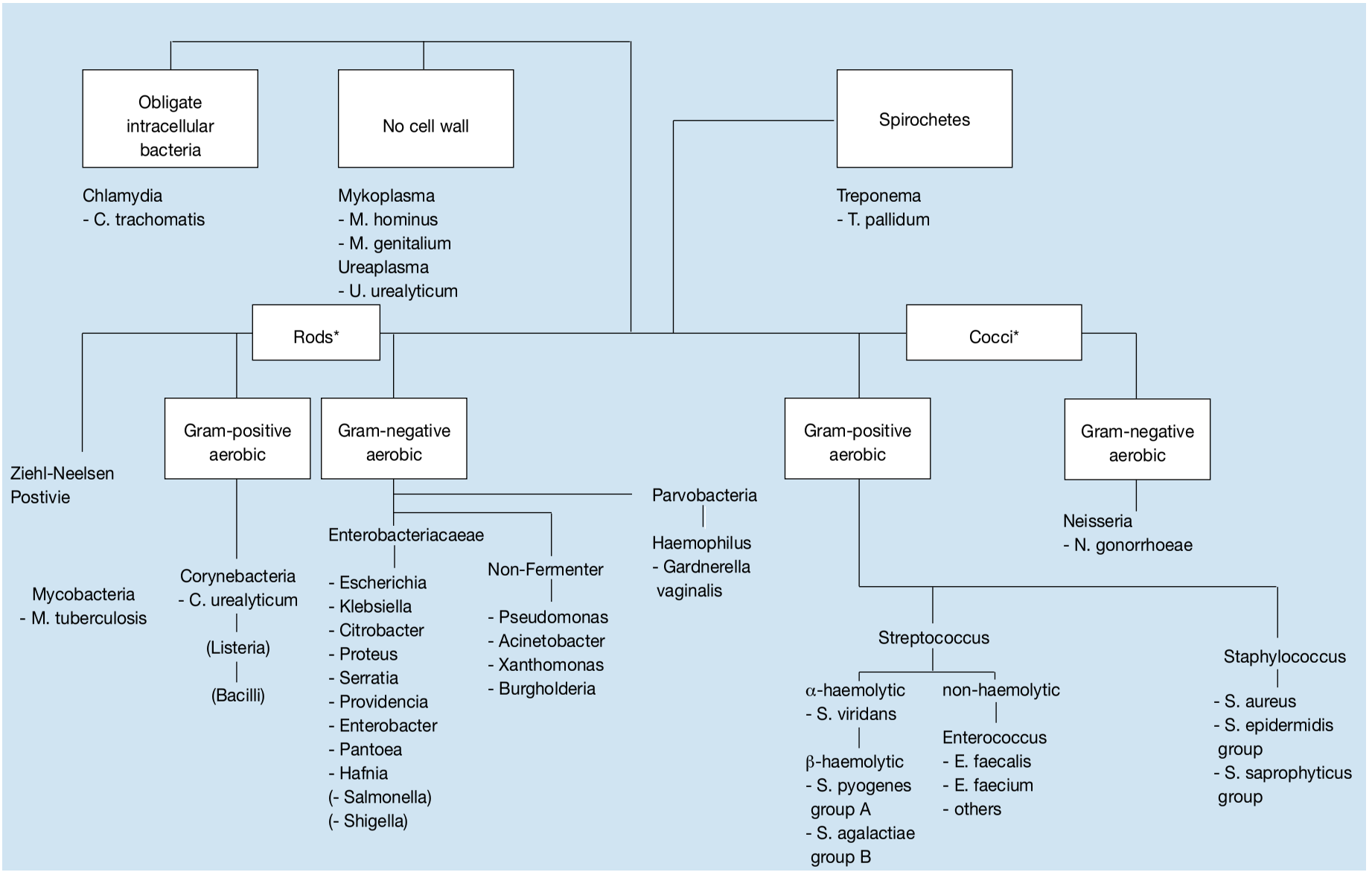
4. APPENDICES

4.1 Criteria for the diagnosis of UTI, as modified according to IDSA/European Society of Clinical Microbiology and Infectious Diseases guidelines [389-391]

Category	Description	Clinical features	Laboratory investigations
1	Asymptomatic bacteriuria	No urinary symptoms	> 10 WBC/mm^3 > 10^5 cfu/mL* in two consecutive MSU cultures > 24 h apart
2	Acute uncomplicated UTI in women; acute uncomplicated cystitis in women	Dysuria, urgency, frequency, suprapubic pain, no urinary symptoms in 4 weeks before this episode	> 10 WBC/mm^3 > 10^3 cfu/mL*
3	Acute uncomplicated pyelonephritis	Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urological abnormalities (ultrasonography, radiography)	> 10 WBC/mm^3 > 10^4 cfu/mL*
4	Complicated UTI	Any combination of symptoms from categories 1 and 2 above; one or more factors associated with a complicated UTI (see text)	> 10 WBC/mm^3 > 10^5 cfu/mL* in women > 10^4 cfu/mL* in men, or in straight catheter urine in women
5	Recurrent UTI (antimicrobial prophylaxis)	At least three episodes of uncomplicated infection documented by culture in past 12 months: women only; no structural/functional abnormalities	< 10^3 cfu/mL*

*All pyuria counts refer to unspun urine. *Uropathogen in MSU culture.*

4.2 Relevant bacteria for urological infections



**Anaerobic bacteria not considered.*

4.3 Summary of recommendations for antimicrobial therapy in urology

Diagnosis	Most frequent pathogens/species	Initial, empirical antimicrobial therapy	Therapy duration
Asymptomatic bacteriuria	*E. coli* (low virulence) Other species can also be found	No treatment Exception: before urological surgery and during pregnancy (under debate)	3 – 5 days prior to surgery according to urine culture[1]
Cystitis, acute, sporadic (uncomplicated), in otherwise healthy women	*E. coli* *Klebsiella sp.* *Proteus sp.* Staphylococci	Fosfomycin trometamol Nitrofurantoin macrocrytsal Pivmecillinam Alternative: Cephalosporin (group 1 or 2) TMP-SMX[2] Fluoroquinolone[3,4]	Single 3 g dose/1day 5 days 3-5 days 3 days 3 days 3 days
Pyelonephritis, acute, sporadic (febrile) (uncomplicated)	*E. coli* *Klebsiella sp.* *Proteus sp.* Other Enterobacteriaceae Staphylococci	Fluoroquinolone[3] Cephalosporin (group 3a) Alternative: Aminopenicillin/BLI Aminoglycoside TMP-SMX[5]	7 – 10 days 10 days After improvement, switch to oral therapy according to sensitivity test
Febrile UTI with urological complicating factors Pyelonephritis, acute, severe and complicated Healthcare associated complicated UTI	*E. coli* *Klebsiella sp.* *Proteus sp.* *Enterobacter* *Serratia* Other Enterobacteriaceae *Pseudomonas sp* High risk of multi-resistant strains Enterococci Staphylococci In case of Candida infection	Fluoroquinolone[3] Aminopenicillin/BLI Cephalosporin (group 3a) Aminoglycoside TMP-SMX[5] In case of initial failure (<3 days) Fluoroquinolone (if not initially used) Piperacillin/BLI Cephalosporin (group 3b) Carbapenem + Aminoglycoside Fluconazole Amphotericin B	7-14 days As for Pyelonephritis 3-5 days after defervescence or control/elimination of complicating factor (drainage, surgery)
Urosepsis			As above Consider combination of two antibiotics in severe infections
Prostatitis, acute bacterial (febrile) Acute Epididymitis (febrile)	*E. coli* Other Enterobacteriaceae *Pseudomonas sp.* *Enterococcus feacalis* Staphylococci	Fluoroquinolone[2] Cephalosporin (group 3a or b) Aminoglycoside TMP-SMX[5]	Initial parenteral After improvement, switch to oral therapy according to sensitivity test 2 (-4) weeks
Prostatitis, chronic bacterial		Fluoroquinolone[2] Alternative to consider based on micro-organism: TMP-SMX Doxycycline Macrolide	Oral 4-6 weeks
Prostatitis, acute/ chronic and Epididymitis caused by	*Chlamydia sp* *Ureaplasma sp*	Doxycycline Fluoroquinolone (e.g. ofloxacin, levofloxacin) Macrolide	7 (-14) days (Follow national guidelines if available)

[1] Bacteriuria is a risk factor, though no clear regimen has been defined in available literature. The given recommendation is a reasonable expert opinion

[2] Only in areas with resistance rate below 20% for E. coli

[3] fluoroquinolones with mainly renal excretion

[4] Avoid fluoroquinolones in acute sporadic cystitis whenever possible

[5] When proven sensitivity

BLI = beta-lactamase inhibitor; SMX = sulphamethoxazole; TMP = trimethoprim.

4.4. Recommendations for antimicrobial prescription in renal failure

Antibiotic	GFR (mL/min)			Comments
	Mild 50-20	**Moderate** 20-10	**Severe** <10	
*Aciclovir	normal dose every 12 h	normal dose every 24 h	50% of normal dose every 24 h	Give post-HD
Aciclovir po		Herpes simplex: normal Herpes zoster: 800 mg Total Dissolved Solids tds	Herpes simplex: 200 mg bid Herpes zoster: 800 mg bd	Give post-HD
Amikacin	5-6 mg/kg 12 h	3-4 mg/kg 24 h HD: 5 mg/kg post HD and monitor levels	2 mg/kg 24-48 h	Give post-HD Monitor pre- and 1 h post-dose levels after 3rd dose and adjust dose as required
Amoxicillin po	normal	normal	250 mg 8 h (normal)	Give post-HD
Amphotericin (Liposonal + lipid complex)	Amphotericin is highly NEPHROTOXIC. Consider using liposomal/lipid complex amphotericin. Daily monitoring of renal function (GFR) essential.			
Ampicillin IV	normal	250-500 mg 6 h	250 mg 6 h (500 mg 6 h)	Give post-HD
Benzylpenicillin	normal	75%	20-50% Max. 3.6 g/day (1.2 g qds)	Give post-HD Refer to microbiology for dosing in SBE
Caspofungin	normal	normal	normal	
Cefotaxime	normal	normal	1 g stat then 50%	Give post-HD
Cefradine	normal	normal	250 mg 6 h	Give post-HD
Ceftazidime	1 g 12 h	1 g 24 h	500 mg 24 h (1 g 24 h)	Give post-HD
Ceftriaxone	normal	normal	normal Max. 2 g/day	
Cefuroxime IV	normal	750 mg-1.5 g 12 h	750 mg 24 h (750 mg 12 h)	Give post-HD
Ciproflazin IV + po	normal	50%	50%	
Clarithromycin IV + po	normal	normal	50%	Give post-HD
Clindamycin IV + po	normal	normal	normal	
Co-amoxiclav IV (Augmentin)	normal	1.2 stat then 50% 12 h (1.2 g 12 h)	1.2 stat then 50% 24 h (1.2 g stat then 600 mg 12 h)	Give post-HD
Co-amoxiclav po (Augmentin)	normal	375-625 mg 12 h (375 mg 8 h)	375 mg 12 h (375 mg 8 h)	Give post-HD
*Co-trimoxazole IV	normal	Normal for 3/7 then 50%	50%	Give post-HD
Doxycycline	normal	normal	normal	All other tetracyclines contraindicated in renal impairment
Erythromycin IV + po	normal	normal	normal Max. 1.5 g/day (500 mg qds)	
*Ethambutol	normal	24-36 h	48 h	Give post-HD
	Monitor levels if GFR < 30 mL/min (contact Mirco)			
Flucloxacillin IV + po	normal	normal	normal Max. 4 g/day	

Fluconazole	normal	normal	50%	Give post-HD No adjustments in single-dose therapy required
*Flucytosine	50 mg/kg 12 h	50 mg/kg 24 h	50 mg/kg stat then dose according to levels	Give post-HD Levels should be monitored predialysis.
Fusidic acid	normal	normal	normal	
1) Gentamicin ONCE DAILY	**GFR 10-40 mL/min** 3 mg/kg stat (max. 300 mg) Check pre-dose levels 18-24 h after first dose Redose only when level < 1 mg/L		**GFR < 10 mL/min** 2 mg/kg (max. 200 mg) redose according to levels	BOTH METHODS Give post-HD Monitor blood levels
2) Gentamicin CONVENTIONAL	80 mg 12 h	80 mg 48 h	80 mg 24 h HD: 1-2 mg/kg Post-HD: redose according to levels	Once daily: pre only Conventional: pre and 1 h post level required
Imipenem	500 mg 8-12 h	250-500 mg bid	Risk of convulsions - use Meropenem: *see below*	Give post-HD
Isoniazid	normal	normal	200-300 mg 24 h	Give post-HD
Itraconazole	normal	normal	normal	
Levoflaxacin	500 mg stat then 250 mg bid**	500 mg stat then 125 mg bid**	500 mg stat then 125 mg od	**Applies if full dose is 500 mg bid If full dose is 500 mg od, five reduced doses daily
Linezolid	normal	normal	normal	Give post-HD
Meropenem	12 h	50% 12 h	50% 24 h	Give post-HD
Metronidazole	normal	normal	12 h (normal)	Give post-HD
Nitrofurantoin	Do **NOT** use in renal impairment			
Penicillin V	normal	normal	normal	Give post-HD
Piperacillin/ Tazobactam (Tazocin)	4.5 g 8 h	4.5 g 12 h	4.5 g 12 h	Give post-HD
Pyrazinamide	normal	normal	normal	
Rifampicin	normal	normal	50-100%	
*Teicoplanin	100% 48 h	100% 72 h	100% 72 h	Dose reduction after day 3 of therapy
Tetracycline	See **Doxycycline**			
Trimethoprim	normal	Normal for 3/7 then 50% 18 h	50% 24 h	Give post-HD
Vancomycin	1 g od Check pre-dose level before 3rd dose	1 g 48 h Check pre-dose level before 2nd dose	1 g stat (or 15 mg/kg, up to max. 2 g). Recheck level after 4-5 days ONLY give subsequent dose when level < 12mg/L	Monitor pre-dose levels and adjust dose as required
Vorinconazole	normal	normal	normal	Give post-HD

bid = twice daily; GFR = glomerular filtration rate; HD = haemodialysis; od = once daily; po = by mouth; qds = quantum dots; qid = four times daily; SBE = subacute bacterial endocarditis; tds = total dissolved solids.

4.5 Antibacterial agents

Groups	Agents
Trimethoprim-sulphonamide combinations	Trimethoprim, co-trimoxazole, co-tetroxoprime (trimethoprim plus sulfametrol)
Fluoroquinolones[1,2]	
Group 1	Norfloxacin, pefloxacin
Group 2	Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin
Group 3	Levofloxacin
Group 4	Gatifloxacin, moxifloxacin
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
Tetracyclines	Doxycycline, minocycline, tetracycline
Fosfomycin	Fosfomycin sodium, fosfomycin trometamol[3]
Nitrofuran[4]	Nitrofurantoin
Penicillins	
Benzylpenicillin	Penicillin G
Phenoxypenicillins	Penicillin V, propicillin, azidocillin
Isoxazolylpenicillins	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin
Aminobenzylpenicillins[5]	Ampicillin, amoxycillin, bacampicillin
Aminopenicillins/BLI[6]	Ampicillin/sulbactam, amoxycillin/clavulanic acid[7]
Acylaminopenicillins	Mezlocillin, piperacillin
±BLI[6]	Piperacillin/tazobactam, sulbactam[6]
Cephalosporins[1]	
Group 1 (oral)	Cefalexin, cefadroxil, cefaclor
Group 2 (oral)	Loracarbef, cefuroxime axetile
Group 3 (oral)	Cefpodoxime proxetile, cefetamet pivoxil, ceftibuten, cefixime
Group 1 (parenteral)	Cefazolin
Group 2 (parenteral)	Cefamandole, cefuroxime, cefotiam
Group 3a (parenteral)	Cefodizime, cefotaxime, ceftriaxone
Group 3b (parenteral)	Cefoperazone, ceftazidime
Group 4 (parenteral)	Cefepime, cefpirome
Group 5 (parenteral)	Cefoxitin
Monobactams	Aztreonam
Carbapenems	Imipenem, meropenem, ertapenem
Aminoglycosides	Gentamicin, netilmicin, tobramycin, amikacin
Glycopeptides	Vancomycin, teicoplanin
Oxazolidones	Linezolid

[1]Classification according to the Paul Ehrlich Society for Chemotherapy [389-391].

[2]Only in adults, except pregnant and lactating women.

[3]Only in acute, uncomplicated cystitis as a single dose.

[4]Contraindicated in renal failure and in newborns.

[5]In cases of resistance, the pathogen is most likely to be a β-lactamase producer.

[6]BLIs can only be used in combination with b-lactam antibiotics.

[7]In solution, storage instability.

Further information regarding the different antibiotics are available in the online version.

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6. CONFLICT OF INTEREST

All members of the Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.