EAU Guidelines on

Urological Infections

G. Bonkat (Co-chair), R. Pickard (Co-chair), R. Bartoletti,
F. Bruyère, S.E. Geerlings, F. Wagenlehner, B. Wullt
Guidelines Associates: T. Cai, B. Köves, A. Pilatz,
B. Pradere, R. Veeratterapillay

European
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of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Urological Infections Guidelines Panel has compiled these clinical guidelines to provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urological tract infections (UTIs). These guidelines also aim to address the important public health aspects of infection control and antimicrobial stewardship. Separate EAU guidelines documents are available addressing paediatric urological infections [1] and infections in patients with neurological urinary tract dysfunction [2].

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Infections Guidelines Panel consists of a multi-disciplinary group of urologists, with particular expertise in this area, and an infectious disease specialist. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions, which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/urologicalinfections/.

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. The 2016 document consisted of the first completed sections of an entirely new Urological Infections Guideline formulated following new EAU guideline production methodology. This 2017 document is an amalgamation of the 2015 and 2016 Guidelines and will be updated over the coming year to cover all key clinical questions related to UTIs.

2. METHODS

2.1 Introduction

For the 2017 Urological Infections Guidelines, specific chapters were updated based on systematic reviews of topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology, http://www.cochranelibrary.com/ about/about-cochrane-systematicreviews.html.

Systematic review results for the following evidence questions are included in the 2017 Urological Infections Guidelines:

1. What is the most effective management for adults with asymptomatic bacteriuria [3]?
2. What is the best antimicrobial prophylaxis strategy to reduce risk of infectious complication of prostate biopsy [4]?

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 [5]. Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

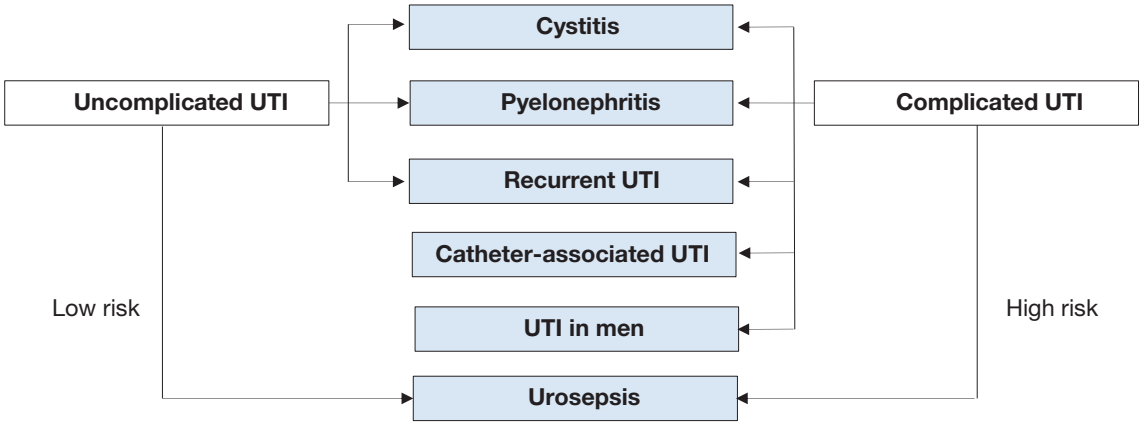
This document was subject to independent peer review prior to publication in 2015 and 2016.

3. THE GUIDELINE

3.1 Classification

Different classification systems of UTI exist. Most widely used are those developed by the Centers for Disease Control and Prevention (CDC) [6], Infectious Diseases Society of America (IDSA) [7], European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [8] as well as the U.S. Food and Drug Administration (FDA) [9, 10]. Current UTI guidelines frequently use the concept of uncomplicated and complicated UTI with a number of modifications (Figure 1). In 2011 the EAU/EAU Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation of the UTI, categorisation of risk factors and availability of appropriate antimicrobial therapy [11].

Figure 1 – Concept of uncomplicated and complicated UTI



The following classification of UTIs is adopted in the EAU Urological Infections Guidelines:

Classification of UTI	
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	Catheter-associated urinary tract infection (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours.
Urosepsis	A systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

3.2 Antimicrobial stewardship

Antimicrobial stewardship programmes aim to optimise the outcome of prevention and treatment of infection whilst curbing overuse and misuse of antimicrobial agents [12-16]. Measures of success include regulating antimicrobial prescribing, and reduction in both the rate of healthcare associated infections such as *Clostridium difficile* and the emergence of resistant organisms [16]. In urology, antimicrobial stewardship programmes should include a series of measures to ensure rational, evidence based use of antimicrobials in the prevention and treatment of infections of the urinary tract and male accessory glands, as well as non-antimicrobial strategies. Programmes require a stewardship team approach comprising urologists, infectious diseases

physicians, microbiologists and clinical pharmacologists or pharmacists [13-16].

The most important components of antimicrobial stewardship programmes are [14]:

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

Several studies in hospital settings have shown that regular ward visits and audit of practice by infectious disease physicians markedly reduce overall use of antimicrobial agents by promoting shorter duration of therapy, earlier step-down to oral medication and avoidance of antimicrobial use when patient outcome is unlikely to be compromised [16, 17]. Studies specific to the urology setting are lacking but a case-control study showed reduction in antimicrobial usage and bacterial resistance in hospitalised urology patients when EAU Guidelines on peri-operative prophylaxis were adhered to, without change in the rate of infectious complications [18].

3.3 Asymptomatic bacteriuria in adults

*3.3.1 **Evidence question***

What is the most effective management for people with asymptomatic bacteriuria?

*3.3.2 **Background***

Urinary growth of bacteria in an asymptomatic individual, asymptomatic bacteriuria (ABU), is common, and relates to commensal colonisation [19]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, therefore, treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting for antimicrobial resistance and eradicating a potentially protective ABU strain [20, 21]. The aim of this section is to support the clinician in deciding when ABU should or should not be treated.

*3.3.3 **Epidemiology, aetiology and pathophysiology***

Asymptomatic bacteriuria occurs in an estimated 1-5% of healthy pre-menopausal females, increasing to 4-19% in otherwise healthy elderly females and men, 0.7-27% in patients with diabetes, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and 23-89% in patients with spinal cord injuries [22]. Asymptomatic bacteriuria in younger men is uncommon, but when detected, 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 of risk factors (see sections 3.4 and 3.7).

*3.3.4 **Diagnostic evaluation***

Asymptomatic bacteriuria in an individual without urinary tract symptoms is defined by a mid-stream sample of urine (MSU), showing bacterial growth ≥ 10^5 cfu/mL, in two consecutive samples in women [23] and in a single sample in men [24]. 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 [22, 25]. Diagnostic work-up should include measurement of residual urine. Cystoscopy and/or imaging of the upper urinary tract is not mandatory if the patient's medical history is otherwise without remark. If persistent growth of urease producing bacteria, *i.e. Proteus mirabilis* is detected, stone formation in the urinary tract must be excluded [26]. In men, a digital rectal examination (DRE) has to be performed to rule out prostate diseases (see section 3.11).

*3.3.5 **Evidence summary***

A systematic search of the literature from January 2000 to September 2016 identified 2,853 titles of which 218 titles were selected for full text review, 61 of these texts were included in the final review [21, 27-83]. For the subgroups of pregnancy, patients scheduled for urologic surgeries, post-menopausal women and institutionalised elderly patients only data from randomised-controlled trials (RCT) was included, on which a meta-analysis was performed. For the remaining subgroups non-RCTs were also included in a narrative synthesis of the evidence. The following patient populations were not covered by the systematic review: immuno-comprised patients, patients with candiduria, dysfunctional and/or reconstructed lower urinary tracts and patients with indwelling catheters.

3.3.6 ***Disease management***

3.3.6.1 *Patients without identified risk factors*

Asymptomatic bacteriuria does not cause renal disease or damage [84]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [61], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven to be unnecessary in high-risk patient subgroups, there is panel consensus that the results of these subgroups can also be applied to patients without identified risk factors. Therefore, screening and treatment of ABU is not recommended in patients without risk factors.

3.3.6.2 *Patients with ABU and recurrent UTI, otherwise healthy*

One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI and without identified risk factors [21] and demonstrated that treatment of ABU increases the risk of a subsequent symptomatic UTI episode, as compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; 673 patients). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI. Therefore, treatment of ABU is not recommended. However, occasionally the eradication of a strain considered the causative agent of recurrent episodes of UTI, may be justified. In men with recurrent symptomatic UTI and ABU, chronic bacterial prostatitis must be considered and, if diagnosed, treated (see chapter 3.11).

3.3.6.3 *Pregnant women*

3.3.6.3.1 Is treatment of ABU beneficial in pregnant women?

Twelve RCTs comparing antimicrobial treatment of ABU with placebo controls or no treatment [27, 29, 38, 39, 42, 44, 45, 48, 50, 54, 55, 57], with different antibiotic doses and regimens were identified. Eleven RCTs (n=2,002) reported on the rate of symptomatic UTIs [27, 29, 33, 38, 42, 44, 45, 48, 50, 54, 55]. Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment (average (RR) 0.20, 95% CI 0.10 to 0.39).

Six RCTs reported on the resolution of bacteriuria [38, 39, 42, 44, 50, 55]. Antibiotic treatment was effective in the resolution of bacteriuria compared to placebo (average RR 2.99, 95% CI 1.65 to 5.39; n=716). Eight RCTs reported on the rate of low birthweights [27, 33, 38, 42, 44, 45, 54, 57]. Antibiotic treatment was associated with lower rates of low birthweight compared to placebo or no treatment (average RR 0,58, 95% CI 0.36 to 0.94; n=1,689). Four RCTs reported on the rate of pre-term deliveries [33, 54, 55, 57]. Antibiotic treatment was associated with lower rate of pre-term delivery compared to placebo or no treatment (average RR 0,34, 95% CI 0.18 to 0.66; n-854).

Based on the beneficial maternal and fetal effects of antibiotic treatment pregnant women should be screened and treated for ABU. However, the panel would like to emphasise that most available studies have low methodological quality and are from the 60's to 80's. Diagnostic and treatment protocols and accessibility to medical services has dramatically changed since then; therefore, the quality of evidence for this recommendation is low. In newer studies of higher methodological quality the beneficial effects of antibiotic treatment are not as evident [33]. Therefore, it is advisable to also consult national recommendations for the treatment of ABU in pregnant women.

3.3.6.3.2 Which treatment duration should be applied to treat ABU in pregnancy?

Sixteen RCTs comparing the efficacy of different antibiotic treatments in pregnant women with ABU were identified [28, 32, 34-37, 40, 41, 43, 46, 47, 49, 51-53, 56]. There was significant heterogeneity amongst the studies. Studies compared different antibiotic regimens or the same antibiotic regimens with different durations. The duration of treatment ranged from single dose to continuous treatment (until delivery). For practical purposes the grouping strategy used by the previously published Cochrane Review by Widmer et. al., was adopted with some modifications [85]. The following treatment groups were used for comparison:

1. single dose (single day);
2. short course (2-7 days);
3. long course (8-14 days);
4. continuous (until delivery).

Nine studies compared single dose to short course treatment [28, 34, 35, 40, 41, 46, 47, 49, 53], one study compared single dose to long course treatment [52] and one study compared long course to continuous treatment [56]. As long term and continuous antibiotic treatment is not used in current practice, only studies comparing single dose to standard short course treatment are presented.

3.3.6.3.2.1 Single dose vs. short course treatment

Three RCTs reported on the rate of symptomatic UTIs [34, 40, 46], with no significant difference between the two durations (average RR 1.00, 95% CI 0.58 to 1.71; n=891). Nine RCTs reported on the rate of ABU resolution [28, 34, 35, 40, 41, 46, 47, 49, 53], with no significant difference between the two durations (average RR 0.95, 95% CI 0.90 to 1.01; 1268 women). Six RCTs reported on the rate of side effects [34, 35, 40, 41, 49, 53]. Single dose treatment was associated with significantly less side effects compared to short course treatment (average RR 0.34, 95% CI 0.19 to 0.62; 458 women). Three RCTs reported on the rate of pre-term deliveries [34, 46, 51], with no significant difference between the two durations (average RR 1.15, 95% CI 0.75 to 1.76; 814 women). One RCT reported on the rate of low birthweights [46]. There were significantly more babies with low birthweight in the single dose regimen compared to short course treatment (average RR 1.65, 95% CI 1.06 to 2.57; 714 women).

According to the data analysis, single dose treatment was associated with a significantly lower rate of side effects but a significantly higher rate of low birthweight. Therefore, standard short course treatment should be applied to treat ABU in pregnancy, however it should be emphasised that the overall quality of the scientific evidence backing this recommendation is low.

3.3.6.4 Patients with identified risk-factors

3.3.6.4.1 Diabetes mellitus

Diabetes mellitus, even when well regulated, is reported to correlate to a higher frequency of ABU [86]. One RCT demonstrated that eradicating ABU did not reduce the risk of symptomatic UTI and infectious complications in patients with diabetes mellitus. The time to first symptomatic episode was also similar in both groups. Furthermore, untreated ABU did not correlated to diabetic nephropathy [87]. Screening and treatment of ABU in well-regulated diabetes mellitus is therefore not recommended. However, poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications.

3.3.6.4.2 ABU in post-menopausal women

Elderly women have an increased incidence of ABU [88]. Four RCTs compared antibiotic treatment of ABU with placebo controls or no treatment, in a post-menopausal female population, with different antibiotic doses and regimens [65-67, 70]. Women in these studies were mostly nursing home residents, which may bias the results of this analysis. Three RCTs reported on the rate of symptomatic UTIs (average RR 0.71, 95% CI 0.49 to 1.05; 208 women) and the resolution of bacteriuria (average RR 1.28, 95% CI 0.50 to 3.24; 203 women) [34, 40, 46], with no significant benefit of antibiotic treatment. Therefore, ABU in post-menopausal women does not require treatment, and should be managed as for pre-menopausal women.

3.3.6.4.3 Elderly institutionalised patients

The rate of ABU is 15-50% in elderly institutionalised patients [89]. Differential diagnosis of ABU from symptomatic UTI is difficult in the multi-diseased and mentally deteriorated patient, and is probably a cause of unnecessary antibiotic treatment [90, 91]. Seven RCTs compared antibiotic treatment of ABU with placebo controls or no treatment in elderly patients, with different antibiotic doses and regimens [63, 65-67, 70, 72, 73].

Three RCTs reported on the rate of symptomatic UTIs [63, 65, 67]. Antibiotic treatment was not significantly beneficial in reducing the rate of symptomatic UTIs compared to placebo or no treatment (average RR 0.68, 95% CI 0.46 to 1.00; 210 patients). Six RCTs reported on the resolution of bacteriuria [63, 65, 67, 70, 72, 73]. There was no benefit of antibiotic treatment compared to placebo in the resolution of ABU (average RR 1.33, 95% CI 0.63 to 2.79; 328 patients). One RCT compared the rates of incontinence in this patient group before and after the eradication of ABU, and found no effect of antibiotic treatment [71]. Therefore, screening and treatment of ABU is not recommended in this patient group.

3.3.6.4.4 Patients with renal transplants

One RCT, one prospective non-randomised and two retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients [74-76, 80]. None of the studies found antibiotic treatment beneficial in terms of reducing the rate of ABU or symptomatic UTIs. Furthermore, there were no significant differences in the rate of graft loss or change in renal function during long-term follow-up [74-76, 80]. Therefore, treatment of ABU is not recommended in renal transplant recipients.

3.3.6.4.5 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, spinal cord injury patients, 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 [92, 93]. Studies have shown no benefit in ABU treatment in these patient groups [92, 94]. Furthermore, in LUTD patients who do not

spontaneously develop ABU, deliberate colonisation with an ABU strain (*Escherichia coli* 83972) has shown a protective effect against symptomatic recurrences [95, 96]. Screening and treatment of ABU in these patient groups is therefore, not recommended. If these patient groups develop recurrent symptomatic UTI (see section 3.5) the potential protective effect of a spontaneously developed ABU against lower UTI must be considered before any treatment.

3.3.6.4.6 Patients with catheters in the urinary tract

Patients with indwelling or suprapubic catheters, and nephrostomy tubes, invariably become carriers of ABU, with antibiotic treatment showing no benefit. This is also applicable for patients with ABU and indwelling ureteral stents [97]. Routine treatment of catheter associated bacteriuria is not recommended. For detailed recommendations see section 3.8.

3.3.6.4.7 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 in itself, and should not be screened or treated [98]. In patients subjected to placement/ exchanges of nephrostomy tubes and indwellling ureteral stents, ABU is considered a risk factor for infectious complications [99]. Therefore, screening and treatment prior to the procedure is recommended.

3.3.6.4.8 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 reviewed in each case. 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 [100].

3.3.6.5 Prior to urological surgery

In diagnostic and therapeutic procedures not entering the urinary tract, ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary. 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.

Two RCTs [78, 81] and two prospective non-randomised studies [82, 83] compared the effect of antibiotic treatment to no treatment prior to transurethral prostate or bladder tumour resection. Antibiotic treatment significantly reduced the number of post-operative symptomatic UTIs compared to no treatment in the meta-analysis of the two RCTs (average RR 0.19, 95% CI 0.05 to 0.82; 167 patients). The rates of post-operative fever and septicaemia were also significantly lower in case of antibiotic treatment compared to no treatment in the two RCTs.

A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment should be given. The recommendations for antibiotic prophylaxis in different urological procedures are given in section 3.15.

3.3.6.6 Prior to orthopaedic surgery

One RCT and one multicentre cohort study comparing the treatment of ABU with no treatment prior to orthopaedic surgery (hip arthroplasty/hemiarthroplasty or total knee arthroplasty) were identified [101, 102]. None of the studies showed a beneficial effect of antibiotic treatment in terms of prosthetic joint infection. One study measured the rate of post-operative symptomatic UTIs and found no significant difference between antibiotic treatment and no treatment [102]. Therefore, treatment of bacteriuria is not recommended prior to arthroplasty surgery.

3.3.6.7 Pharmacological management

If the decision is taken to eradicate ABU, the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (section 3.4.4.4) or complicated (section 3.7.5) UTI could be given, depending on gender, medical background and presence of complicating factors. Treatment should be tailored and not empirical. Based on clinical experience, if ABU patients complain of odour and mild dysuria, methenamine hippurate 1 g two to three times daily, and/or increased water intake, may be considered.

3.3.7 ***Follow-up***

There are no studies focusing on follow-up after treatment of ABU. However, if the resolution of ABU has a clinical significance (e.g. in pregnancy), follow-up with subsequent urine culture is needed to secure the treatment effect.

3.3.8 *Recommendations for the management of ABU*

Recommendations	LE	GR
Do not screen or treat asymtomatic bacteriuria in the following conditions:		
• women without risk factors;	2a	A*
• patients with well-regulated diabetes mellitus;	1b	A
• post-menopausal women;	1a	A
• elderly institutionalised patients;	1a	A
• patients with dysfunctional and/or reconstructed lower urinary tracts;	2b	B
• patients with catheters in the urinary tract;	4	C
• patients with renal transplants;	1b	A
• patients prior to arthoplasty surgeries;	1b	A
• patients with recurrent urinary tract infections.	1b	A
Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	1a	A
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.	1a	A
Take a urine culture following treatment of asymptomatic bacteriuria to secure treatment effect.	4	C

** Upgraded based on panel consensus*

3.4 Uncomplicated cystitis

3.4.1 *Introduction*

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

3.4.2 *Epidemiology, aetiology and pathophysiology*

Almost half of all women will experience at least one episode of cystitis during their lifetime. Nearly one in three women will have had at least one episode of cystitis by the age of 24 years [103]. Risk factors include sexual intercourse, use of spermicide, a new sexual partner, a mother with a history of UTI and a history of UTI during childhood. The spectrum of aetiological agents is similar in uncomplicated cystitis and pyelonephritis, with *E. coli* being the causative pathogen in 70-95% of cases and *Staphylococcus saprophyticus* in 5-10%. Occasionally, other Enterobacteriaceae, such as *P. mirabilis* and *Klebsiella spp*., are isolated [104].

3.4.3 *Diagnostic evaluation*

3.4.3.1 *Clinical diagnosis*

The diagnosis of 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 [105, 106]. In elderly women genitourinary symptoms are not necessarily related to cystitis [107].

3.4.3.2 *Differential diagnosis*

Uncomplicated cystitis should be differentiated from ABU, which is considered not to be infection but rather a commensal colonisation, which should not be treated and therefore not screened for, except if it is considered a risk factor in clearly defined situations see section 3.3.

3.4.3.3 *Laboratory diagnosis*

Urine dipstick testing is a reasonable alternative to culture for diagnosis of uncomplicated cystitis [108, 109]. Urine cultures are recommended in the following situations:

- suspected acute pyelonephritis;
- symptoms that do not resolve or recur within two to four weeks after the completion of treatment;
- women who present with atypical symptoms [110, 111];
- pregnant women;
- males with suspected UTI.

A colony count of 10^3 cfu/mL of uropathogens is microbiologically diagnostic in women who present with symptoms of uncomplicated cystitis [112]. Women who present with atypical symptoms of either uncomplicated cystitis or uncomplicated pyelonephritis, as well as those who fail to respond to appropriate antimicrobial therapy should be considered for additional diagnostic studies.

3.4.3.4 Recommendations for the diagnostic evaluation of uncomplicated cystitis

Recommendations	LE	GR
Diagnose uncomplicated cystitis based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated urinary tract infections.	2a	B
Use urine dipstick testing, as an alternative to culture for diagnosis of acute uncomplicated cystitis.	2a	B
Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within two-four weeks after the completion of treatment; • women who present with atypical symptoms; • pregnant women.	4	B*

** Upgraded based on panel consensus*

*3.4.4 **Disease management***

Antimicrobial therapy is recommended because clinical success is significantly more likely in women treated with antimicrobials compared with placebo [113]. The choice of antimicrobial therapy should be guided by [105]:

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

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day for three to five days, and nitrofurantoin macrocrystal 100 mg twice daily for 5 days, are considered as drugs of first choice, when available [114-116].

Alternative antimicrobials include trimethoprim alone or combined with a sulphonamide. Co-trimoxazole (160/800 mg twice daily of three days) or trimethoprim (200 mg twice daily for five days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [117, 118]. Despite lower resistance rates in certain countries, fluoroquinolones are not considered first choice because of adverse effects including negative ecological effects and selection for resistance.

Aminopenicillins are no longer suitable for empirical therapy because of worldwide high *E. coli* resistance. Aminopenicillins in combination with a beta-lactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins are in general not effective as short-term therapy and are not recommended for empirical therapy due to ecological collateral damage, but may be used in selected cases [119, 120].

3.4.4.1 Cystitis in pregnancy

Short courses of antimicrobial therapy can also be considered for treatment of cystitis in pregnancy [121], but not all antimicrobials are suitable during pregnancy. In general penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of glucose-6-phosphate dehydrogenase deficiency and during the end of pregnancy), trimethoprim (not in the first trimenon) and sulphonamides (not in the last trimenon), can be considered.

3.4.4.2 Cystitis in men

Uncomplicated cystitis without involvement of the prostate is uncommon, and therefore treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI. A treatment duration of at least seven days is recommended, preferably with trimethoprim sulphamethoxazole or a fluoroquinolone if in accordance with susceptibility testing (see section 3.4.4.4) [122].

3.4.4.3 *Renal insufficiency*

In patients with renal insufficiency the choice of antimicrobials may be influenced by decreased renal excretion. However, most antimicrobials, have a wide therapeutic index. No adjustment of dose is necessary until glomerular filtration rate (GFR) is < 20 mL/min, except for antimicrobials 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 [122].

3.4.4.4 *Recommendations for antimicrobial therapy for uncomplicated cystitis*

Recommendations					
Antimicrobial	**Daily dose**	**Duration of therapy**	**Comments**	**LE**	**GR**
First choice					
Fosfomycin trometamol	3 g SD	1 day	Recommended in women not men.	1	A
Nitrofurantoin macrocrystal	100 mg b.i.d	5 days			
Pivmecillinam	400 mg t.i.d	3-5 days			
Alternatives					
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable.	1b	B
If the local resistance pattern for E. coli is < 20%					
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy.	1b	B
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy.		
Treatment in men					
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.	4	C

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

3.4.5 ***Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [123]. In women whose symptoms do not resolve by end of treatment, and in those whose symptoms resolve but recur within two weeks, urine culture and antimicrobial susceptibility testing should be performed [124]. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a seven day regimen using another agent should be considered [124].

3.5 Recurrent UTIs

3.5.1 ***Introduction***

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated aetiology.

3.5.2 ***Diagnostic evaluation***

Recurrent UTIs are common. Risk factors are outlined in Table 1. Diagnosis of rUTI should be confirmed by urine culture. An extensive routine workup including cystoscopy, imaging, etc. is not routinely recommended as the diagnostic yield is low [125]. However, it should be performed without delay in atypical cases, for example, if renal calculi or outflow obstruction is suspected.

Table 1: Age-related risk factors for rUTI in women [89, 107, 126]

Young and pre-menopausal women	Post-menopausal 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	Blood group antigen secretory status
	Urine catheterisation and functional status deterioration in elderly institutionalised women

*3.5.3 **Disease management and follow-up***

Prevention of rUTIs includes counselling regarding avoidance of risk factors, non-antimicrobial measures and antimicrobial prophylaxis [124]. These interventions should be attempted in this order. Any urological risk factors must be identified and treated. Significant residual urine should be treated optimally, including by clean intermittent catheterisation when judged to be appropriate.

3.5.3.1 Behavioural modifications

A number of behavioural and personal hygiene measures (e.g. reduced fluid intake, habitual and post-coital delayed urination, wiping from back to front after defection, douching and wearing occlusive underwear) have been suggested to decrease the risk of rUTI. However, studies that have explored these risk factors have consistently documented the lack of association with rUTI [124].

3.5.3.2 Non-antimicrobial prophylaxis

There are many non-antimicrobial measures recommended for rUTIs but only a few are supported by well-designed studies [127, 128].

3.5.3.2.1 Hormonal replacement

In post-menopausal women vaginal oestrogen replacement, but not oral oestrogen, showed a trend towards preventing rUTI [127, 129].

3.5.3.2.2 Immunoactive prophylaxis

OM-89 (Uro-Vaxom®) is sufficiently well documented and has been shown to be more effective than placebo in several randomised trials with a good safety profile. Therefore, it can be recommended for immunoprophylaxis in female patients with rUTIs [127, 130-132]. Efficacy in other groups of patients and relative to antimicrobial prophylaxis remains to be established.

The vaginal vaccine Urovac® slightly reduced rUTIs. Primary immunisation followed by booster immunisation increased time to re-infection [127].

3.5.3.2.3 Prophylaxis with probiotics (*Lactobacillus* spp.)

Pooled data from a recent meta-analysis shows no convincing benefit of lactobacillus products as prophylaxis for rUTI [133]. However, differences in effectiveness between available preparations suggest further trials are needed before any definitive recommendation for or against their use can be made.

3.5.3.2.4 Prophylaxis with cranberry

Limited studies have suggested that cranberry is useful in reducing the rate of lower UTIs in women [134, 135]. However, a meta-analysis including 24 studies and comprising 4,473 participants showed that cranberry products did not significantly reduce the occurrence of symptomatic UTI for women with rUTI [136]. Due to these contradictory results, no recommendation on the daily consumption of cranberry products can be made.

3.5.3.2.5 Prophylaxis with D-mannose

In a randomised placebo-controlled non-blinded clinical trial, it was shown that a daily dose of 2 g D-mannose was significantly superior to placebo and as effective as 50 mg nitrofurantoin in preventing rUTI [137]. This is indicative but not sufficient for a recommendation therefore, D-mannose should at present only be used within the context of clinical investigations.

3.5.3.2.6 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 rUTI [138]. A recent review of 27 clinical studies concluded that large-scale trials are urgently needed to assess the benefit of this type of therapy [139]. Therefore, no general recommendation is possible at this stage.

3.5.3.3 Antimicrobials for preventing rUTI

3.5.3.3.1 Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis

Antimicrobials may be given as continuous low-dose prophylaxis for longer periods (three to six months), or as post-coital prophylaxis, as both regimens reduce the rate of rUTI [140]. It is mandatory to offer both options after counselling, and when behavioural modifications and non-antimicrobial measures have been unsuccessful. Regimens include nitrofurantoin 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every ten days, and during pregnancy cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [124]. Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [141].

3.5.3.3.2 Self-diagnosis and self-treatment

In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [142]. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI (section 3.4.4.4).

*3.5.4 **Recommendations for the diagnostic evaluation and treatment of rUTIs***

Recommendations	LE	GR
Do not perform an extensive routine workup in women with recurrent UTI without risk factors.	1b	B
Advise patients on behavioural modifications which might reduce the risk of recurrent UTI.	3	C
Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.	1b	A
Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	1a	A
When non-antimicrobial interventions have failed, continuous or post-coital antimicrobial prophylaxis should be used to prevent recurrent UTI, but patients should be counselled regarding possible side effects.	2b	B
For patients with good compliance, self-administrated short term antimicrobial therapy should be considered.	2b	A*

** Upgraded based on panel consensus.*

3.6 Uncomplicated pyelonephritis

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

*3.6.1 **Diagnostic evaluation***

3.6.1.1 Clinical diagnosis

Pyelonephritis is suggested by fever (> 38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis [143]. Pregnant women with acute pyelonephritis need special attention, as 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 child with more frequent pre-term labour and birth [144].

3.6.1.2 Differential diagnosis.

It is vital to differentiate as soon as possible between uncomplicated and complicated mostly obstructive pyelonephritis, as the latter can rapidly lead to urosepsis. This differential diagnosis should be made by the appropriate imaging technique (see section 3.6.1.4).

3.6.1.3 Laboratory diagnosis

Urinalysis including the assessment of white and red blood cells and nitrite, is recommended for routine diagnosis [145]. In addition, urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis.

3.6.1.4 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary obstruction or renal stone disease [146]. 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 hours of treatment [146]. For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus [146].

*3.6.2 **Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis***

Recommendations	LE	GR
Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	4	A*
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	4	A*
Perform ultrasound of the upper urinary tract to exclude obstructive pyelonephritis.	4	A*
Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.	4	A*

**Upgraded based on panel consensus.*

*3.6.3 **Disease management***

3.6.3.1 Outpatient treatment

Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis. However, oral cephalosporines achieve significantly lower concentrations than intravenous cephalosporines. Local fluoroquinolone resistance should be < 10%. Other agents such as nitrofurantoin, fosfomycin, and pivmecillinam should be avoided because these agents do not achieve adequate renal tissue levels [147]. In the setting of fluoroquinolone hypersensitivity or known resistance, other acceptable choices include trimethoprim-sulfamethoxazole (160/800 mg) or an oral beta-lactam, if the uropathogen is known to be susceptible. If such agents are used in the absence of antimicrobial susceptibility results, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.

3.6.3.2 Inpatient treatment

Patients with uncomplicated pyelonephritis requiring hospitalisation should be treated initially with an intravenous antimicrobial regimen such as a fluoroquinolone, an aminoglycoside (with or without ampicillin), an extended-spectrum cephalosporin, an extended-spectrum penicillin, or a carbapenem [148]. The choice between these agents should be based on local resistance patterns and optimised on the basis of drug susceptibility results. In patients presenting with signs of urosepsis empiric antimicrobial coverage for extended-spectrum beta-lactamases (ESBL)-producing organisms is warranted [149]. Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antimicrobial therapy [150].

3.6.3.2.1 Recommendations for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

Recommendations					
Antimicrobial	**Daily dose**	**Duration of therapy**	**LE**	**GR**	**Comments**
Ciprofloxacin	500-750 mg b.i.d	7-10 days	1b	B	Fluoroquinolone resistance should be less than 10 percent.
Levofloxacin	750 mg q.d	5 days	1b	B	
Trimethoprim sulphamethoxazol	160/800 mg b.i.d	7-14 days	1b	B	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	4	B*	
Ceftibuten	400 mg q.d	10 days	4	B*	

**Upgraded based on panel consensus.*
b.i.d = twice daily; q.d = every day.

3.6.3.2.2 Recommendations for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Recommendations				
Antimicrobials	**Daily dose**	**LE**	**GR**	**Comments**
Ciprofloxacin	400 mg b.i.d	1b	B	
Levofloxacin	750 mg q.d	1b	B	
Cefotaxime	2 g t.i.d	2	A*	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftazidime	1-2 g t.i.d	2	A*	
Co-amoxiclav	1.5 g t.i.d	2	C	Not studied as monotherapy in acute uncomplicated pyelonephritis. Mainly for Gram-positive pathogens.
Ceftriaxone	1-2 g q.d	1b	A*	Lower dose studied, but higher dose recommended. Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Cefepime	1-2 g b.i.d	1b	B	
Piperacillin/tazobactam	2.5-4.5 g t.i.d	1b	A*	
Ceftolozane/tazobactam	1.5 g t.i.d	1b	B	
Ceftazidime/avibactam	2.5 g t.i.d	1b	B	
Gentamicin	5 mg/kg q.d	1b	B	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	1b	B	
Ertapenem	1 g q.d	1b	B	Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Imipenem/cilastatin	0.5/0.5 g t.i.d	1b	B	
Meropenem	1 g t.i.d	2	B	
Doripenem	0.5 g t.i.d	1b	B	

** Upgraded based on panel consensus.*
b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

In pregnant women with pyelonephritis, outpatient management with appropriate antimicrobials may also be considered, provided symptoms are mild and close follow-up is feasible [151, 152]. 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 seven to ten days. In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of two weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent [153].

*3.6.4 **Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated, except in pregnant women, if asymptomatic bacteriuria is an issue (see section 3.3.6.3).

3.7 Complicated UTIs

*3.7.1 **Introduction***

A complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection [154-156]. The underlying factors that are generally accepted to result in a cUTIs are outlined in Table 2. The designation of cUTI encompasses a wide variety of underlying conditions that result in a remarkably heterogeneous patient population. Therefore, it is readily apparent that a universal approach to the evaluation and treatment of cUTIs is not sufficient, although there are general principles of management that can be applied to the majority of patients with cUTIs. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [157].

Table 2: Factors associated with complicated UTIs [154-156]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes
Vesicoureteral reflux	Immunosuppression
Recent history of instrumentation	Healthcare-associated infections

*3.7.2 **Diagnostic evaluation***

3.7.2.1 Clinical presentation

A cUTI is 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 be atypical for example, in neuropathic bladder disturbances or catheter-associated UTI (CA-UTI). Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. Clinicians must also recognise that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as, for example, benign prostatic hyperplasia and autonomic dysfunction in patients with spinal lesions and neurogenic bladders. Concomitant medical conditions, such as diabetes mellitus and renal failure, which can be related to urological abnormalities, are often also present in a cUTI.

3.7.2.2 Urine culture

Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI.

*3.7.3 **Microbiology (spectrum and antimicrobial resistance)***

A broad range of microorganisms cause cUTIs. The spectrum is much larger than in uncomplicated UTIs and the bacteria are more likely to be resistant (especially in treatment-related cUTI) than those isolated in uncomplicated UTIs [158, 159]. *E. coli, Proteus spp., Klebsiella spp., Pseudomonas spp., Serratia spp*. and *Enterococcus spp*. are the most common strains found in cultures. Enterobacteriaceae predominate (60-75%), 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 [160].

*3.7.4 **General principles of cUTI treatment***

Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antimicrobial agent on the basis of the isolated uropathogen.

3.7.4.1 Choice of antimicrobials

In the recently updated IDSA guidelines for the treatment of uncomplicated UTI, it is recommended that the resistance percentages of causative micro-organisms must be < 20% to consider an agent suitable for empirical treatment of a lower UTI and must be < 10% for treatment of an upper UTI. Considering the current resistance percentages of amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, it can be concluded that these agents are not suitable for the empirical treatment of pyelonephritis in a normal host and, therefore, also not for treatment of all cUTIs [161]. The same applies to ciprofloxacin and other fluoroquinolones in urological patients [161].

Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin or a second or third generation cephalosporin or an extended-spectrum penicillin with or without an aminoglycoside [157]. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results [147]. These recommendations are not only suitable for pyelonephritis but for all other cUTIs.

In view of the high degree of resistance, particularly among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last six months [162]. Fluoroquinolones can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to beta-lactam antimicrobials.

3.7.4.2 Duration of antimicrobial therapy

Treatment for seven to fourteen days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality [7].

3.7.5 ***Recommendations for the treatment of complicated UTIs.***

Recommendations	LE	GR
Do not use amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole for empirical treatment of complicated UTI.	2	A
Use the combination of: • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms.	2	A
Only use ciprofloxacin provided that the local resistance percentages are < 10% when; • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials.	2	A
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from the urology department or when patients have used fluoroquinolones in the last six months.	2	A
Use an initial one-time intravenous dose of a long-acting antimicrobial, such as a third generation cephalosporin or an aminoglycoside if the prevalence of fluoroquinolone resistance is thought to be > 10% and resistance data are pending.	2	A
If the prevalence of fluoroquinolone resistance is thought to be > 10% and the patient has contra indications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with uncomplicated pyelonephritis.	2	A
In the event of hypersensitivity to penicillin, a third generation cephalosporin can still be prescribed, with the exception of systemic anaphylaxis in the past.	2	A
In patients with a UTI with systemic symptoms, empirical treatment should cover ESBL in the initial treatment only in patients who are colonised with ESBL-producing micro-organisms. The resistance pattern of the ESBL strain should guide empirical therapy.	2	A

ESBL = Extended-spectrum beta-lactamase.

3.8 Catheter-associated UTIs

3.8.1 ***Introduction***

Catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours. The urinary catheter literature is problematic as many published studies use the term CA-bacteriuria without providing information on what proportion are CA-ABU and CA-UTI, and some studies use the term CA-UTI when referring to CA-ABU or CA-bacteriuria [158]. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [157] as well as the IDSA Guidelines [158].

3.8.2 ***Epidemiology, aetiology and pathophysiology***

Catheter-associated UTIs are the leading cause of secondary health care-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract, and the mortality associated with this condition is approximately 10% [163]. The incidence of bacteriuria associated with indwelling catheterisation is 3-8% per day [164-168]. The duration of catheterisation is presumable the most important risk factor for the development of a CA-UTI [169, 170]. Urinary catheterisation perturbs host defence mechanisms and provides easier access of uropathogens to the bladder. Indwelling urinary catheters facilitate colonisation with uropathogens by providing a surface for the attachment of host cell binding receptors recognised by bacterial adhesins, thus enhancing microbial adhesion. In addition, the uroepithelial mucosa is disrupted, exposing new binding sites for bacterial adhesins, and residual urine in the bladder is increased through pooling below the catheter bulb [171]. Catheter-associated UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens.

3.8.3 ***Diagnostic evaluation***

3.8.3.1 Clinical diagnosis

Signs and symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental

status, malaise, or lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed dysuria, urgent or frequent urination and suprapubic pain or tenderness [157]. In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI [157, 158].

3.8.3.2 Laboratory diagnosis

Microbiologically CA-UTI is defined by microbial growth of ≥ 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours. In catheterised patients, pyuria is not diagnostic for CA-UTI. The presence, absence, or degree of pyuria should not be used to differentiate CA-ABU from CA-UTI. Pyuria accompanying CA-ABU should not be interpreted as an indication for antimicrobial treatment. The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI [158].

3.8.3.3 Recommendations for diagnostic evaluation of CA-UTI

Recommendations	LE	GR
Do not carry out routine urine culture in an asymptomatic catheterised patients.	1a	A
Do not use pyuria as an indicator for catheter-associated UTI.	2	A
Do not use the presence, absence, or degree of pyuria to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	2	A
Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	3	C

3.8.4 ***Disease management***

A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for presumed CA-UTI due to the wide spectrum of potential infecting organisms and the increased likelihood of antimicrobial resistance. The urine culture should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy [158].

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and two to fourteen days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterised or not [158]. A five-day regimen of levofloxacin may be considered in patients with CA-UTI who are not severely ill. Data are insufficient to make such a recommendation about other fluoroquinolones.

A three-day antimicrobial regimen may be considered for women aged ≤ 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed. If an indwelling catheter has been in place for twelve weeks at the onset of CA-UTI and is still indicated, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI. If use of the catheter can be discontinued, a culture of a voided midstream urine specimen should be obtained prior to the initiation of antimicrobial therapy to help guide treatment [158].

3.8.4.1 Recommendations for disease management and prevention of CA-UTI

Recommendations	LE	GR
Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.	3	A*
Do not treat catheter-associated asymptomatic bacteriuria in general.	1a	A
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	1a	A
Replace or remove the indwelling catheter before starting antimicrobial therapy.	4	B*
Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	1a	A
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	1a	A
The duration of catheterisation should be minimal.	2a	B
Remove an indwelling catheter after non-urological operation within the same day.	1b	B
Change long-term indwelling catheters at intervals adapted to the individual patient.	3	C

** Upgraded based on panel consensus.*

3.8.5 *Follow-up*

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated.

3.9 Urosepsis

3.9.1 *Introduction*

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a cUTI. Systemic inflammatory response syndrome (SIRS), characterised by fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia and tachypnoea, is recognised as the first event in a cascade leading to multi-organ failure (Figure 2). Mortality is considerably increased the more severe the sepsis is.

The treatment of urosepsis involves adequate life-supporting care, appropriate and prompt antimicrobial therapy, adjunctive measures and the optimal management of urinary tract disorders [172]. The decompression of any obstruction and drainage of larger infectious abscess in the urinary tract is essential as first-line focus control [172]. Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists.

Urosepsis is seen in both community-acquired and healthcare associated infections. Nosocomial urosepsis may be reduced 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 aseptic techniques to avoid cross-infection.

Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

3.9.2 *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 a very short time.

Mortality rates associated with severe sepsis vary depending on the organ source [173] with urinary tract sepsis generally having a lower mortality than that from other sources [174]. Sepsis is more common in men than in women [175]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [173], 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) [176]. 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 [177, 178].

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 and patients receiving cancer chemotherapy or corticosteroids. 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.

3.9.3 *Diagnostic evaluation*

Clinical diagnosis of a UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. Table 3 details the current criteria for the diagnosis of sepsis and septic shock.

Table 3. Definition and criteria of sepsis and septic shock [179-181]

Disorder	Definition
Systematic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may also be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following criteria: • temperature > 38°C or < 36°C; • heart rate > 90 bpm; • respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg (< 4.3 kPa); • white blood cell count > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms.
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. For rapid identification a quickSOFA (qSOFA) score was developed: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less.
Septic shock	Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

*3.9.4 **Physiology and biochemical markers***

E. coli remains the most prevalent microorganism. In several countries, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [178]. 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.

3.9.4.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis syndrome [174]. They are molecules 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. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. 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 [174].

3.9.4.2 Procalcitonin and mid-regional proadrenomedulline

Procalcitonin is the inactive pro-peptide of calcitonin. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels rise [182]. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. Mid-regional proadrenomedulline is another sepsis marker. Mid-regional proadrenomedullin has been shown to play a decisive role in the induction of hyperdynamic circulation during the early stages of sepsis and progression to septic shock [183]. Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [182, 184]. In addition serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [185]. Serum lactate should therefore also be monitored in patients with severe infections.

*3.9.5 **Disease management***

3.9.5.1 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Urosepsis treatment requires a combination of treatment including treatment of the cause (obstruction of the urinary tract), adequate life-support care, and appropriate antimicrobial therapy [174]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3.9.5.1.1 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 [186, 187] they include:

- 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 [188]. 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.

3.9.5.1.2 Appropriate peri-operative antimicrobial prophylaxis

For appropriate peri-operative antimicrobial prophylaxis see section 3.15. The potential side-effects of antibiotics must be considered before their administration in a prophylactic regimen.

3.9.5.2 Treatment

During the first six hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following:

- central venous pressure (CVP) 8-12 mmHg;
- mean arterial pressure (MAP) 65-90 mmHg;
- central venous oxygen (CVO2) > 70%;
- haematocrit (HKT) > 30 %;
- urine output > 0.5 mL/kg/hr.

Early goal-directed resuscitation was initially shown to improve survival for emergency department patients presenting with septic shock in a randomised, controlled, single-centre study [189]. However, recent follow up studies in an improved emergency medicine background have not achieved positive effects with this strategy [190-192].

3.9.5.2.1 Antimicrobial therapy

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available [172]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure [172]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis (Figure 2) [172].

3.9.5.2.1.1 Recommendations for parenteral antimicrobial therapy of urosepsis

Recommendations				
Antimicrobials	**Daily dose**	**LE**	**GR**	**Comments**
Cefotaxime	2 g t.i.d	2	A*	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftazidime	1-2 g t.i.d	2	A*	
Ceftriaxone	1-2 g q.d	1b	A*	Lower dose studied, but higher dose recommended. Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Cefepime	1-2 g b.i.d	1b	B	
Piperacillin/tazobactam	2.5-4.5 g t.i.d	1b	A*	
Ceftolozane/tazobactam	1.5 g t.i.d	1b	B	
Ceftazidime/avibactam	2.5 g t.i.d	1b	B	
Gentamicin	5 mg/kg q.d	1b	B	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	1b	B	
Ertapenem	1 g q.d	1b	B	Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Imipenem/cilastatin	0.5/0.5 g t.i.d	1b	B	
Meropenem	1 g t.i.d	2	B	
Doripenem	0.5 g t.i.d	1b	B	

** Upgraded based on panel consensus.*
b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

3.9.5.2.2 Source control

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.

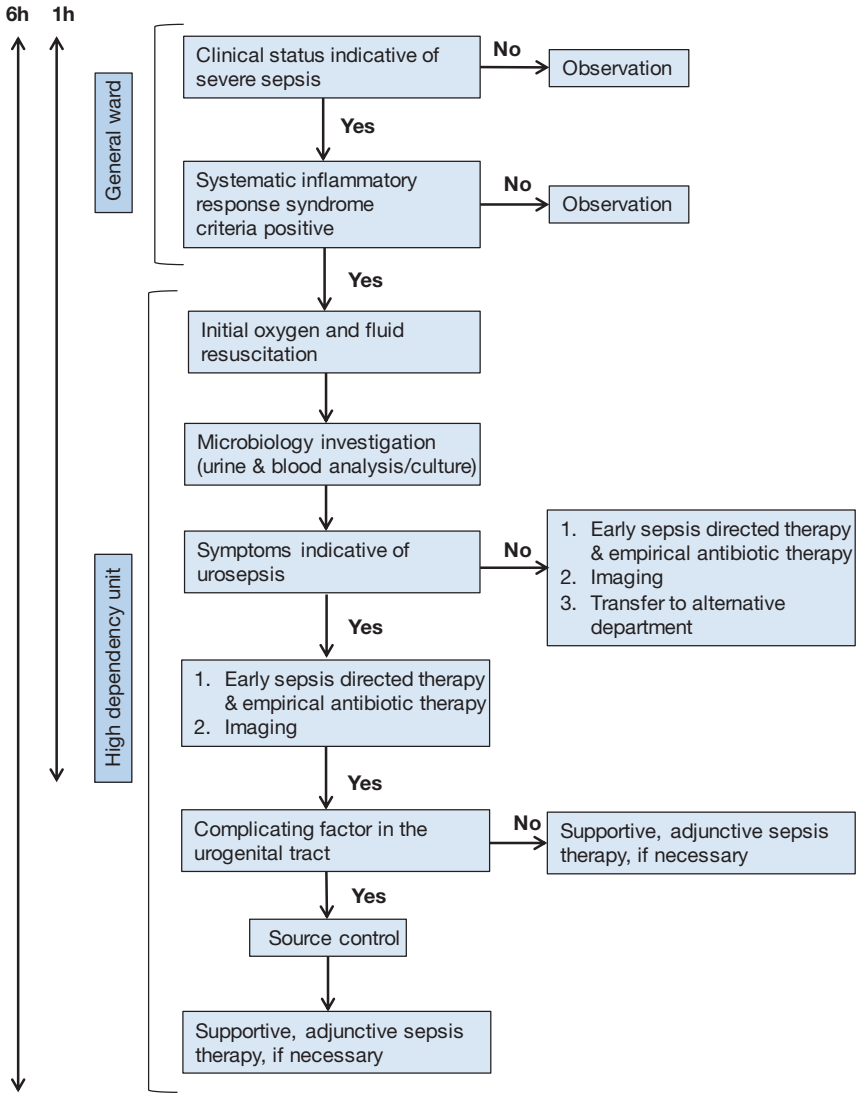
3.9.5.2.3 Adjunctive measures

The most important adjunctive measures in the management of sepsis are the following [172]:

- fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure;
- as vasopressors norepinephrine should be used primarily, dobutamine in myocardial dysfunction;
- hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of ≥ 65 mmHg;
- blood products should be given to target a haemoglobin level of 7-9 g/dL;
- mechanical ventilation should be applied with a tidal volume 6 ml/kg and plateau pressure ≤ 30 cm H_2O and a high positive end-expiratory pressure;
- sedation should be given minimally, neuromuscular blocking agents should be avoided;
- glucose levels should be target at ≤ 180 mg/dL;
- deep vein thrombosis prevention should be given with low-molecular weight heparin subcutaneously;
- stress ulcer prophylaxis should be applied in patients at risk, using protone pump inhibitors;
- enteral nutrition should be started early (< 48 hours).

In conclusion, sepsis syndrome in urology remains a severe situation with an considerable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next years [172, 193]. 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 antimicrobial 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 antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

Figure 2: Clinical algorithm for the management of urosepsis



3.10 Urethritis

*3.10.1 **Introduction***

Inflammation of the urethra presents usually with symptoms of the LUT and must be distinguished from other infections of the LUT. The following recommendations are based on a review of several European national guidelines and are aligned with the CDC's guidelines on sexual transmitted diseases (STDs) [194-197].

*3.10.2 **Epidemiology, aetiology and pathogenesis***

From a therapeutic and clinical point of view, *gonorrhoeal urethritis* (GU) must be differentiated from non-*gonococcal urethritis* (NGU). Infection is spread by sexual contact. Causative pathogens include *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), *Trichomonas vaginalis* (TV), and *Ureaplasma urealyticum* (UU) [198-203]. In a study of 367 patients with NGU isolated causative pathogens 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 29.2% [198]. There is limited evidence to support the role of *Mycoplasma hominis* in urethritis [204, 205].

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 [206-208].

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

*3.10.3 **Diagnostic evaluation***

A Gram stain of 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 [209]. Laboratories should use validated nucleic acid amplification tests (NAATs) to detect chlamydia and gonorrhoea, in first void urine samples, as they are better than any of the other tests available for the diagnosis of chlamydial and gonococcal infections [210]. *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. *Trichomonas* spp. can usually be identified microscopically [208].

3.10.3.1 Recommendations for the diagnostic evaluation of urethritis

Recommendations	LE	GR
Use a gram stain of urethral discharge or a urethral smear to preliminarily diagnosis pyogenic urethritis.	3	B
Use a validated nucleic acid amplification tests to diagnosis chlamydial and gonococcal infections.	3	B

*3.10.4 **Disease management***

Broad spectrum empirical antibiotic therapy may be started on presentation followed by antibiotic treatment refinement according to the results of microbiological investigations.

3.10.4.1 Recommendations for antimicrobial therapy of Urethritis [211, 212]

Pathogen	Antimicrobial	Dosage & Duration of therapy	LE	GR	Alternative regimens
Gonococcal Infection	Ceftriaxone	1 g i.m., SD	1a	A	Cefixime 400 mg p.o., SD Or Azithromycin 1-1.5 g p.o., SD
	Azithromycin	1-1.5 g p.o., SD			
	Cefixime	800 mg p.o., SD			
Non-Gonococcal infection (non-identified pathogen)	Doxycycline	100 mg b.i.d, p.o., 7-10 days	1b	A	Azithromycin 0.5 g p.o., day 1, 250 mg p.o., days 2-5
Chlamydia trachomatis	Azithromycin	1.0-1.5 g p.o., SD	1b	A	Doxycycline 100 mg b.i.d, p.o., for 7 days
Mycoplasma genitalium	Azithromycin	0.5 g p.o., day 1, 250 mg p.o., day 2-5	2a	B	Moxifloxacin 400 mg q.d., 5 days however, because of reported failures, some experts recommend 10 -14 days
Ureaplasma urealiticum	Doxycycline	100 mg b.i.d, p.o., 7 days	1b	A	Azithromycin 1.0-1.5 g p.o., single dose Or Clarithromycin 500 mg b.i.d, 7 days (resistance against macrolides is possible)
Trichomonas vaginalis	Metronidazole	2 g p.o., SD	1a	A	In case of persistence 4 g daily for 3-5 days

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

*3.10.5 **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 seven days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and source tracing should be done in accordance with national guidelines and in co-operation 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.

3.11 Bacterial Prostatitis

*3.11.1 **Introduction***

Bacterial prostatitis is a clinical condition caused by bacterial infection of the prostate gland. It is

recommended that urologists use the classification suggested by the National Institute of Diabetes, 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) (Table 4) [213-215].

Table 4: Classification of prostatitis and CPPS according to NIDDK/NIH [213-215]

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis – chronic pelvic pain syndrome
IIIA	Inflammatory chronic pelvic pain syndrome (white cells in semen/expressed prostatic secretion/voided bladder urine 3)
IIIB	Non-inflammatory chronic pelvic pain syndrome (no white cells in semen/expressed prostatic secretion/voided bladder urine 3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

*3.11.2 **Epidemiology, aetiology and pathogenesis***

A causative pathogen is detected by routine methods in only 5-10% of cases [216], antimicrobial therapy in these patients therefore, has a rational basis [217, 218]. 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 [218, 219]. Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in acute bacterial prostatitis [220]. In chronic bacterial prostatitis, the spectrum of strains is wider [218]. 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* [221]. The significance of intracellular bacteria, such as *C. trachomatis*, is uncertain [222] however, two studies have highlighted its role as a causative pathogen in chronic bacterial prostatitis [223, 224].

*3.11.3 **Diagnostic evaluation***

3.11.3.1 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 three months [225-227]. The predominant symptoms are pain at various locations (Table 5) and LUTS such as a frequent need to urinate, difficulty urinating e.g. weak stream, straining and pain on urination, or that increases during urination [213-215]. Chronic bacterial prostatitis is the most frequent cause of rUTI in men [228].

Table 5: Localisation of pain in patients with prostatitis like symptoms [215]

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

3.11.3.2 Symptom questionnaires

Symptoms appear to have a strong basis for use as a classification parameter in bacterial prostatitis [229]. Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms [229, 230]. They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH [231]. The questionnaire contains four questions regarding pain or discomfort, two regarding urination, and three related to quality of life.

*3.11.4 **Clinical findings***

In acute prostatitis, the prostate may be swollen and tender on DRE. Prostatic massage is contraindicated. Otherwise, the prostate is usually normal on palpation. 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 haematospermia in

men in endemic regions or with a history of tuberculosis should prompt investigation for urogenital tuberculosis [218].

3.11.4.1 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of a patient with acute prostatitis is MSU culture [232]. If the patient presents with clinical signs suggestive of blood-stream infection, a blood culture should be taken following local protocols. 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 [217] are important investigations.

3.11.4.2 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 [232].

3.11.4.3 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 [233].

3.11.4.4 Additional investigations

3.11.4.4.1 Ejaculate analysis

An analysis of the ejaculate is not recommended for microbiological investigation due to the low sensitivity and specificity compared to the two or three-glass tests [232]. Ejaculate analysis is however frequently involved as part of the investigation of a generalised male accessory gland infection. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3.11.4.4.2 Prostate specific antigen

Prostate specific antigen (PSA) is often increased in acute bacterial prostatitis and other urogenital infections. If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalise after antimicrobial treatment of four weeks in about 50% of patients [234]. A delay of at least three 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 [235].

*3.11.5 **Recommendations for the diagnostic evaluation of bacterial prostatitis***

Recommendations	**LE**	**GR**
Perform digital rectal examination to assess the condition of the prostate.	4	A*
Take a mid-stream urine culture in patients with acute prostatitis-related symptoms for diagnosis and targeted treatment planning.	3	A*
Perform the Meares and Stamey four-glass test in patients with chronic bacterial prostatitis.	2b	B
Accurate microbiological evaluation for atypical pathogens such as *Chlamydia trachomatis* or *Mycoplasmata* is recommended in patients with chronic bacterial prostatitis.	2b	B
Perform transrectal ultrasound only in selected cases to rule out the presence of prostatic abscess, calcification in the prostate and dilatation of the seminal vesicles.	3	B
Ejaculate analysis and prostate specific antigen measurement should not be performed as routine, due to the high number of false positive results.	3	B

**Upgraded based on panel consensus.*

*3.11.6 **Disease management***

3.11.6.1 Antimicrobials

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

Acute bacterial prostatitis is a serious infection with fever and intense localised and general pain. Parenteral administration of high doses of bactericidal antimicrobials, such as a broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone, is recommended [232]. For initial therapy, any of these antimicrobials may be combined with an aminoglycoside [218, 232]. After defervescence and normalisation of infection parameters, oral therapy can be substituted in and continued for a total of two to four weeks [236].

Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties [237], their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including *Pseudomonas aeruginosa*. In addition, levofloxacin is

active against Gram-positive and atypical pathogens, such as *C. trachomatis* and genital mycoplasmas.

The duration of antimicrobial treatment is based on clinical experience [238]. In chronic bacterial prostatitis antimicrobials should be given for four to six weeks after initial diagnosis [218, 232]. Relatively high doses are needed and oral therapy is preferred [237, 238]. If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given [237, 239].

3.11.6.2 Recommendations for the disease management of bacterial prostatitis

Antimicrobial	Daily dose	Duration of therapy	LE	GR	Comments
Acute febrile bacterial prostatitis with symptoms and fever					
Levofloxacin	500 mg q.d	All parental treatment should be given until defervescence	2	B	All of these antimicrobials can be administered in conjunction with aminoglycosides e.g. Gentamicin 5 mg/kg q.d or Amikiacin 15 mg/kg q.d.
Ciprofloxacin	500 mg b.i.d				
Ceftriaxone	2 g q.d				
Piperacillin/ tazobactam	4.5 g t.i.d				
Cefepime	2 g b.i.d				
Acute afebrile bacterial prostatitis with symptoms or after defervescence					
Levofloxacin	500 mg q.d	2-4 weeks	2	B	
Ciprofloxacin	500 mg b.i.d or 1000 mg p.d	2-4 weeks			
Trimethoprim	200 mg b.i.d	2-4 weeks			
Co-trimoxazole	960 mg b.id	2-4 weeks			
Doxycycline	100 mg b.i.d	10 days	2	B	Only for *Chlamydia trachomatis* or mycoplasma infections.
Chronic bacterial prostatitis					
Levofloxacin	500 mg q.d	4-6 weeks	3	B	
Ciprofloxacin	500 mg b.i.d or 1000 mg q.d	4-6 weeks			
Trimethoprim	200 mg b.i.d	4-6 weeks			
Co-trimoxazole	960 mg b.i.d	4-6 weeks			
Doxycycline	100 mg b.i.d	10 days	2	B	Only for *Chlamydia trachomatis* or mycoplasma infections.

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

3.11.6.3 Intraprostatic injection of antimicrobials

This treatment has not been evaluated in controlled trials and should not be considered [240, 241].

3.11.6.4 Drainage and surgery

Approximately 10% of men with acute prostatitis will experience urinary retention [242] 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 [243]. Alpha-blocker treatment has also been recommended, but clinical evidence of benefit is poor [218, 232].

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [244]. 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 [245].

3.11.7 ***Follow-up***

In asymptomatic post-treatment patients routine urinalysis and/or urine culture is not mandatory. The Meares and Stamey four-glass test should be repeated in patients representing with persistent symptoms. In patients with persistent symptoms and repeated positive microbiological results for sexually transmitted infectious pathogens, microbiological screening of the patients partner(s) is recommended [218, 232].

3.12 Acute Infective Epididymitis

3.12.1 ***Evidence question***

In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

3.12.2 ***Epidemiology, Aetiology and Pathophysiology***

Epididymitis is a common condition with incidence ranging from 25 to 65 cases per 10,000 adult males per year and can be acute, chronic or recurrent [246]. Acute epididymitis is clinically characterised by pain, swelling and increased temperature of the epididymis, which may involve the testis and scrotal skin. It is generally caused by migration of pathogens from the urethra or bladder. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

The predominant pathogens isolated are *C. trachomatis*, Enterobacteriaceae (typically *E. coli*) and *N. gonorrhoeae* [247]. Men who have anal intercourse and those with abnormalities of the urinary tract resulting in bacteriuria are at higher risk of epididymitis caused by Enterobacteriaceae. The mumps virus should be considered if there are viral prodromal symptoms and salivary gland enlargement. Tuberculous epididymitis may occur in high-risk groups such as men with immunodeficiency and those from high prevalence countries, it frequently results in a discharging scrotal sinus. *Brucella* or *Candida* species are rare possible pathogens.

3.12.3 ***Diagnostic Evaluation***

Culture of a mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infection with *C. trachomatis* or *N. gonorrhoeae* should be detected by NAAT on first voided urine. A urethral swab or smear should be performed for Gram staining and culture if *N. gonorrhoeae* is likely. Detection of these pathogens should be reported according to local arrangements. All patients with probable STI should be advised to attend an appropriate clinic to be screened for other sexually transmitted infections. Men with Enterobacteriaceae may require investigation for lower urinary tract abnormalities. If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *M. tuberculosis* DNA [248]. Prostate secretion, ejaculate, discharge from a draining scrotal fistula, as well as fine needle aspiration and biopsy specimens should be investigated using microscopy, AFB culture and NAAT, respectively.

3.12.4 ***Disease Management***

Men with suspected STI should be informed of the risks to others and advised not to have sex until free of infection. Empirical antimicrobial therapy has to be chosen by consideration of the most probable pathogen and degree of penetration into the inflamed epididymis and may need to be varied according to local pathogen sensitivities and guidance. Generally, both *C. trachomatis* and Enterobacteriaceae should be covered initially and the regimen modified according to pathogen identification. Doxycycline and some specific fluoroquinolones have good clinical and microbiological cure rates in patients with suspected *C. trachomatis* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *C. trachomatis* but not tested in epididymitis. Fluoroquinolones remain effective for oral treatment of Enterobacteriaceae although resistance is increasing and local advice should be sought. Fluoroquinolones should not be considered for gonorrhoea. Single high parenteral dose of a third generation cephalosporin is effective against *N. gonorrhoeae*; current resistance patterns and local public health recommendations should guide choice of agent.

Clinical response to antibiotics in men with severe epididymitis should be assessed after about three days and men with likely or proven STI should be assessed at fourteen days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

3.12.5 ***Evidence Summary***

Relating to this chapter three guidelines based on systematic reviews were identified [249-251] with search dates of December 2009, March 2012 and April 2013 respectively. A structured search of the literature from January 2010 to March 2015 identified 553 titles of which 45 were selected for full text review and five were included [252-256]. Data from a large comparative case series suggested that young age and history of sexual activity are not sufficiently predictive of a sexually transmitted pathogen to guide antibiotic treatment in acute epididymitis [256].

Empiric antibiotic regimens from existing guidelines [249-251] and panel consensus:

1. For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge) a single agent or combination of two agents of sufficient dose and duration to eradicate *C. trachomatis* and Enterobacteriaceae should be used. Appropriate options are:

    A. A fluoroquinolone active against *C. trachomatis* orally once daily for ten to fourteen days*

    OR

    B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days* ***plus*** an antibiotic active against Enterobacteriaceae** for ten to fourteen days*

2. For men with likely gonorrhoeal acute epididymitis a combination regimen active against Gonococcus and *Chlamydia trachomatis* must be used such as:

   A. Ceftriaxone 500 mg intramuscularly single dose **plus**
   Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days*

3. For non-sexually active men with acute epididymitis a single agent of sufficient dose and duration to eradicate Enterobacteriaceae should be used. Appropriate option is a fluoroquinolone by mouth once daily for ten to fourteen days*

**Depending upon pathogen identification and clinical response.*
*** A parenteral option will be required for men with severe infection requiring hospitalisation.*

Surgical exploration may be required to drain abscesses or debride tissue. A comparative cohort study found that lack of separation of epididymis and testis on palpation and the presence of abscess on US may predict requirement for surgery following initial antibiotic treatment [252].

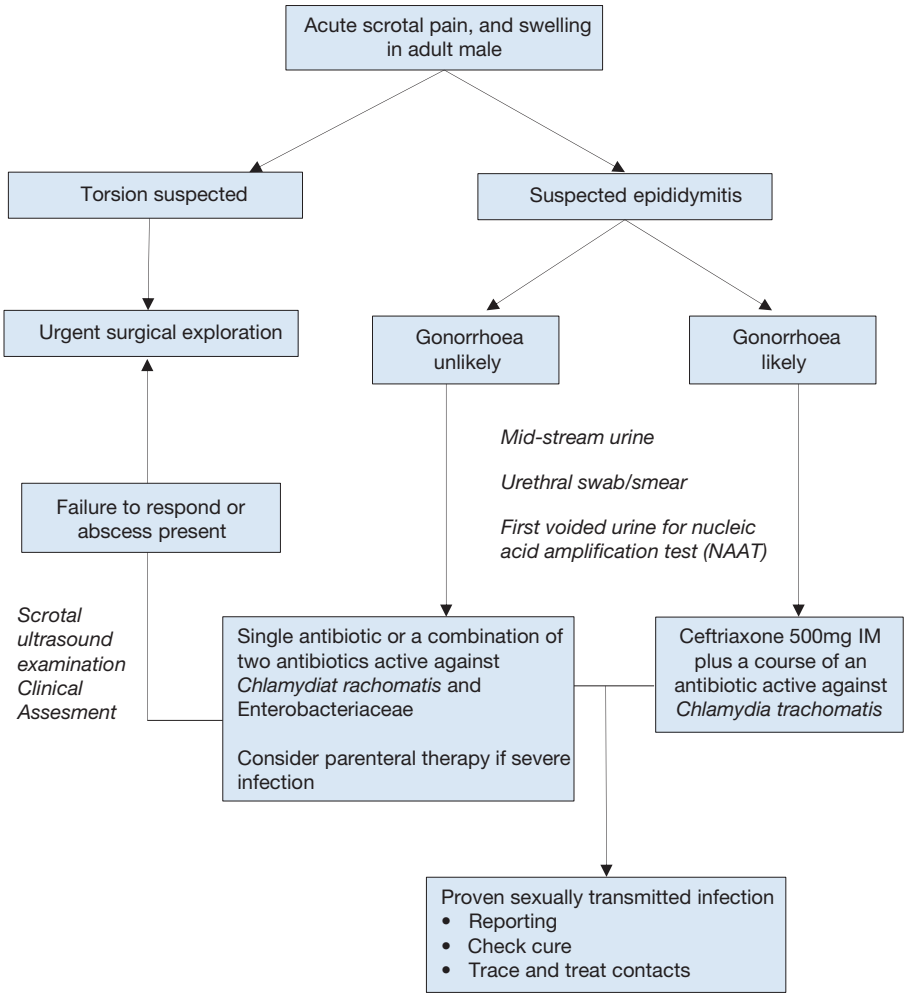
A cohort study found semen parameters may be impaired during epididymitis but recovered following successful treatment [255]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [253] and by primary care physicians [254].

*3.12.6 **Recommendations for the treatment of acute infective epididymitis***

Recommendations	**LE**	**GR**
Obtain a mid-stream urine and first voided urine for pathogen identification.	3	A*
Initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.	3	A*
If gonorrhoeal infection is likely, give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against *Chlamydia trachomatis*.	3	A*
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	3	A*
Follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.	3	A*

** Upgraded based on Panel consensus.*

Figure 3: Diagnostic and treatment algorithm for adult men with acute epididymitis.



3.13 Fournier's Gangrene

3.13.1 ***Introduction***

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia [257]. 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.

3.13.2 ***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 [258]. 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 [259]. 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 [260, 261]. A high index of suspicion and careful examination, particularly of obese patients, is required.

3.13.2.1 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 anerobes; involvement of *Clostridium* sp. is now less common [258, 260, 262]. 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.

3.13.3 ***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 [263]. Disease-specific severity scoring systems do not appear superior to generic critical illness scores and are therefore not recommended for routine use [264-266]. Computed tomography or MRI can help define para-rectal involvement, suggesting the need for colostomy [267]. Consensus from case series suggests that surgical debridement should be early (< 24 hours) and complete, as delayed and/or inadequate surgery results in higher mortality [268]. Concurrent parenteral antibiotic treatment should be given that covers all causative organisms and can penetrate inflammatory tissue. 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 [267, 269, 270]. With aggressive early surgical and medical management, survival rates are > 70% depending upon patient group and availability of critical care [271]. Following resolution, reconstruction using skin grafts is required [272-275].

3.13.3.1 Recommendations for the disease management of Fournier's Gangrene

Recommendations	LE	GR
Commence full, repeated, surgical debridement within 24 hours of presentation.	3	B
Start treatment with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.	3	A*
Do not use adjunctive treatments such as pooled immunoglobulin and hyperbaric oxygen, except in the context of clinical trials.	3	A*

** Upgraded based on panel consensus.*

3.14 Detection of bacteriuria prior to urological procedures

*3.14.1 **Evidence question***

What is the diagnostic accuracy of alternative urinary investigations compared with urine culture for the diagnosis of bacteriuria in adult patients prior to urological interventions?

*3.14.2 **Background***

Identifying bacteriuria prior to diagnostic and therapeutic procedures aims to reduce the risk of infectious complications by controlling any pre-operative detected bacteriuria and to optimise antimicrobial coverage in conjunction with the procedure. However, the absence of bacteriuria by itself is not an assurance against infectious complications and antimicrobial prophylaxis according to section 3.15 is recommended.

The standard method, laboratory culture of an appropriate urine sample, is time consuming and logistically difficult. Alternative rapid near-patient methods such as reagent strip (dipstick) urinalysis, automated microscopy, flow cytometry, and dipslide culture have been developed but their diagnostic accuracy is uncertain.

*3.14.3 **Evidence summary***

A systematic search of the literature to February 2015 identified 3,033 titles of which 210 were selected for full text review and 18 studies investigating diagnostic accuracy of different index tests with urine culture as the reference standard were included [276-293]. None of the studies focused on a urology patient population.

3.14.3.1 Reagents strip (dipstick) urinalysis

Sixteen studies assessed dipstick urine analysis using a variety of criteria for a positive test [276-284, 287-289]. The criterion that resulted in the best overall diagnostic accuracy was when a positive test was defined as at least one of nitrite and leucocyte esterase being detected however, low sensitivity (0.8) limits clinical usefulness, in the setting of assessment of bacteriuria, prior to urological surgery.

3.14.3.2 Automated microscopy

Two studies used automated microscopy of urine sediment following centrifugation [285, 289]. Although sensitivity was high (0.98), specificity was too low for effective use in this setting (0.59) and optimum diagnostic thresholds were not determined.

3.14.3.3 Dipslide culture

Two studies on dipslide technology using different culture media were identified [286, 293]. In one study diagnostic accuracy was high (0.98) although contaminated samples were excluded [31]. The other study showed lower accuracy, below the level required in this setting [286]. Overall, dipslide technology is currently unsuited for routine use in this setting with further studies required to determine the best combination of culture media.

3.14.3.4 Flow cytometry

No studies on this technology that met the inclusion criteria. The poor quality of available studies was confirmed in a meta-analysis [294]. In summary, laboratory urine culture remains the standard investigation to detect both the presence and absence of clinically relevant concentrations of bacteria in urine.

Recommendation	LE	GR
Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients prior to undergoing urological interventions.	3	B

3.15 Peri-operative antibacterial prophylaxis in urology

3.15.1 Introduction

The aim of antimicrobial prophylaxis (AMP) in urology is to prevent infectious complications resulting from diagnostic and therapeutic procedures. However, evidence for the best choice of antimicrobials and regimens is limited.

As microbial resistance is dramatically increasing, there is a strong need to change unproven paradigms. In the absence of high level evidence regarding the benefit of AMP, prior to a specific procedure, the Guideline panel recommends to individually assess its need for each case. It is important to keep in mind that AMP is only one of several measures to prevent infections and can never compensate for poor hygiene and operative technique. The CDC has presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications [295]. These definitions have also been used in the Global Prevalence Study on Infections in Urology (GPIU) point prevalence studies [296].

3.15.2 Risk factors

The risk of infection varies with the type of intervention. The wide spectrum of interventions and the recent advances in minimal invasive surgery have further complicated the provision of clear-cut recommendations. Furthermore, the bacterial load, the duration and difficulty of the procedure, the surgeon's skill, and peri-operative bleeding may also influence the risk of infection [295, 297, 298]. For elective urological surgery, general and urinary-tract-specific risk factors must be controlled (i.e. bacteriuria, obstruction).

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

- their general health status according to the 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; even though these risk factors were not proven in level one evidence studies;
- 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 intervention and surgical field contamination burden;
- the expected level of invasiveness, duration and technical aspects of the procedure.

3.15.3 Principles of antimicrobial prophylaxis

3.15.3.1 Timing

Overall, administration of the first dose of antimicrobial within 60 minutes before surgical incision is recommended. Administration of vancomycin and fluoroquinolones should begin within 120 minutes before surgical incision due to the prolonged infusion times required for these drugs [299, 300].

3.15.3.2 Route of administration

The preferred route of administration varies with the type of procedure, however, for a majority of procedures, intravenous administration is ideal as it produces rapid, reliable, and predictable serum and tissue concentrations [299, 300].

3.15.3.3 Duration of the regimen

For most procedures, duration of AMP has not yet been adequately addressed and rarely can a defined regimen be recommended. In principle, the duration of peri-operative prophylaxis should be minimised, ideally to a single dose.

3.15.3.4 Choice of antimicrobials

No clear-cut recommendations can be given, as there is considerable variation in Europe regarding bacterial spectra and their susceptibility to different antimicrobials. Therefore, knowledge of the local pathogen profiles, susceptibility and virulence is mandatory in establishing local AMP 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.

*3.15.4 **Antimicrobial prophylaxis by procedure***

3.15.4.1 Diagnostic procedures

3.15.4.1.1 Transrectal prostate biopsy

See section 3.16 for the results of a recent systematic review on which strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy.

3.15.4.1.2 Cystoscopy

The frequency of infectious complications after cystoscopy, standard urodynamic studies and diagnostic simple ureteroscopy in otherwise healthy individuals with sterile pre-operative urine is low [301-303]. In view of the very large number of cystoscopic examinations, the low infectious risk and the potential adverse effect on bacterial sensitivity, AMP is not recommended. However, bacteriuria, indwelling catheters, neurogenic LUTD and a history of urogenital infection are risk factors that must be considered [304-317].

3.15.4.2 Endourological treatment procedures (urinary tract entered)

3.15.4.2.1 Transurethral resection of the bladder (TURB)

There is little evidence for any benefit of AMP prior to TURB. Studies do not distinguish between simple fulguration (cystoscopy) and large or multiple tumours, or the presence or absence of necrotic material. Therefore, the present Guidelines recommend that clinicians choose the appropriate AMP regime based on tumour differentiation, see section 3.15.5 [303, 318-320].

3.15.4.2.2 Transurethral resection of the prostate (TURP)

Transurethral resection of the prostate is the best studied urological intervention. At least two meta-analyses of a large number of prospective, randomised controlled studies, including several thousand patients, showed a marked benefit of AMP with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively [303, 318-320].

3.15.4.2.3 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. Therefore the present Guidelines recommend clinicians choose the appropriate AMP regime based on the degree of severity, stone anatomic position and patient related risk factors, all of which are supported by a large database study [321].

3.15.4.2.4 Percutaneous nephrolithotripsy (PNL)

The risk of infection in PNL is high and use of AMP has been shown to significantly reduce the risk of infectious complications [99, 322-329]. A single dose was shown to be sufficient [330]. Retrograde intra-renal stone treatment could be expected to have a similar risk profile [321].

3.15.4.2.5 Shock-wave lithotripsy

No standard AMP is recommended. However, control of bacteriuria and AMP is recommended in cases of increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, or infectious stones) [331-340].

3.15.4.3 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.

3.15.4.4 Nephrectomy, adrenalectomy

No standard AMP can be recommended, however, AMP may be considered optional in certain circumstances [341-345].

3.15.4.5 Prostatectomy

In open enucleation of prostatic adenoma, the risk of post-operative infection is particularly high and AMP is recommended [346]. As there are no studies on AMP in radical prostatectomy the use of AMP may be considered optional.

3.15.4.6 Cystectomy with bowel use

Single or one day dosage AMP is recommended, although prolonged operation and other morbidity risk factors might support the use of pre-emptive antimicrobial treatment, which should be < 72 hours. The choice of antimicrobials should focus on aerobic and anaerobic pathogens. Evidence is based on colorectal surgery, but experience is limited for specific urological interventions [347-350].

3.15.4.7 Post-operative drainage of the urinary tract

When continuous urinary drainage is left in place after surgery, prolongation of AMP is not recommended. Asymptomatic bacteriuria should not be treated.

3.15.4.8 Implantation of prosthetic devices: testis, penile prosthesis and artificial sphincter

Antimicrobial prophylaxis is recommended. 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, AMP used must be chosen to target these strains [351-354].

*3.15.5 **Recommendations for peri-operative antibacterial prophylaxis in urology***

Recommendations				
Procedure	**Comments**	**Antimicrobial prophylaxis**	**LE**	**GR**
Diagnostic procedures				
Cystoscopy	Low frequency of infection. Consider individual risk factors for UTI (i.e. asymptomatic bacteriuria, history of febrile UTI)	No	1b	A
Urodynamic study	Low frequency of infections. Consider individual risk factors for UTI (i.e. asymptomatic bacteriuria, history of febrile UTI)	No	1a	A
Transrectal core biopsy of prostate	High risk of infection	Fluoroquinolones Trimethoprim ± sulphamethoxazole Targeted alternative	1b	A
Diagnostic ureteroscopy	No available studies	Optional	4	C
Common endourological/endoscopic therapeutic procedures (examples)				
Fulguration of small bladder tumours	Low frequency of infections.	Optional	2b	C
Transurethral resection of the bladder	Poor data. No concern given to burden of tumour, i.e. size, multiplicity, necrosis	Trimethoprim ± sulphamethoxazole Aminopenicillin/ Beta-lactamase inhibitor Cephalosporin group 2 or 3	2b	C
Transurethral resection of the prostate	High risk of infection		1a	A
Shock-wave lithotripsy	Low frequency of infections		1a	A
Ureteroscopy for stone management	Distal stone removal.		2b	B
Percutaneous and retrograde intra-renal stone management	High risk of infection		1b	A
Common open and/or laparoscopic surgery				
Nephrectomy ± ureterectomy Adrenalectomy Radical prostatectomy	Surgical site infection/wound infection poorly documented Secondary post-operative catheter-related asymptomatic bacteriuria/ UTI	Optional	3	C
Planned scrotal surgery, vasectomy, surgery for varicocele	Conflicting data	No	3	C

Prosthetic implants, artificial sphincter	Limited documentation	Aminopenicillin/ Beta-lactamase inhibitor Piperacillin/Tazobactam	3	B
Uretero-pelvic junction repair		Optional	4	C
Partial bladder resection		Optional	3	C
Cystectomy with urine deviation	High risk of infection	Cefuroxim Aminopenicillin/ Beta-lactamase inhibitor + Metronidazole	2a	B

3.16 Prostate biopsy

*3.16.1 **Evidence question***

Which strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy?

*3.16.2 **Epidemiology, Aetiology and Pathophysiology***

Histological examination of needle biopsies of the prostate is the principle method for prostate cancer diagnosis. Prostate biopsy is a common procedure in high-resource countries with, for example, about 32,000 procedures performed in England during 2013 [355] giving a rate of 2.6/1,000 men at risk per year. Transrectal ultrasound-guided biopsy (TRUS) is the current standard technique although the transperineal route is also used [356]. Infection is the most clinically significant harm experienced by men following prostate biopsy. There is some evidence that the risk is increasing [357]. Infection generally occurs by implantation of rectal commensal organisms into the prostate, urethra or bloodstream during needle insertion. Severity of infection will depend on bacterial inoculum, virulence and status of host defence.

*3.16.3 **Diagnostic Evaluation***

Urine culture prior to prostate biopsy has an uncertain predictive value [358].

*3.16.4 **Disease Management***

The focus is on prevention of infectious complications. Possible strategies include antimicrobial prophylaxis and non-antimicrobial strategies, the effectiveness of which will be described in this section. Established infection is treated according to standard pathways [355].

*3.16.5 **Evidence summary***

A systematic search of the literature to March 2015 identified 1,556 titles of which 189 were selected for full text review and 93 RCTs were included [359-453]

*3.16.6 **Non-antimicrobial interventions***

3.16.6.1 Number of biopsy cores

Meta-analysis of seven trials involving 1,290 men found no evidence that extended biopsy (> 6-24 cores) templates resulted in more infectious complications than standard templates (6-12 cores) [(95% CIs) = 1.71 (0.70 – 4.16)] [359-365].

3.16.6.2 Peri-prostatic injection of local anaesthetic

A meta-analysis of 25 RCTs with 3,533 participants found no evidence that use of peri-prostatic injection of local anaesthesia resulted in a higher rate of infectious complications compared to no injection [366-370, 372-388, 429, 430, 434]. Four other RCTs with 497 patients compared different numbers of injections performed for peri-prostatic injection of local anaesthetic. Here, no difference was found in infective complications [RR (95% CIs) = 1.51 (0.26 – 8.97)] [405-408]

3.16.6.3 Route of biopsy

Three RCTs involving 646 men compared transrectal and transperineal routes of biopsy. Overall two men (0.4%) suffered infectious complications after transperineal biopsy, compared to five (1.1%) after transrectal biopsy [RR (95% CIs) = 0.45 (0.10 – 1.97)]. The studies were heterogeneous in design, did not state how infectious outcomes were assessed and used differing antimicrobial prophylaxis between arms.

3.16.6.4 Rectal preparation

A meta-analysis of three studies including 209 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications [RR (95% Cis) =0.76

(0.40 to 1.46)] [400, 447, 450].

Meta-analysis of six trials including 1,373 men showed that use of a rectal povidone-iodine preparation before biopsy in addition to antimicrobial prophylaxis resulted in a lower rate of infectious complications [RR (95% CIs) = 0.58 (0.43 to 0.76)] [392-397]. Single RCTs showed no evidence of benefit for perineal skin disinfection [398] but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [453].

3.16.6.5 Other interventions

Combining data from two RCTs with 253 participants showed that biopsy using disposable needle guides resulted in nine infectious complications compared to 22 with reusable biopsy needle guides. The difference was not significant [RR (95% CIs) = 0.51 (0.24 to 1.06)] [402, 403]. A single RCT found no evidence that disinfection of a single patient use needle between cores resulted in fewer infectious complications [404]. Another single study evaluated the needle size and did not find significant differences between a 16 G and an 18 G needle size [446].

Recommendation	LE	GR
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	1a	B*

**Downgraded as highest quality trial in meta-analysis showed no difference [391].*

*3.16.7 **Antimicrobial prophylaxis***

The meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using AMP as compared to placebo/control [RR (95% CIs) = 0.56 (0.40 to 0.77)] [393, 397, 413, 423, 431, 433, 437, 442, 447, 448, 452]. Thus, antimicrobial prophylaxis is strongly recommended. However, the choice of regimens and duration of prophylaxis remains debatable. Most commonly fluorochinolones are applied [419, 421, 422, 431, 435, 451]. Due to the increase in fluorochinolone resistance recent studies have investigated alternatives like fosfomycin trometamol [435], or suggest targeted antimicrobial prophylaxis based on rectal swab [401]. While the available Cochrane review of 2011 suggests a one-day prophylaxis with a single agent [454], a recent systematic analysis has pointed towards an augmented antimicrobial therapy [455]. A meta-analysis on this issue by the guideline panel is ongoing on and will be finalised next year.

Recommendation	LE	GR
Use antimicrobial prophylaxis in men prior to transrectal prostate biopsy.	1a	A

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5. CONFLICT OF INTEREST

All members of the EAU 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 EAU website: http://www.uroweb.org/guidelines/. These Guidelines were 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.