EAU Guidelines on

Urological Infections

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European Association 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 urinary tract infections (UTIs) and male accessory gland infections. 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, an infectious disease specialist and a clinical microbiologist. 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, the Pocket Guidelines, is available in print and as an app for iOS and Android 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/urological-infections/.

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. This 2020 document presents a limited update of the 2019 publication.

2. METHODS

2.1 Introduction

For the 2020 Urological Infections Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for sections 3.4, 3.6, 3.7 and 3.10. Broad and comprehensive literature searches, covering these sections were performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries. The time frames covered and the number of unique records identified, retrieved and screened for relevance for each section were:

Section	No. of unique records	Search time frame
3.4 Uncomplicated cystitis	694	Jan 1st 2014 – Feb 1st 2019
3.7 Complicated UTI	1,331	
3.10 Urethritis	488	
3.6 Uncomplicated pyelonephritis	1,006	Jan 1st 2015 – Feb 1st 2019

Detailed search strategies are available online: http://uroweb.org/guideline/urological-infections/?type=-appendices-publications. For the 2021 Urological Infections Guidelines the following sections will be updated:

- 3.5 Recurrent UTI;
- 3.8 Catheter associated UTI.

The 2020 edition of the EAU Guidelines uses a modified GRADE methodology [3]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and on 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

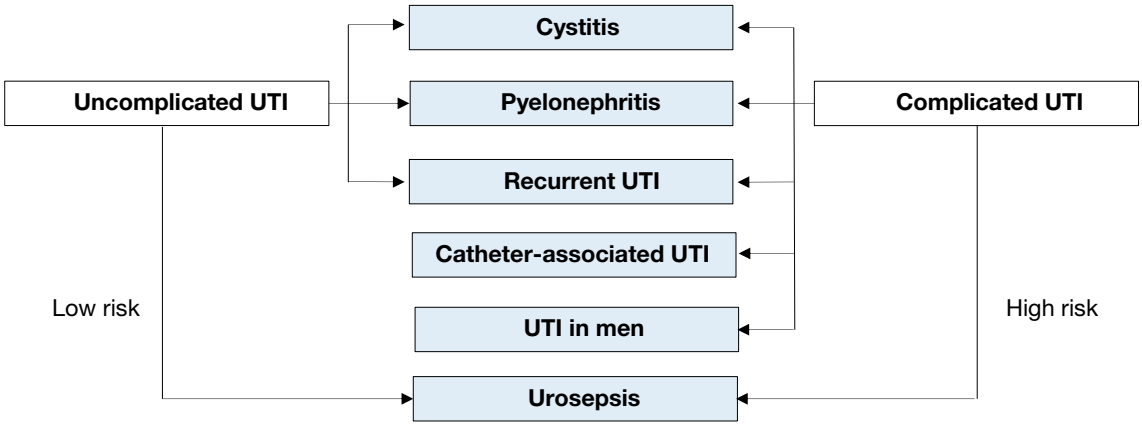
This document was subject to independent peer review prior to publication in 2019.

3. THE GUIDELINE

3.1 Classification

Different classification systems of UTI exist. Most widely used are those developed by the Centres 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 Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation of the UTI, the anatomical level of the UTI, the grade of severity of the infection, the 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 women with no known relevant 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 relevant 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 had a catheter in place within the past 48 hours.
Urosepsis	Urosepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs [12].

3.2 Antimicrobial Stewardship

Although the benefits to patients of antibiotic use are clear, overuse and misuse have contributed to the growing problem of resistance amongst uropathogenic bacteria, which is a serious threat to public health [13, 14]. In acute care hospitals, 20-50% of prescribed antibiotics are either unnecessary or inappropriate [15]. In response, a worldwide initiative seeks to incorporate Antimicrobial Stewardship programs in healthcare [16]. Antimicrobial Stewardship aims to optimise clinical outcomes and ensure cost-effective therapy whilst minimising unintended consequences of antimicrobial use such as healthcare associated infections including *Clostridium difficile*, toxicity, selection of virulent organisms and emergence of resistant bacterial strains [17].

Stewardship programs have two main sets of actions. The first set mandates use of recommended care at the patient level conforming to guidelines. The second set describes strategies to achieve adherence to the mandated guidance. These include persuasive actions such as education and feedback together with restricting availability linked to local formularies. A Cochrane review of effectiveness of interventions to improve antibiotic prescribing practices for hospital inpatients, updated in 2017, found high-certainty evidence that such interventions are effective in increasing adherence with antibiotic policy leading to reduced antibiotic treatment duration and that it may also reduce hospital stay. The review found no evidence that reduced antibiotic usage increased mortality [18].

The important components of antimicrobial stewardship programs are [19]:

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

A 2016 systematic review of evidence for effectiveness of various Antimicrobial Stewardship interventions in healthcare institutions identified 145 studies of nine Stewardship objectives. Guideline-driven empirical therapy using a restricted choice of antibiotics and including de-escalation, intravenous to oral switch, therapeutic drug monitoring, and bedside consultation resulted in a 35% (95% CI 20-46%) relative risk reduction (RRR) in mortality. Use of de-escalation (tailoring to a more narrow spectrum agent), showed a RRR of 56% (95% CI 34 – 70%) for mortality [20].

To facilitate local initiatives and audit, a set of valid, reliable, and applicable indicators of the quality of antibiotic use in the treatment of hospitalised patients with complicated UTI was developed [21]. Its use in the Netherlands appeared to result in shortened hospital stay [22]. A literature search of Pubmed from April 2014 [20], to February 2017 identified no further randomised controlled trials (RCTs) relating to stewardship

programmes for UTIs. Studies to provide high-quality evidence of effectiveness of Stewardship programmes in urology patients are urgently needed.

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 corresponds to a commensal colonisation [23]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [24, 25]. 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 in 23-89% in patients with spinal cord injuries [26]. 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 showing bacterial growth ≥ 10^5 cfu/mL in two consecutive samples in women [27] and in one single sample in men [28]. 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 [26, 29]. Cystoscopy and/or imaging of the upper urinary tract is not mandatory if the 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 [30]. In men, a digital rectal examination (DRE) has to be performed to investigate the possibility of prostate diseases (see section 3.11).

3.3.5 Evidence summary

A systematic search of the literature from January 2000 to November 2016 identified 3,582 titles of which 224 were selected for full text review and 50 were included [31]. For the subgroups of pregnancy, prior to urologic surgeries, post-menopausal women and institutionalised elderly patients only data from RCTs were included, on which a meta-analysis was performed [31]. For the other subgroups non-RCTs were also included in the narrative analysis [31]. The following patient populations were not covered by the systematic review: immuno-compromised patients; patients with candiduria; patients with dysfunctional and/or reconstructed lower urinary tracts; and patients with indwelling catheters. For these groups the guideline was updated using a structured PubMed search.

3.3.6 Disease management

3.3.6.1 Patients without identified risk factors

Asymptomatic bacteriuria does not cause renal disease or damage [32]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [33], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven to be unnecessary in most 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 without identified risk factors [25] and demonstrated that treatment of ABU increases the risk for a subsequent symptomatic UTI episode, compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; n=673). 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.

3.3.6.3 Pregnant women

3.3.6.3.1 Is treatment of ABU beneficial in pregnant women?

Twelve RCTs comparing antibiotic treatments of ABU with placebo controls or no treatment [34-45], with different antibiotic doses and regimens were identified, ten published before 1988 and one in 2015. Eleven RCTs (n=2,002) reported on the rate of symptomatic UTIs [34, 36-44, 46]. Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment (average RR 0.22, 95% CI 0.12 to 0.40).

Six RCTs reported on the resolution of bacteriuria [34-36, 38, 41, 43]. 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 [34, 36-39, 42, 45, 46]. 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=1689). Four RCTs reported on the rate of preterm deliveries [42, 43, 45, 46]. Antibiotic treatment was associated with lower rates of preterm 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 foetal 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 60s to 80s. Diagnostic and treatment protocols and accessibility to medical services have dramatically changed since then; therefore, the quality of evidence for this recommendation is low. In a newer study of higher methodological quality the beneficial effects of antibiotic treatment are not as evident [46]. Therefore, it is advisable to consult national recommendations for 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 [47-62]. 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 [63]. 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 [48, 52, 53, 57-62], one study compared single dose to long course treatment [56] and one study compared long course to continuous treatment [49]. 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 [52, 61, 62], with no significant difference between the two durations (average RR 1.07, 95% CI 0.47 to 2.47; n=891). Nine RCTs reported on the rate of ABU resolution [48, 52, 53, 57-62], with no significant difference between the two durations (average RR 0.97, 95% CI 0.89 to 1.07; n=1,268). Six RCTs reported on the rate of side effects [48, 52, 57, 58, 60, 61]. Single dose treatment was associated with significantly less side effects compared to short course treatment (average RR 0.40, 95% CI 0.22 to 0.72; n=458). Three RCTs reported on the rate of preterm deliveries [52, 54, 62], with no significant difference between the two durations (average RR 1.16, 95% CI 0.75 to 1.78; n=814). One RCT reported on the rate of low birthweights [62]. There were significantly more babies with low birthweight in the single dose duration compared to short course treatment (average RR 1.65, 95% CI 1.06 to 2.57; n=714).

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 [64]. 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 correlate to diabetic nephropathy [65]. Screening and treatment of ABU in well-controlled 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 [66]. 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 [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) [52, 61, 62], 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 [71]. 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 [72, 73]. Seven RCTs compared antibiotic treatment of ABU with placebo controls or no treatment in elderly patients, with different antibiotic doses and regimens [67-70, 74-76].

Three RCTs reported on the rate of symptomatic UTIs [67, 69, 74]. 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; n=210). Six RCTs reported on the resolution of bacteriuria [67, 69, 70, 74-76]. 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; n=328). 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 [77]. Therefore, screening and treatment of ABU is not recommended in this patient group.

3.3.6.4.4 Patients with renal transplants

Two RCTs and two retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients [78-81]. Meta-analysis of the two RCTs did not find antibiotic treatment beneficial in terms of reducing symptomatic UTIs (RR 0.86, 95% CI 0.51 to 1.45; n=200). The two retrospective studies reached the same conclusion. Furthermore, there were no significant differences in the rate of ABU clearance, graft loss or change in renal function during long-term follow-up up to 24 months [78-81]. 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 [82, 83]. Studies have shown no benefit in ABU treatment in these patient groups [84, 85]. 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 [84, 85]. 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 [86]. This is also applicable for patients with ABU and indwelling ureteral stents [87]. 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 urethral catheters ABU is not considered a risk factor and should not be screened or treated [88]. In patients subjected to placement/exchanges of nephrostomy tubes and indwelling ureteral stents, ABU is considered a risk factor for infectious complications [89]; therefore, screening and treatment prior to the procedure is recommended.

3.3.6.4.8 Immuno-compromised 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, although not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended [90].

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 [91, 92] and two prospective non-randomised studies [93, 94] compared the effect of antibiotic treatment to no treatment before transurethral prostate or bladder tumour resections. 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 0.20, 95% CI 0.05 to 0.86; n=167). 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. One RCT including patients with spinal cord injury undergoing elective endoscopic urological surgeries found no significant difference in the rate of post-operative UTIs between single-dose or 3-5 days short term pre-operative antibiotic treatment of ABU [95].

A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment is recommended.

3.3.6.6 Prior to orthopaedic surgery

One RCT (n=471) and one multicentre cohort study (n=303) comparing the treatment of ABU with no treatment prior to orthopaedic surgery (hip arthroplasty/hemiarthroplasty or total knee arthroplasty) were identified [96, 97]. Neither of the studies showed a beneficial effect of antibiotic treatment in terms of prosthetic joint infection (3.8% vs. 0% and 3.9% vs. 4.7%, respectively). The cohort study reported no significant difference in the rate of post-operative symptomatic UTI (0.65% vs. 2.7%) [97]. 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 can be given, depending on gender, medical background and presence of complicating factors. Treatment should be tailored and not empirical.

*3.3.7 **Follow-up***

There are no studies focusing on follow-up after treatment of ABU.

*3.3.8 **Summary of evidence and recommendations for the management of ABU***

Summary of evidence	**LE**
Treatment of asymptomatic bacteriuria is not beneficial in the following conditions:	
• women without risk factors;	3b
• patients with well-regulated diabetes mellitus;	1b
• post-menopausal women;	1a
• elderly institutionalised patients;	1a
• patients with dysfunctional and/or reconstructed lower urinary tracts;	2b
• patients with renal transplants;	1a
• patients prior to arthoplasty surgeries.	1b
Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections.	1b
Treatment of asymptomatic bacteriuria is beneficial prior to urological procedures breaching the mucosa.	1a
Treatment of asymptomatic bacteriuria in pregnant women was found to be beneficial by meta-analysis of the available evidence; however, most studies are old. A recent study reported lower rates of pyelonephritis in low-risk women.	1a

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

3.4 Uncomplicated cystitis

*3.4.1 **Introduction***

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

*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 [98]. Risk factors include sexual intercourse, use of spermicides, a new sexual partner, a mother with a history of UTI and a history of UTI during childhood. The majority of cases of uncomplicated cystitis are caused by *E. coli*.

*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 [99, 100]. In elderly women genitourinary symptoms are not necessarily related to cystitis [101, 102].

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

In patients presenting with typical symptoms of an uncomplicated cystitis urine analysis (i.e. urine culture, dip stick testing, etc.) leads only to a minimal increase in diagnostic accuracy [103]. However, if the diagnosis is unclear dipstick analysis can increase the likelihood of an uncomplicated cystitis diagnosis [104, 105]. Taking a urine culture is recommended in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy [106, 107].

3.4.3.4 Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis

Summary of evidence	LE
An accurate diagnosis of uncomplicated cystitis can be based on a focused history of lower urinary tract symptoms and the absence of vaginal discharge or irritation.	2b

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

*3.4.4 **Disease management***

Antimicrobial therapy is recommended because clinical success is significantly more likely in women treated with antimicrobials compared with placebo [108]. In female patients with mild to moderate symptoms, symptomatic therapy (e.g. Ibuprofen), as an alternative to antimicrobial treatment, may be considered in consultation with individual patients [109-112]. The choice of antimicrobial therapy should be guided by [99]:

- 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, oral treatment with fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day for three to five days, and nitrofurantoin (e.g. nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for five days), should be considered for first-line treatment, when available [113-116].

Alternative antimicrobials include trimethoprim alone or combined with a sulphonamide. Co-trimoxazole (160/800 mg twice daily for 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].

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 not recommended for empirical therapy due to ecological collateral damage, but may be used in selected cases [119, 120].

Important notice:

On March 11, 2019 the European Commission implemented stringent regulatory conditions regarding the use of fluoroquinolones due to their disabling and potentially long-lasting side effects [121]. This legally binding decision is applicable in all EU countries. National authorities have been urged to enforce this ruling and to take all appropriate measures to promote the correct use of this class of antibiotics. In uncomplicated cystitis a fluoroquinolone should only be used when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections [121].

3.4.4.1 Cystitis in pregnancy

Short courses of antimicrobial therapy can also be considered for treatment of cystitis in pregnancy [122], 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

Cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection. 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 sulfamethoxazole or a fluoroquinolone if in accordance with susceptibility testing (see section 3.4.4.4) [123].

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, with the exception of antimicrobials with nephrotoxic potential, e.g. aminoglycosides. The combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m2 as accumulation of the drug leads to increased side effects as well as reduced urinary tract recovery, with the risk of treatment failure [124].

3.4.4.4 *Summary of evidence and recommendations for antimicrobial therapy for uncomplicated cystitis*

Summary of evidence	**LE**
Clinical success for the treatment of uncomplicated cystitis is significantly more likely in women treated with antimicrobials than placebo.	1b
Aminopenicillins are no longer suitable for antimicrobial therapy in uncomplicated cystitis because of negative ecological effects, high resistance rates and their increased selection for extended spectrum beta-lactamase (ESBL)-producing bacteria.	3

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

Table 1: Suggested regimens for antimicrobial therapy in uncomplicated cystitis

Antimicrobial	**Daily dose**	**Duration of therapy**	**Comments**
First-line women			
Fosfomycin trometamol	3 g SD	1 day	Recommended only in women with uncomplicated cystitis.
Nitrofurantoin macrocrystal	50-100 mg four times a day	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg b.i.d	5 days	
Nitrofurantoin macrocrystal prolonged release	100 mg b.i.d	5 days	
Pivmecillinam	400 mg t.i.d	3-5 days	
Alternatives			
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable
If the local resistance pattern for E. coli is < 20%			
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy
Treatment in men			
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.

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

3.4.5 ***Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [26]. 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 [125]. 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 [125].

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 2. 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 [126]. However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or urothelial cancer is suspected.

Table 2: Age-related associations of rUTI in women [71, 101, 127]

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	Cystocele
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 [125]. These interventions should be attempted in this order. Any urological risk factor must be identified and treated. Significant residual urine should be treated optimally, including by CIC 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 front to back after defecation, douching and wearing occlusive underwear) have been suggested to decrease the risk of rUTI. However, studies that have explored underlying behavioural risk factors have consistently documented the lack of association with rUTI [125].

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 [128, 129].

3.5.3.2.1 Hormonal replacement

In post-menopausal women vaginal oestrogen replacement, but not oral oestrogen, showed a trend towards preventing rUTI [128, 130].

3.5.3.2.2 Immunoactive prophylaxis

OM-89 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 [128, 131-133]. Efficacy in other groups of patients relative to antimicrobial prophylaxis remains to be established.

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 [134]. 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 [135, 136]. However, a meta-analysis including 24 studies and comprising 4,473 participants showed that current

cranberry products did not significantly reduce the occurrence of symptomatic UTI for women with rUTI [137]. 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 [138]. 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 instillations of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment in the treatment of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of rUTI [139]. A review of 27 clinical studies concluded that large-scale trials are urgently needed to assess the benefit of this type of therapy [140]; 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 [141]. 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, trimethoprim 100 mg once daily and during pregnancy cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [125, 142]. 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 [143].

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 [144]. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI (section 3.4.4.4).

3.5.4 Summary of evidence and recommendations for the diagnostic evaluation and treatment of rUTIs

Summary of evidence	LE
Extensive routine workup including cystoscopy, imaging, etc. has a low diagnostic yield for the diagnosis of rUTI.	3
Studies that have investigated behavioural risk factors in the development of rUTIs have consistently documented the lack of association with rUTI.	3
Vaginal oestrogen replacement has shown a trend towards preventing rUTI in post-menopausal women.	1b
OM-89 has been shown to be more effective than placebo for immunoprophylaxis in female patients with rUTIs in several randomised trials with a good safety profile.	1a
Both continuous low-dose antimicrobial prophylaxis and post-coital antimicrobial prophylaxis, have been shown to reduce the rate of rUTI.	1b
A prospective cohort study showed that intermittent self-start therapy is effective, safe and economical in women with rUTIs.	2b

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

3.6 Uncomplicated pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known relevant 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 [145]. Pregnant women with acute pyelonephritis need special attention, as this kind of infection may not only have an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn child with more frequent preterm labour and birth [146].

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 [147]. 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 tract obstruction or renal stone disease in patients with a history of urolithiasis, renal function disturbances or a high urine pH [148]. Additional investigations, such as a contrast enhanced computed tomography (CT) scan, or excretory urography should be considered if the patient remains febrile after 72 hours of treatment, or immediately if there is deterioration in clinical status [148]. 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 [148].

*3.6.2 **Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis***

Summary of evidence	**LE**
Urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis in addition to urinalysis.	4
A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule.	2b
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

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

*3.6.3 **Disease management***

3.6.3.1 Outpatient treatment

Fluoroquinolones and cephalosporines are the only antimicrobial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis [149]. However, oral cephalosporines achieve significantly lower blood and urinary concentrations than intravenous cephalosporines. Other agents such as nitrofurantoin, oral fosfomycin, and pivmecillinam should be avoided as there is insufficient data regarding their efficacy [150]. 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. A short outpatient antibiotic course of treatment, for acute pyelonephritis, has been shown to be equivalent to longer durations of therapy in terms of clinical and microbiological success. However, this is associated with a higher recurrence rate of infection within four to six weeks and needs to be tailored to local policies and resistance patterns [151].

3.6.3.2 Inpatient treatment

Patients with uncomplicated pyelonephritis requiring hospitalisation should be treated initially with an intravenous antimicrobial regimen e.g. a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin [152]. Ceftolozane/tazobactam achieved a clinical response rate of over 90% in patients with uncomplicated pyelonephritis [153, 154]. It also demonstrated significantly higher composite cure rates than levofloxacin among levofloxacin-resistant pathogens [155]. Ceftazidime-avibactam combination has been shown to be effective for treating ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* UTIs [156].

Novel antimicrobial agents include imipenem/cilastatin, cefiderocol, meropenem-vaborbactam and plazomicin. Imipenem/cilastatin has been investigated in a phase 2 randomised trial and showed good clinical response rates [157]. Cefatazidime-avibactam and doripenem showed similar efficacy against ceftazidime non-susceptible pathogens and may offer an alternative to carbapenems in this setting [158]. Meropenem-vaborbactam has been shown to be non-inferior to piperacillin-tazobactam in a phase 3 RCT [159]. It was also effective for treating carbapenem-resistant Enterobacteriaceae with cure rates of 65% compared to best available treatment [160]. Once daily plazomicin was non-inferior to meropenem for the treatment of cUTIs and acute pyelonephritis caused by Enterobacteriaceae, including multidrug-resistant strains [161]. Cefiderocol was non-inferior to imipenem/cilastatin for the treatment of complicated UTI in people with multidrug-resistant Gram-negative infections in a phase 2 RCT [162].

Carbapenems and novel broad spectrum antimicrobial agents should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms. 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 ESBL-producing organisms is warranted [163]. Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antimicrobial therapy [164].

3.6.3.2.1 Summary of evidence and recommendations for the treatment of uncomplicated pyelonephritis

Summary of evidence	**LE**
Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis.	1b
Intravenous antimicrobial regimens for uncomplicated pyelonephritis may include a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin.	1b
Carbapenems should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms.	4
The appropriate antimicrobial should be chosen based on local resistance patterns and optimised on the basis of drug susceptibility results.	3

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

Table 3: Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

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

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

Table 4: Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobials	Daily dose	Comments
First-line treatment		
Ciprofloxacin	400 mg b.i.d	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1-2 g q.d	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1-2 g b.i.d	Lower dose studied, but higher dose recommended.
Piperacillin/tazobactam	2.5-4.5 g t.i.d	
Gentamicin	5 mg/kg q.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	
Last-line alternatives		
Imipenem/cilastatin	0.5 g t.i.d	Consider carbapenems only in patients with early culture results indicating the presence of multi-drug resistant organisms.
Meropenem	1 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Cefiderocol	2g t.i.d	
Meropenem-vaborbactam	2g t.i.d	
Plazomicin	15mg/kg o.d	

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

In pregnant women with pyelonephritis, outpatient management with appropriate parenteral antimicrobials may also be considered, provided symptoms are mild and close follow-up is feasible [165, 166]. 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 [167].

*3.6.4 **Follow-up***

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

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 [168-170]. New insights into the management of cUTIs also suggest to consider infections caused by multi-drug resistant uropathogens [171]. The underlying factors that are generally accepted to result in a cUTI are outlined in Table 5. 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 [172].

Table 5: Common factors associated with complicated UTIs [171-174]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes mellitus
Vesicoureteral reflux	Immunosuppression
Recent history of instrumentation	Healthcare-associated infections
Isolated ESBL-producing organisms	Isolated multi-drug resistant organisms

*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, CA-UTI or patients who have undergone radical cystectomy with urinary diversion. In addition, all patients with nephrostomy may have an atypical clinical presentation. 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 micro-organisms 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 [173, 174]. *E. coli*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Serratia* spp. and *Enterococcus* spp. are the most common species 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 [175].

*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

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 [176]. The same applies to ciprofloxacin and other fluoroquinolones in urological patients [176].

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 [172]. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results [150]. These recommendations are not only suitable for pyelonephritis, but for all other cUTIs.

Alternative regimens for the treatment of cUTIs, particularly those caused by multidrug-resistant pathogens have been studied. Ceftolozane/tazobactam 1.5 g every eight hours demonstrated high clinical

cure rates for cUTIs caused by ESBL-producing Enterobacteriaceae in a pooled analysis of phase 3 clinical trials [177]. Cefiderocol (2 g) three times daily was non-inferior to imipenem-cilastatin (1 g) three times daily for the treatment of cUTI in patients with multidrug-resistant Gram-negative infections [162]. Imipenem/cilastatin plus relebactam (250 or 125 mg) was as effective as imipenem/cilastatin alone for treatment of cUTI in a phase 2 RCT [157]. Ceftazidime/avibactam has been shown to be as effective as carbapenems for the treatment of cUTI in a systematic review reporting a baseline of 25% for ESBL-producing Enterobacteriaceae, but more severe adverse events were reported in the ceftazidime/avibactam group [178]. Once-daily plazomicin was shown to be non-inferior to meropenem for the treatment of cUTIs caused by Enterobacteriaceae, including multidrug-resistant strains [161].

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 [179]. 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. Intravenous levofloxacin 750 mg once daily for five days has been shown to be non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms) [180].

3.7.4.2 Duration of antimicrobial therapy

Treatment for seven [181] to fourteen days (for men fourteen days when prostatitis cannot be excluded) [182] is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality. When the patient is hemodynamically stable and afebrile for at least 48 hours, a shorter treatment duration (e.g. seven days) may be considered in patients where a short-course treatment is desired due to relative-contraindications to the administered antibiotic [180].

*3.7.5 **Summary of evidence and recommendations for the treatment of complicated UTIs***

Summary of evidence	**LE**
Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen chosen based on local resistance data and previous urine culture results from the patient, if available. The regimen should be tailored on the basis of susceptibility result.	1b
If the prevalence of fluoroquinolone resistance is thought to be < 10% and the patient has contraindications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with complicated pyelonephritis.	2
In the event of hypersensitivity to penicillin a cephalosporins can still be prescribed, unless the patient has had systemic anaphylaxis in the past.	2
In patients with a cUTI with systemic symptoms, empirical treatment should cover ESBL-producing organisms if there is an increased likelihood of ESBL infection based on prevalence in the community, earlier collected cultures and prior antimicrobial exposure of the patient.	2
Intravenous levofloxacin 750 mg once daily for five days, is non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms).	2

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

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 [173]. The following recommendations are based on the SWAB Guidelines from the Dutch Working Party on Antibiotic Policy [172] as well as the IDSA Guidelines [173].

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

Catheter-associated UTIs are the leading cause of secondary healthcare-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract, and the mortality associated with this condition is approximately 10% [183]. The incidence of bacteriuria associated with indwelling catheterisation is 3-8% per day [184-188]. The duration of catheterisation is the most important risk factor for the development of a CA-UTI [189, 190]. 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 [191]. 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 [172]. 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 [172, 173].

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 mid-stream 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 [173].

3.8.3.3 Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI

Summary of evidence	**LE**
Patients with indwelling or suprapubic catheters become carriers of ABU, with antibiotic treatment showing no benefit.	1a
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.	2
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 mid-stream voided urine specimen from a patient whose catheter has been removed within the previous 48 hours.	3

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

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 [173]. Based on the global prevalence on infections in urology (GPIU) study, the causative micro-organisms in CA-UTI are comparable with the causative micro-organisms in other cUTIs; therefore, symptomatic CA-UTIs should be treated according to the recommendations for cUTI (see section 3.7.5) [192].

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and fourteen days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterised or not [173]. 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 two 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 mid-stream urine specimen should be obtained prior to the initiation of antimicrobial therapy to help guide treatment [173]. Long-term indwelling catheters should not be changed routinely. Follow appropriate practices for catheter insertion and care [193].

3.8.4.1 *Recommendations for disease management and prevention of CA-UTI*

Recommendations	Strength rating
Treat symptomatic catheter-associated UTI according to the recommendations for complicated UTI (see section 3.7.5).	Strong
Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.	Strong
Do not treat catheter-associated asymptomatic bacteriuria in general.	Strong
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	Strong
Replace or remove the indwelling catheter before starting antimicrobial therapy.	Strong
Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	Strong
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	Strong
The duration of catheterisation should be minimal.	Strong

3.8.5 *Removal of indwelling bladder catheter*

3.8.5.1 *Evidence question*

1. Does antibiotic prophylaxis reduce the rate of symptomatic UTI in adults following indwelling bladder catheter removal?

3.8.5.2 *Review of evidence*

A structured literature search identified one systematic review and meta-analysis [194] with a search date of November 2012 and one subsequent RCT [195]. Marschall *et al.*, identified seven RCTs with 1,520 participants. Meta-analysis showed overall benefit for use of prophylaxis RR (95%CI) = 0.45 (0.28-0.72); ARR 5.8% (from 10.5% to 4.7%) with a number needed to treat (NNT) of 17. Results for individual trials were inconsistent with five trials including the possibility of no benefit [194]. The trial reported by Fang *et al.*, recruited 172 participants undergoing laparoscopic radical prostatectomy randomised to seven days of ciprofloxacin (n=80) or no treatment (n=80). At the time of catheter removal which, occurred at a mean of nine days post-operatively, there was no difference in infective complications recorded at up to four weeks after catheter removal. More isolates obtained from the prophylaxis group (11) were resistant to ciprofloxacin compared to the no treatment group (3) [195].

3.8.5.3 Summary of evidence and recommendations for diagnostic evaluation of CA-UTI

Summary of evidence	LE
A meta-analysis showed overall benefit for use of prophylaxis for reduction of infective complications after catheter removal; however, results from individual trials were inconsistent with five out of seven trials including the possibility of no benefit.	1a
A subsequent RCT found no benefit of antibiotic prophylaxis for reduction of infective complications at up to four weeks after catheter removal.	1b

Recommendation	Strength rating
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal.	Weak

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, leukocytosis or leukopenia, tachycardia and tachypnoea, has been recognised as a set of alerting symptoms [196, 197]; however, SIRS is no longer included in the recent terminology of sepsis (Table 6) [12]. 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 [198]. Source control by decompression of any obstruction and drainage of larger abscesses in the urinary tract is essential [198]. 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 urinary 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 (Table 6).

*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 sepsis vary depending on the organ source [199] with urinary tract sepsis generally having a lower mortality than that from other sources [200]. Sepsis is more common in men than in women [201]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [199], 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) [202]. Although the rate of sepsis due to Gram-positive and fungal organisms has increased, Gram-negative bacteria remain predominant in urosepsis [192, 203].

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***

For diagnosis of systemic symptoms in sepsis either the full Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, or the quickSOFA score should be applied (Table 6). Microbiology sampling should be applied to urine, two sets of blood cultures [204], and if appropriate drainage fluids. Imaging investigations, such as sonography and CT-scan should be performed early [205].

Table 6. Definition and criteria of sepsis and septic shock [12, 196, 197]

Disorder	Definition
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 mm Hg 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 micro-organism. In several countries, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [203]. 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 [200]. 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 [200].

3.9.4.2 Biochemical markers

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 [206]. 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 [207]. Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [206, 208]. In addition, serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [209]. 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 source control (obstruction of the urinary tract), adequate life-support care, and appropriate antimicrobial therapy [200, 205]. 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 [210, 211] they include:

- Isolation of patients with multi-resistant organisms following local and national recommendations.
- 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. 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 [212]. 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

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 [213]. However, follow-up studies in an improved emergency medicine background have not achieved positive effects with this strategy [214-216]. An individual patient data meta-analysis of the later three multicentre trials concluded that early goal-directed therapy did not result in better outcomes than usual care and was associated with higher hospitalisation costs [217].

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 [198, 205]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with appropriate adjustment for renal function [198]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis [198].

3.9.5.2.2 Source control

Obstruction in the urinary tract is the most frequent urological source of urosepsis. Drainage of obstruction and abscesses, and removal of foreign bodies, such as urinary catheters or stones is therefore the most important source control strategy. 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 [198, 205]:

- fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure: passive leg raising-induced changes in cardiac output and in arterial pulse pressure are predictors of fluid responsiveness in adults [218];
- 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 in urology remains a severe situation with a considerable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next years [198, 205, 219]. 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 is dependent on good practice to avoid nosocomial infections and using antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

3.9.5.3 Summary of evidence and recommendations for the diagnosis and treatment of urosepsis

Summary of evidence	LE
Initial high dose empiric antimicrobial therapy, administered within the first hour, should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available.	2b
Source control interventions should be implemented as soon as possible to control or eliminate diagnosed and/or suspected infectious foci.	3

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

Table 7: Suggested regimens for antimicrobial therapy for urosepsis.

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

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

3.10 Urethritis

*3.10.1 **Introduction***

Urethritis can be of either infectious or non-infectious origin. Inflammation of the urethra presents usually with LUTS and must be distinguished from other infections of the lower urinary tract. Urethral infection is typically spread by sexual contact.

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

From a therapeutic and clinical point of view, gonorrhoeal urethritis (GU) caused by *Neisseria gonorrhoeae* must be differentiated from non-gonococcal urethritis (NGU). Non-gonococcal urethritis is a non-specific diagnosis that can have many infectious aetiologies. Causative pathogens include *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum* and *Trichomonas vaginalis*. The role of *Ureaplasma* spp. as urethritis

causative pathogens is controversial. Recent data suggests that *U. urealyticum*, but not *U. parvum* is an aetiological agent in NGU [220]. The prevalence of isolated causative pathogens are: *C. trachomatis* 11-50%; *M. genitalium* 6-50%; Ureaplasmas 5-26%; *T. vaginalis* 1-20%; and adenoviruses 2-4% [221].

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 [222].

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

*3.10.3 **Evidence Questions***

1. In patients with urethritis what is the best method of detecting the causative pathogen?
2. In patients with urethritis what are the best treatment strategies for clinical or microbiological cure?

*3.10.4 **Evidence Summary***

A systematic search of the literature form January 2014 until February 2019 identified 488 titles of which 71 were selected for full text review. Thirteen systematic reviews or guidelines based on systematic literature searches [220-232], and seventeen original publications [233-249] were selected for further analysis. In addition, a further eleven relevant publications were identified from the references of the reviewed literature [250-260].

*3.10.5 **Diagnostic evaluation***

In symptomatic patients the diagnosis of urethritis can be made based on the presence of any of the following criteria [221, 222]:

- Mucoid, mucopurulent, or purulent urethral discharge.
- Gram or methylene-blue stain of urethral secretions demonstrating inflammation. Five or more polymorphonuclear leucocytes (PMNL) per high power field (HPF) is the historical cut-off for the diagnosis of urethritis. A threshold of ≥ 2 PMNL/HPF was proposed recently based on better diagnostic accuracy [237, 250-252], but this was not supported by other studies [236]. Therefore, in line with the 2016 European Guideline on the management of NGU [221] the use of ≥ 5 PMNL/HPF cut-off level is recommended until the benefit of alternative cut-off levels is confirmed.
- The presence of ≥ 10 PMNL/HPF in the sediment from a spun first-void urine sample or a positive leukocyte esterase test in first-void urine.

Evidence of urethral inflammation in the Gram stain of urethral secretions with gonococci located intracellularly as Gram-negative diplococci indicates GU. Non-gonococcal urethritis is confirmed when staining of urethral secretions indicates inflammation in the absence of intracellular diplococci. Clinicians should always perform point-of-care diagnostics (e.g. Gram staining, first-void urine with microscopy, leukocyte esterase testing) if available to obtain objective evidence of urethral inflammation and to guide treatment [221, 222, 235]. Recent studies showed that processing time of point-of-care diagnostics is highly relevant in terms of patient compliance and real-life applicability [233, 234].

Men who meet the criteria for urethritis should be tested for *C. trachomatis, M. genitalium and N. gonorrhoea* with nucleic acid amplification tests (NAAT), even if point-of-care tests are negative for gonorrhoeae [221, 224]. The sensitivity and specificity of NAATs is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections [225, 253]. The performance of first-catch urine is non-inferior to urethral swabs [253]. In case of delayed treatment, if a NAAT is positive for gonorrhoea, a culture using urethral swabs should be performed before treatment to assess the antimicrobial resistance profile of the infective strain [222]. *N. gonorrhoeae and C. trachomatis* cultures are mainly used to evaluate treatment failures and monitor developing resistance to current treatment. *Trichomonas* spp. can usually be identified microscopically [222] or by NAATs [227].

Non-gonococcal urethritis is classified as persistent when symptoms do not resolve within three to four weeks following treatment. When this occurs NAATs should be performed for urethritis pathogens including *T. vaginalis* four weeks after completion of therapy [221, 238].

*3.10.6 **Disease management***

For severe urethritis empirical treatment should be started following diagnosis. If the patients symptoms are mild, delayed treatment guided by the results of NAATs is recommended. All sexual partners at risk should be assessed and treated whilst maintaining patient confidentiality [221, 241].

3.10.6.1 Gonococcal urethritis

For GU, a combination treatment using two antimicrobials with different mechanisms of action is recommended to improve treatment efficacy and to hinder increasing resistance to cephalosporins [222]. Ceftriaxone 1 g intramuscularly or intravenously with azithromycin 1 g single oral dose should be used as first-line treatment. Azithromycin is recommended because of its favourable susceptibility rates compared to other antimicrobials, good compliance with the single-dose regimen and the possibility of a *C. trachomatis* co-infection [222]. In case of azithromycin allergy, doxycycline can be used instead in combination with ceftriaxone or cefixime [222]. A 400 mg oral dose of cefixime is recommended as an alternative regimen to ceftriaxone; however, it has less favourable pharmacodynamics and may lead to the emergence of resistance [223, 259].

A number of alternative regimens for the treatment of GU have been studied. In a randomised, open label, non-comparative clinical study dual treatment with a combination of intramuscular gentamicin 240 mg plus oral azithromycin 2 g (n=202) single doses and a combination of oral gemifloxacin 320 mg plus oral azithromycin 2 g (n=199) single doses were associated with microbiological cure rates of 100% and 99.5%, respectively [255]. A 2014 systematic review focusing on the use of single-dose intramuscular gentamicin concluded that there is insufficient data to support or refute the efficacy and safety of this regimen in the treatment of uncomplicated gonorrhoea [229]. In three prospective single arm studies enrolling men with GU the use of extended-release azithromycin 2 g single oral dose resulted in microbiological cure rates of 83% (n=36), 93.8% (n=122) and 90.9% (n=33), respectively [245, 246, 248]. However, azithromycin monotherapy is generally not recommended because of its effect on increasing macrolide resistance rates [222]. Intramuscular spectinomycin 2 g single dose shows microbiological cure rates above 96% [256, 259] in urogenital gonorrhoeal infections where available, it can be a valid treatment alternative. An open label, randomised trial compared oral fosfomycin trometamol 3 g on days one, three and five (n=60) with intramuscular ceftriaxone 250 mg plus oral azithromycin 1 g single dose (n=61) in men with uncomplicated GU. In the per-protocol analysis clinical and microbiologic cure rates were 96.8% and 95.3% respectively [249].

The worldwide increase in gonorrhoeal antimicrobial resistance and the emergence of multidrug-resistant gonorrhoeal strains is a globally recognised healthcare crisis which emphasises the importance of guideline adherence [228, 240, 260].

3.10.6.2 Non-gonococcal urethritis

For NGU without an identified pathogen oral doxycycline 100 mg twice daily for seven days should be used as first-line treatment. Alternatively, single dose oral azithromycin 500 mg day one and 250 mg days two to four can be used. This regimen provides better efficacy compared to azithromycin 1 g single dose for *M. genitalium* infections, in which azithromycin 1 g single dose treatment is associated with the development of increasing macrolide resistance significantly decreasing the overall cure rate [221, 224, 230, 244]. However, a retrospective cohort study did not find significant difference between the extended and 1 g single dose azithromycin regimen regarding cure rates and the selection of macrolide resistance in *M. genitalium* urethritis [242]. If macrolide resistant *M. genitalium* is detected moxifloxacin 400 mg can be used for seven to fourteen days [221, 222, 231]. In case of failure after both azithromycin and moxifloxacin treatment, pristinamycin (registered in France) is the only antimicrobial agent with documented activity against *M. genitalium* [224, 243, 254]. Josamycin 500 mg three times a day for ten days is used in Russia, but will not eradicate macrolide-resistant strains [224].

For chlamydial urethritis azithromycin 1 g single dose and doxycycline 100 mg twice daily for seven days are both effective options [258]. A Cochrane review found that in men with urogenital *C. trachomatis* infection regimens with azithromycin are probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure [232]. Fluoroquinolones, such as ofloxacin or levofloxacin, may be used as second-line treatment only in selected cases where the use of other agents is not possible [257].

For *U. urealyticum* infections the efficacy of doxycycline 100 mg twice daily for seven days is similar to azithromycin 1 g single dose treatment [221, 239]. For urethritis caused by *T. vaginalis* oral metronidazole or tinidazole 2 g single dose is recommended as first-line treatment. For treatment options for persistent or recurrent *T. vaginalis* infection refer to the review of Sena *et. al.*, [227]. In case of persistent NGU treatment should cover *M. genitalium* and *T. vaginalis* [221, 222].

3.10.7 ***Follow-up***

Patients should be followed-up for control of pathogen eradication after completion of therapy only if therapeutic adherence is in question, symptoms persist or reoccurrence is suspected. 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 cooperation with specialists in venereology, whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV [226].

3.10.8 Summary of evidence and recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis

Summary of evidence	**LE**
A Gram stain of urethral discharge or a urethral smear that shows ≥ 5 leukocytes per high power field (× 1,000) and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis.	3b
Validated NAATs of first-void urine samples have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections.	2a
For GU dual treatment with ceftriaxone and azithromycin is the most effective combination.	2a
In case of urogenital *C. trachomatis* infection in men azithromycin is probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure.	1a
In case of *U. urealyticum* infection the efficacy of doxycycline 100 mg twice for seven days is similar to azithromycin 1 g single dose treatment.	2a

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

Table 8: Suggested regimens for antimicrobial therapy for urethritis

Pathogen	Antimicrobial	Dosage & Duration of therapy	Alternative regimens
Gonococcal Infection	Ceftriaxone Azithromycin	1 g i.m. or i.v., SD 1 g p.o., SD	• Cefixime 400 mg p.o., SD plus Azithromycin 1 g p.o., SD In case of cephalosporin allergy: • Gentamicin 240 mg i.m SD plus Azithromycin 2 g p.o., SD • Gemifloxacin 320 mg p.o., SD plus Azithromycin 2 g p.o., SD • Spectinomycin 2 g i.m., SD • Fosfomycin trometamol 3 g p.o., on days 1, 3 and 5 In case of azithromycin allergy, in combination with ceftriaxone or cefixime: • Doxycycline 100 mg b.i.d, p.o., 7 days
Non-Gonococcal infection (non-identified pathogen)	Doxycycline	100 mg b.i.d, p.o., 7-10 days	Azithromycin 500 mg p.o., day 1, 250 mg p.o., 4 days
Chlamydia trachomatis	Azithromycin Or Doxycycline	1.0-1.5 g p.o., SD 100 mg b.i.d, p.o., for 7 days	• Levofloxacin 500 mg p.o., q.d., 7 days • Ofloxacin 200 mg p.o., b.i.d., 7 days
Mycoplasma genitalium	Azithromycin	500 mg p.o., day 1, 250 mg p.o., 4 days	In case of macrolide resistance: • Moxifloxacin 400 mg q.d., 7-14 days
Ureaplasma urealyticum	Doxycycline	100 mg b.i.d, p.o., 7 days	Azithromycin 1.0-1.5 g p.o., SD
Trichomonas vaginalis	Metronidazole Tinidazole	2 g p.o., SD 2 g p.o., SD	Metronidazole 500 mg p.o., b.i.d., 7 days
Persistent non-gonococcal urethritis			
After first-line doxycycline	Azithromycin plus Metronidazole	500 mg p.o., day 1, 250 mg p.o., 4 days 400 mg b.i.d. p.o., 5 days	If macrolide resistant M. genitalium is detected moxifloxacin should be substituted for azithromycin
After first-line azithromycin	Moxifloxacin plus Metronidazole	400 mg p.o. q.d., 7–14 days 400 mg b.i.d. p.o., 5 days	

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

3.11 Bacterial Prostatitis

*3.11.1 **Introduction***

Bacterial prostatitis is a clinical condition caused by bacterial pathogens. It is recommended that urologists use the classification suggested by the National Institute of Diabetes, Digestive and Kidney Diseases (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 9) [261-263].

Table 9: Classification of prostatitis and CPPS according to NIDDK/NIH [261-263]

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

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

*3.11.2 **Evidence Question***

In men with NIDDK/NIH Category I or II prostatitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

*3.11.3 **Evidence Summary***

A systematic literature search from 1980 until June 2017 was performed. One systematic review [264], six RCTs [265-270], two narrative reviews [271, 272], one prospective cohort study [273], two prospective cross-sectional studies [274, 275], and one retrospective cohort study [267], were selected from 856 references.

A retrospective study [276], investigated the potential role of unusual pathogens in prostatitis syndrome in 1,442 patients over a four year period. An infectious aetiology was determined in 74.2% of patients; *C. trachomatis*, *T. vaginalis* and *U. urealyticum* infections were found in 37.2%, 10.5% and 5% of patients, respectively whilst *E. coli* infection was found in only 6.6% of cases. Cross sectional studies confirmed the validity of the Meares and Stamey test to determine the bacterial strain and targeted antibiotic therapies [274, 275]. The evidence levels were very good, in particular those regarding information on atypical strains, epidemiology and antibiotic treatments.

A systematic review on antimicrobial therapy for CBP [264] compared multiple antibiotic regimens from eighteen selected studies enrolling a total of 2,196 patients. The role of fluoroquinolones as first line agents was confirmed with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events. The efficacy of macrolides and tetracyclines on atypical pathogens was confirmed.

Randomised controlled trials on combined treatments [269, 270] indicated that the combination of plants/herbal extracts or PDE5Is with antibiotics may improve quality of life and symptoms in patients with CBP; however, the number of enrolled patients was inadequate to obtain definitive conclusions.

A review of treatment of bacterial prostatitis [271] indicated that the treatment of CBP is hampered by the lack of an active antibiotic transport mechanism into infected prostate tissue and fluids. The review underlined the potential effect of different compounds in the treatment of ABP and CBP on the basis of over 40 studies on the topic.

One RCT compared the effects of two different metronidazole regimens for the treatment of CBP caused by *T. vaginalis* [268]. Metronidazole 500 mg three times daily for fourteen days was found to be efficient for micro-organism eradication in 93.3% of patients with clinical failure in 3.33% of cases.

*3.11.4 **Epidemiology, aetiology and pathogenesis***

Prostatitis is a common diagnosis, but less than 10% of cases have proven bacterial infection [228]. Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in ABP [277]. In CBP, the spectrum of species is wider and may include atypical micro-organisms [271]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis*, *Candida* spp. and other rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum* [278]. The significance of identified intracellular bacteria, such as *C. trachomatis*, is uncertain [279]; however, two studies have highlighted its possible role as a causative pathogen in CBP [280, 281].

*3.11.5 **Diagnostic evaluation***

3.11.5.1 History and symptoms

Acute bacterial prostatitis usually presents abruptly with voiding symptoms and distressing but poorly localised pain. It is often associated with malaise and fever. Transrectal prostate biopsy increases the risk of ABP despite antibiotic prophylaxis and antiseptic prevention procedures [265]. Chronic bacterial prostatitis is defined by symptoms that persist for at least three months [282-284]. The predominant symptoms are pain at various locations including the perineum, scrotum, penis and inner part of the leg as well as LUTS [261-263].

3.11.5.2 Symptom questionnaires

In CBP symptoms appear to have a strong basis for use as a classification parameter [285]. Prostatitis symptom questionnaires have therefore been developed to assess severity and response to therapy [285, 286]. They include the validated Chronic Prostatitis Symptom Index (CPSI); however, its usefulness in clinical practice is uncertain [273].

3.11.5.3 Clinical findings

In ABP, the prostate may be swollen and tender on DRE. Prostatic massage should be avoided as it can induce bacteraemia and sepsis. Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% [287]. Blood culture and complete blood count are useful in ABP. Imaging studies can detect a suspected prostatic abscess [271].

In case of longer lasting symptoms CPPS as well as other urogenital and anorectal disorders must be taken into consideration. Symptoms of CBP or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should trigger investigation for urogenital tuberculosis.

3.11.5.4 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of a patient with ABP is mid-stream urine culture [271]. In CBP, quantitative bacteriological localisation cultures and microscopy of the segmented urine and expressed prostatic secretion (EPS), as described by Meares and Stamey [288], are still important investigations to categorise clinical prostatitis [274, 275]. Accurate microbiological analysis of samples from the Meares and Stamey test may also provide useful information on the presence of atypical pathogens such as *C. trachomatis*, *T. vaginalis* and *U. urealiticum* [276]. The two-glass test has been shown to offer similar diagnostic sensitivity to the four-glass test [289].

3.11.5.5 Prostate biopsy

Prostate biopsies cannot be recommended as routine work-up and are not advisable in patients with untreated bacterial prostatitis due to the increased risk of sepsis.

3.11.5.6 Other tests

Transrectal US may reveal endoprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles; however, it is unreliable as a diagnostic tool for prostatitis [290].

3.11.5.7 Additional investigations

3.11.5.7.1 Ejaculate analysis

Performing an ejaculated semen culture improves the diagnostic utility of the four glass test [274]; however, semen cultures are more often positive than EPS cultures in men with non-bacterial prostatitis [275]. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3.11.5.7.2 First-void urine sample

First-void urine is the preferred specimen for the diagnosis of urogenital *C. trachomatis* infection in men by NAATs, since it is non-invasive and yet allows the detection of infected epithelial cells and associated *C. trachomatis* particles [291].

3.11.5.7.3 Prostate specific antigen (PSA)

Prostate specific antigen is increased in about 60% and 20% of men with ABP and CBP, respectively [272]. The PSA level decreases after antibiotic therapy (which occurs in approximately 40% of patients) and correlates with clinical and microbiological improvement [266]. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [292].

3.11.5.8 Summary of evidence and recommendations for the diagnosis of bacterial prostatitis

Summary of evidence	LE
Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% in patients with ABP.	3
The four-glass Meares and Stamey test is the optimum test for diagnosis of CBP. The two-glass test has been shown to offer similar diagnostic sensitivity in a comparison study.	2b
First-void urine is the preferred specimen for the diagnosis of urogenital *C. trachomatis* infection in men by NAATs.	2b
Transrectal ultrasound is unreliable and cannot be used as a diagnostic tool in prostatitis.	3
Semen culture sensitivity is reported to be approximately 50%; therefore, it is not routinely part of the diagnostic assessment of CBP.	3
Prostate specific antigen levels may be elevated during active prostatitis; therefore, PSA testing should be avoided as it offers no practical diagnostic information for prostatitis.	3

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

*3.11.6 **Disease management***

3.11.6.1 Antimicrobials

Antimicrobials are life-saving in ABP and recommended in CBP. Culture-guided antibiotic treatments are the optimum standard; however, empirical therapies should be considered in all patients with ABP.

In ABP parenteral administration of high doses of bactericidal antimicrobials, such as broad-spectrum penicillins, a third-generation cephalosporin or fluoroquinolones, is recommended [293]. For initial therapy, any of these antimicrobials may be combined with an aminoglycoside [277-286, 293-297]. Ancillary measures include adequate fluid intake and urine drainage [228]. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks [298].

Fluoroquinolones, despite the high resistance rates of uropathogens, are recommended as first-line agents in the empirical treatment of CBP because of their favourable pharmacokinetic properties [299], their generally good safety profile and antibacterial activity against Gram-negative pathogens including *P. aeruginosa* and C. trachomatis [264, 300]. However, increasing bacterial resistance is a concern. Azithromycin and doxycycline are active against atypical pathogens such as *C. trachomatis* and genital mycoplasmata [267, 276]. Levofloxacin did not demonstrate significant clearance of *C. trachomatis* in patients with CBP [301]. Metronidazole treatment is indicated in patients with *T. vaginalis* infections [268].

Duration of fluoroquinolone treatment must be at least fourteen days while azithromycin and doxycycline treatments should be extended to at least three to four weeks [267, 276]. In CBP antimicrobials should be given for four to six weeks after initial diagnosis [271]. If intracellular bacteria have been detected macrolides or tetracyclines should be given [264, 299, 302].

3.11.6.2 Intraprostatic injection of antimicrobials

This treatment has not been evaluated in controlled trials and should not be considered [303, 304].

3.11.6.3 Combined treatments

A combination of fluoroquinolones with various herbal extracts may attenuate clinical symptoms without increasing the rate of adverse events [269]. However, a combination of fluoroquinolones with vardenafil neither improved microbiological eradication rates or attenuated pain or voiding symptoms in comparison with fluoroquinolone treatment alone [270].

3.11.6.4 Drainage and surgery

Approximately 10% of men with ABP will experience urinary retention [305] which can be managed by uretheral or suprapubic catheterisation. However, recent evidence suggests that suprapubic catheterisation can reduce the risk of development of CBP [306].

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [307]; however, the abscess 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 [308].

3.11.6.5 Summary of evidence and recommendations for the disease management of bacterial prostatitis

Summary of evidence	**LE**
The treatment regimen for ABP is based on clinical experience and a number of uncontrolled clinical studies. For systemically ill patients with ABP, parenteral antibiotic therapy is preferable. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks.	3
The role of fluoroquinolones as first-line agents for antimicrobial therapy for CBP was confirmed in a systematic review, with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events.	1a
Metronidazole 500 mg three times daily for fourteen days was found to be efficient for eradication in 93.3% of patients with *T. vaginalis* CBP.	1b
In patients with CBP caused by obligate intracellular pathogens, macrolides showed higher microbiological and clinical cure rates compared to fluoroquinolones.	1a
Clinicians should consider local drug-resistance patterns when choosing antibiotics.	3

Recommendations	**Strength rating**
Acute bacterial prostatitis	
Treat acute bacterial prostatitis according to the recommendations for complicated UTIs (see section 3.7.5).	Strong
Chronic bacterial prostatitis (CBP)	
Prescribe a fluoroquinolone (e.g. ciprofloxacin, levofloxacin) as first-line treatment for CBP.	Strong
Prescribe a macrolide (e.g. azithromycin) or a tetracycline (e.g. doxycycline) if intracellular bacteria have been identified as the causative agent of CBP.	Strong
Prescribe metronidazole in patients with *Trichomonas vaginalis* CBP.	Strong

Table 10: Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis

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

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

3.11.7 ***Follow-up***

In asymptomatic post-treatment patients routine urinalysis and/or urine culture is not mandatory as there are no validated tests of cure for bacterial prostatitis except for cessation of symptoms [271]. In patients with persistent symptoms and repeated positive microbiological results for sexually transmitted infectious pathogens, microbiological screening of the patient's partner/s is recommended. Antibiotic treatments may be repeated with a more prolonged course, higher dosage and/or different compounds [271].

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 in:

1. men at low risk of gonorrhoea infection;
2. men at high risk of gonorrhoea infection?

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 [309]. 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* [310]. 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, typically as chronic epididymitis, 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* spp. 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 [311]. Detection of these pathogens should be reported according to local procedures. All patients with probable sexually transmitted infections (STIs) should be advised to attend an appropriate clinic to be screened for other STIs. 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 [312]. If appropriate 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.

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 with 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* or *M. genitalium* 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 approximately three days. 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 [311, 313, 314] with search dates of December 2009, March 2012 and April 2013, respectively. No evidence quality assessments were detailed. A structured search of the literature from January 2010 to May 2017 identified 1,108 titles of which 46 were selected for full text review and six were included [315-320]. In addition, a high quality RCT outside the search dates was identified which demonstrated that a ten-day course of ciprofloxacin was superior to pivampicillin for clinical cure (80% vs. 60%) in men aged > 40 years [321]. 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 [319].

Empiric antibiotic regimens from existing guidelines [311, 313, 314] 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 *C. 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 [315].

A cohort study found semen parameters may be impaired during epididymitis but recovered following successful treatment [318]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [316] and by primary care physicians [317].

*3.12.6 **Screening***

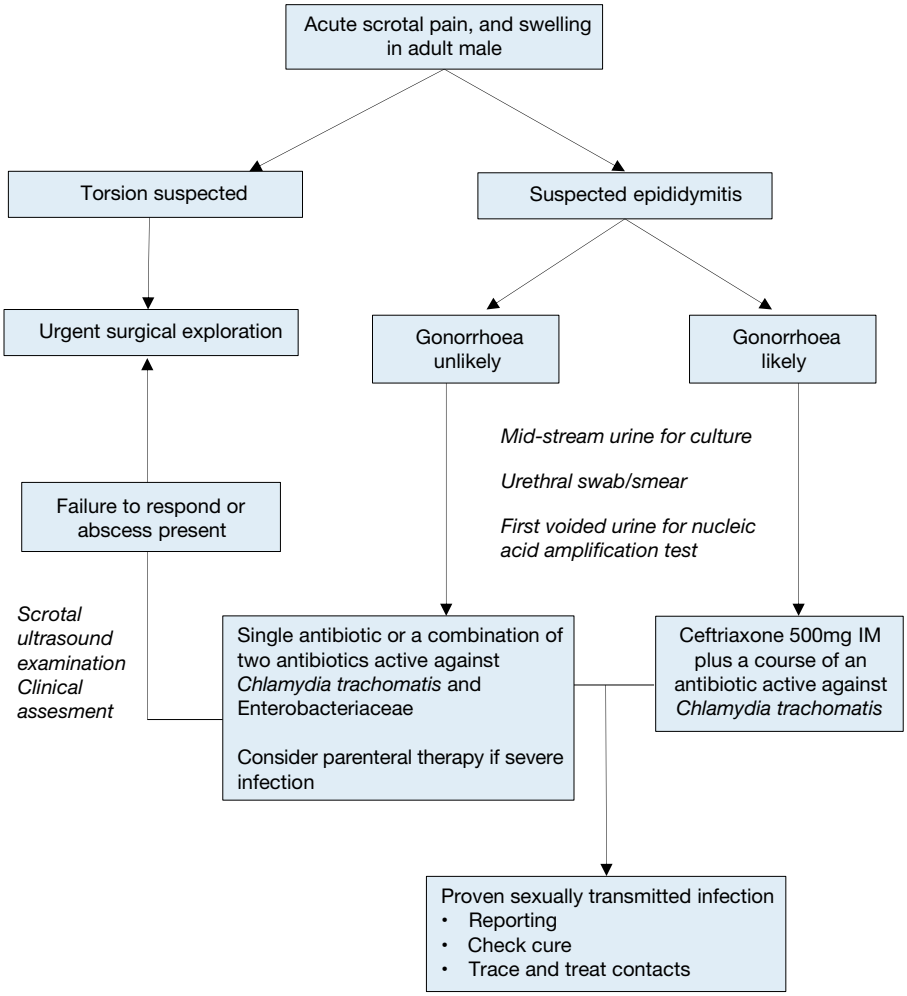
A large cohort screening study for carriage of *C. trachomatis* including a randomly selected group of 5,000 men of whom 1,033 were tested showed no benefit in terms of reduction in risk of epididymitis over nine years of observation [320].

*3.12.7 **Summary of evidence and recommendations for the diagnosis and treatment of acute infective epididymitis***

Summary of evidence	**LE**
In young sexually active patients both STIs and Enterobacteriaceae have to be considered as aetiological agents.	3
In patients > 40 years antibiotic therapy with ciprofloxacin is superior to pivmecillinam.	1b
A negative sexual risk history does not exclude STIs in sexually active men.	3

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

Figure 2: Diagnostic and treatment algorithm for adult men with acute epididymitis



3.13 Fournier's Gangrene (Necrotising fasciitis of the perineum and external genitalia)

3.13.1 Evidence questions

1. What is the best antimicrobial treatment strategy to reduce mortality?
2. What is the best debridement and reconstruction strategy to reduce mortality and aid recovery?
3. Are there any effective adjuvant treatments that improve outcome?

3.13.2 Epidemiology, Aetiology and Pathophysiology

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia [322]. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway.

3.13.3 Diagnostic Evaluation

Typically, there is painful swelling of the scrotum or perineum with sepsis [322]. 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. Patient risk factors for occurrence and mortality include being immunocompromised, most commonly diabetes or malnutrition, recent urethral or perineal surgery, and high body mass index (BMI). In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment [323]. A high index of suspicion and careful examination, particularly of obese patients, is required. Computed tomography or MRI can help define para-rectal involvement, suggesting the need for bowel diversion [322].

3.13.4 Disease Management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement with urinary diversion by suprapubic catheter is necessary to reduce

mortality [322]. Consensus from case series suggests that surgical debridement should be early (< 24 hours) and complete, as delayed and/or inadequate surgery may result in higher mortality [322]. Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue. A suggested regime would comprise a broad-spectrum penicillin or third-generation cephalosporin, gentamicin and metronidazole or clindamycin [322]. This can then be refined, guided by microbiological culture.

*3.13.5 **Evidence Summary***

A systematic literature search from 1980 to July 2017 was performed. From 640 references one RCT [324], two systematic reviews [325, 326], one narrative review [322], three registry studies [327-329], one prospective cohort study [330] and two retrospective comparative cohort studies with at least 25 patients [331, 332] were selected. The three registry studies from the United States [327-329], found mortality rates of 10%, 7.5% and 5% from 650, 1,641 and 9,249 cases, respectively. Older age, diabetes and high BMI were associated with higher risk. A prospective cohort study showed that disease-specific severity scores did predict outcome, but were not superior to generic scoring systems for critical care [330]. Concerning the evidence questions:

1. A low quality retrospective case series [331] with 168 patients found no significant difference in mortality between patients given ≤ 10 days of parenteral antibiotics (80 patients) and those given > 10 days (88 patients).
2. A systematic review of wound closure techniques [326] found low-quality evidence from 16 case series involving 425 male patients. They recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.
3. A systematic review on the use of hyperbaric oxygen therapy [325] included three comparative case series and four other case series. All were retrospective and published prior to 2000. No consistent evidence of benefit was found; an RCT was advised. A more recent comparative case series [332] suggested benefit for use of hyperbaric oxygen therapy in 16 patients compared to 12 cases without use of such therapy in terms of reduced mortality and fewer debridements (low quality evidence). A low-quality RCT [324] with 30 patients found that use of honey soaked dressings resulted in a shorter hospital stay (28 vs. 32 days) than dressing soaked with Edinburgh solution of lime (EUSOL). We found no evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene.

*3.13.6 **Summary of evidence and recommendations for the disease management of Fournier's Gangrene***

Summary of evidence	**LE**
Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue.	3
A systematic review of wound closure techniques recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.	3
No consistent evidence of benefit for hyperbaric oxygen therapy was found.	3
A low quality RCT found that dressings soaked in honey resulted in a shorter hospital stay than dressing soaked with EUSOL.	3
No evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene was found.	4

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

Table 11: Suggested regimens for antimicrobial therapy for Fournier's Gangrene of mixed microbiological aetiology adapted from [333]**.**

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

IV = intravenous

3.14 Peri-Procedural Antibiotic Prophylaxis

3.14.1 ***General Principles***

3.14.1.1 Definition of infectious complications

The European Centre for Disease Prevention and Control (ECDC) and the CDC have both presented similar definitions recommended for the evaluation of infectious complications [334, 335].

3.14.1.2 Non-antibiotic measures for asepsis

There are a number of non-antibiotic measures designed to reduce the risk of surgical site infection (SSI), many are historically part of the routine of surgery. The effectiveness of measures tested by RCTs are summarised in systematic reviews conducted by the Cochrane Wounds Group (http://wounds.cochrane.org/news/reviews). Urological surgeons and the institutions in which they work should consider and monitor maintenance of an aseptic environment to reduce risk of infection from pathogens within patients (microbiome) and from outside the patient (nosocomial/healthcare-associated). This should include use of correct methods of instrument cleaning and sterilisation, frequent and thorough cleaning of operating rooms and recovery areas and thorough disinfection of any contamination. The surgical team should prepare to perform surgery by effective hand washing [336], donning of appropriate protective clothing and maintenance of asepsis. These measures should continue as required in recovery and ward areas.

Patients should be encouraged to shower pre-operatively, but use of chlorhexidine soap does not appear to be beneficial [337]. Although evidence quality is low, any required hair removal appears best done by clipping, rather than shaving, just prior to incision [338]. Mechanical bowel preparation should not be used as evidence review suggests harm not benefit [339, 340]. There is some weak evidence that skin preparation using alcoholic solutions or chlorhexidine result in a lower rate of SSI than iodine solutions [341]. Studies on the use of plastic adherent drapes showed no evidence of benefit in reducing SSI [342].

3.14.1.3 Detection of bacteriuria prior to urological procedures

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. A systematic review of the evidence identified eighteen studies comparing the diagnostic accuracy of different index tests (dipstick, automated microscopy, dipslide culture and flow cytometry), with urine culture as the reference standard [343]. The systematic review concluded that none of the alternative urinary investigations for the diagnosis of bacteriuria in adult patients prior to urological interventions can currently be recommended as an alternative to urine culture [343].

3.14.1.4 Choice of agent

Urologists should have knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence in order to establish written local guidelines. These guidelines should cover the five modalities identified by the ECDC following a systematic review of the literature [344]. The agent should ideally not be one that may be required for treatment of infection. When risk of skin wound infection is low or absent, an aminoglycoside (gentamicin) should provide cover against likely uropathogens provided the eGFR is > 20 mL/min; second generation cephalosporins are an alternative [345]. Recent urine culture results including presence of any multi-resistant organisms, drug allergy, history of *C. difficile* associated diarrhoea,

recent antibiotic exposure, evidence of symptomatic infection pre-procedure and serum creatinine should be checked. The panel have decided not to make recommendations for specific agents for particular procedures as there is considerable variation in Europe and worldwide regarding bacterial pathogens, their susceptibility and availability of antibiotic agents.

3.14.2 ***Specific procedures and evidence question***

A literature search from 1980 to February 2017 identified RCTs, systematic reviews and meta-analyses that investigated the benefits and harms of using antibiotic prophylaxis prior to specific urological procedures. The available evidence enabled the panel to make recommendations concerning urodynamics, cystoscopy, stone procedures (extracorporeal shockwave lithotripsy [ESWL], ureteroscopy and percutaneous nephrolithotomy [PCNL]), transurethral resection of the prostate (TURP) and transurethral resection of the bladder (TURB). For nephrectomy and prostatectomy the scientific evidence was too weak to allow the panel to make recommendations either for or against antibiotic prophylaxis. The general evidence question was: Does antibiotic prophylaxis reduce the rate of post-operative symptomatic UTI in patients undergoing each named procedure?

3.14.2.1 Urodynamics

The literature search identified one Cochrane review with search date of December 2009 [346] and two later RCTs [347, 348]. Foon *et al.*, identified nine RCTs enrolling 973 patients with overall low quality and high or unclear risks of bias. The outcome of clinical UTI was reported in four trials with no benefit found for antibiotic prophylaxis versus placebo [RR (95%CI) 0.73 (0.52-1.03)]. A meta-analysis of nine trials showed that use of antibiotics reduced the rate of post-procedural bacteriuria [RR (95%CI) 0.35 (0.22-0.56)] [346]. Neither Hirakauva *et al.*, or Gurburz *et al.*, reported a clinical UTI outcome and had conflicting findings for reduction in risk of bacteriuria [347, 348].

3.14.2.2 Cystoscopy

The literature search identified two systematic reviews and meta-analyses with search dates of April 2014 and December 2013, respectively [349, 350]. No additional RCTs subsequent to these dates were found. Garcia-Perdomo *et al.*, included seven RCTs with a total of 3,038 participants. The outcome of symptomatic UTI was measured by five trials of moderate overall quality and meta-analysis showed a benefit for using antibiotic prophylaxis [RR (95%CI) 0.53 (0.31 – 0.90)]; ARR 1.3% (from 2.8% to 1.5%) with a NNT of 74 [350]. This benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis. Carey *et al.*, included seven RCTs with 5,107 participants. Six trials were included in meta-analysis of the outcome of symptomatic bacteriuria which found benefit for use of antibiotic prophylaxis [RR (95%CI) 0.34 (0.27 – 0.47)]; ARR 3.4% (from 6% to 2.6%) with NNT of 28 [349]. Given the low absolute risk of post-procedural UTI in well-resourced countries, the high number of procedures being performed, and the high risk of contributing to increasing antimicrobial resistance the panel consensus was to strongly recommend not to use antibiotic prophylaxis in patients undergoing urethrocystoscopy (flexible or rigid).

3.14.2.3 Interventions for urinary stone treatment

3.14.2.3.1 Extracorporeal shockwave lithotripsy

For patients without bacteriuria undergoing ESWL two systematic reviews and meta-analyses were identified with latest search dates of November 2011 and October 2012, respectively [351, 352]. The literature search to February 2017 identified one further trial [353]. Lu *et al.*, included nine RCTs with a total of 1,364 patients and found no evidence of benefit in terms of reducing the rate of post-procedural fever or bacteriuria [351]. Mrkobrada *et al.*, included eight RCTs with a total of 940 participants and found no evidence of benefit for antibiotic prophylaxis to reduce rate of fever or trial-defined infection [352]. The RCT reported by Hsieh *et al.*, with 274 patients had a severe risk of bias. It found no reduction in fever at up to one week post-procedure using a single dose of levofloxacin 500 mg and no difference in the rate of bacteriuria [353].

For patients with bacteriuria or deemed at high risk of complications one RCT comparing the use of ofloxacin or trimethoprim-sulphamethoxazole for three days prior and four days subsequent to ESWL in 56 patients with ureteric stents was identified [354]. They found no difference in rate of clinical UTI at seven days (no events) and no difference in post-ESWL bacteriuria.

3.14.2.3.2 Ureteroscopy

A single systematic review [355] and two meta-analyses [356, 357] with latest search date of December 2013 were identified. Bootsma *et al.*, and Dahm *et al.*, included two low quality RCTs with a total of 233 participants and showed low-grade evidence that antibiotic prophylaxis reduced risk of bacteriuria but not of clinical UTI [355, 356]. Lo *et al.*, included four RCTs with a total of 386 patients and found no evidence of benefit in reducing rate of clinical UTI [357]. The rate of bacteruria was reduced using antibiotic prophylaxis. Panel

discussion considered that despite low quality evidence suggesting no benefit in reducing risk of clinical UTI, clinicians and patients would prefer to use prophylaxis to prevent kidney infection or sepsis. Ideally this should be examined in a robustly designed clinical study.

3.14.2.3.3 Percutaneous neprolithotomy (PNL)

A single systematic review and meta-analysis with latest search date of October 2012 was identified which addressed whether or not antibiotic prophylaxis reduce the rate of clinical urinary infection following PNL [352]. The update search to February 2017 identified no further trials. Mrkobrada *et al.*, included five RCTs with 448 participants and pooled patients undergoing PNL or ureteroscopy. They showed a moderate level of evidence that antibiotic prophylaxis was associated with a statistically significant reduction in the risk of post-procedural UTI.

Two RCTs with overall low risk of bias comparing different antibiotic regimes in PNL were identified [358, 359]. Seyrek *et al.*, compared the rate of SIRS following PNL in 191 patients receiving either a combination of sulbactam/ampicillin or cefuroxime. There was no difference in SIRS or urosepsis rates [358]. Tuzel *et al.*, investigated single dose ceftriaxone versus ceftriaxone and subsequently an oral third-generation cephalosporin until after nephrostomy catheter withdrawal at mean (SD) of 3 (1) days in 73 participants undergoing PNL. They found no difference in rate of infectious complications between the two antibiotic regimens [359]. These two studies give moderate evidence that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.

3.14.2.4 Transurethral resection of the prostate

A systematic review of 39 RCTs with search date up to 2009 was identified [356]. The update search to February 2017 did not reveal any further relevant studies. Of the 39 RCTs reviewed by Dahm *et al.*, six trials involving 1,666 men addressed the risk of septic episodes, 17 trials reported procedure related fever and 39 investigated bacteriuria. Use of prophylactic antibiotics compared to placebo showed a relative risk reduction (95% CI) for septic episode of 0.51 (0.27-0.96) with ARR of 2% (3.4%-1.4%) and a NNT of 50. The risk reduction (95% CI) for fever was 0.64 (0.55-0.75) and 0.37 (0.32-0.41) for bacteriuria.

3.14.2.5 Transurethral resection of the bladder

A literature search to February 2017 found one systematic review [355] which included two trials with a total of 152 participants. No more recent RCTs were identified. The two trials found no difference in rate of bacteriuria and either had no clinical UTI events, or did not report any. The review did not attempt sub-group analysis according to presence of risk factors for post-operative infection such as tumour size. Panel discussion concluded that a weak recommendation to use antibiotic prophylaxis for patients undergoing TURB who had a high risk of suffering post-operative sepsis would be appropriate.

3.14.2.6 Transrectal prostate biopsy

3.14.2.6.1 Non-antimicrobial interventions

A meta-analysis of four studies including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications [RR (95% CIs) 0.96 (0.64 to 1.54)] [360-362].

Meta-analysis of eight trials including 1,717 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) 0.55 (0.41 to 0.72)] [363-368]. Single RCTs showed no evidence of benefit for perineal skin disinfection [369], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [370].

No evidence was found that extended biopsy templates or use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than standard templates or no injection, respectively [371].

A total of seven studies including 1,330 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (37 events among 657 men) compared to transperineal biopsy (22 events among 673 men), [RR (95% CIs) 1.81 (1.09 to 3.00)] [372-378].

3.14.2.6.2 Antimicrobial prophylaxis

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using antimicrobial prophylaxis as compared to placebo/control [RR (95% CIs) 0.56 (0.40 to 0.77)] [360, 366, 368, 379-385]; therefore, antimicrobial prophylaxis is strongly recommended.

Fluoroquinolones have been traditionally used for antibiotic prophylaxis; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European

Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones for antibiotic prophylaxis in urological treatment and diagnostic interventions due to their disabling and potentially long-lasting side effects [121].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, is recommended [386]. In countries where fluoroquinolones are prohibited cephalosporins, aminoglycosides or fosfomycin can be used as individual agents. In the available RCTs, fosfomycin was superior to fluoroquinolones, but routine general use should be critically assessed due to the relevant infectious complications reported in non-randomised studies [387]. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date.

*3.14.3 **Summary of evidence and recommendations for peri-procedural antibiotic prophylaxis***

Summary of evidence	**LE**
The outcome of clinical UTI was reported in four out of eleven RCTs with no benefit found for antibiotic prophylaxis vs. placebo in patients following filling and voiding cystometry.	1b
A meta-analysis of five trials of moderate quality showed a benefit for using antibiotic prophylaxis for the reduction of symptomatic UTI in patients undergoing cystoscopy. However, this benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis.	1a
Two meta-analyses found no benefit for antibiotic prophylaxis following ESWL in terms of reducing the rate of post-procedural fever and bacteriuria or trial-defined infection in patients without bacteriuria.	1a
Two meta-analyses found no evidence of benefit for antibiotic prophylaxis prior to ureteroscopy in reducing the rate of clinical UTI; however, the rate of bacteriuria was reduced.	1a
A meta-analysis of five RCTs demonstrated a moderate level of evidence that antibiotic prophylaxis was associated with a statistically significant reduction in the risk of post-procedural UTI following PNL.	1a
Two RCTs concluded that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.	1b
A systematic review of 39 RCTs concluded that antibiotic prophylaxis reduced the rate of infectious complications in men undergoing TURP.	1b
A systematic review of two RCTs found no benefit for antibiotic prophylaxis in patients undergoing TURB.	1b
Meta-analysis of six trials showed that use of a rectal povidone-iodine preparation before biopsy in addition to antimicrobial prophylaxis resulted in a lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a
A meta-analysis of seven studies including 1,330 patients showed significantly reduced infectious in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a

Recommendations	**Strength rating**
Do not use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following: • urodynamics; • cystoscopy; • extracorporeal shockwave lithotripsy.	Strong
Use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following ureteroscopy.	Weak
Use single dose antibiotic prophylaxis to reduce the rate of clinical urinary infection following percutaneous nephrolithotomy.	Strong
Use antibiotic prophylaxis to reduce infectious complications in men undergoing transurethral resection of the prostate.	Strong
Use antibiotic prophylaxis to reduce infectious complications in high-risk patients undergoing transurethral resection of the bladder.	Weak
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Use antimicrobial prophylaxis in men prior to transrectal prostate biopsy.	Strong

Table 12: Suggested regimens for antimicrobial prophylaxis prior to urological procedures.
As stated in section 3.14.1.4 the panel have decided not to make recommendations for specific agents for particular procedures, those listed below represent possible choices only. Urologists should choose a specific antimicrobial based on their knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence.

Procedure	Prophylaxis recommended	Antimicrobial
Urodynamics	No	N/A
Cystoscopy	No	
Extracorporeal shockwave lithotripsy	No	
Ureteroscopy	Yes	Trimethoprim Trimethoprim-sulphamethoxazole Cephalosporin group 2 or 3 Aminopenicillin plus a beta-lactamase inhibitor
Percutaneous nephrolithotomy	Yes (single dose)	
Transurethral resection of the prostate	Yes	
Transurethral resection of the bladder	Yes, in patients who have a high risk of suffering post-operative sepsis.	
Transrectal prostate biopsy	Yes	Fluoroquinolones if permitted Cephalosporins, fosfomycin, aminoglycosides, if fluoroquinolones are not permitted

4. REFERENCES

1. Stein, R., *et al.* Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol, 2015. 67: 546. https://www.ncbi.nlm.nih.gov/pubmed/25477258
2. Blok, B., *et al.* EAU Guidelines on Neuro-urology. In: EAU Guidelines, edition presented at the annual EAU Congress Amsterdam 2020. ISBN 978-94-92671-07-3.
3. Guyatt, G.H., *et al.* What is "quality of evidence" and why is it important to clinicians? BMJ, 2008. 336: 995. https://www.ncbi.nlm.nih.gov/pubmed/18456631
4. Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march2009/
5. Guyatt, G.H., *et al.* Going from evidence to recommendations. BMJ, 2008. 336: 1049. https://www.ncbi.nlm.nih.gov/pubmed/18467413
6. Horan, T.C., *et al.* CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control, 2008. 36: 309. https://www.ncbi.nlm.nih.gov/pubmed/18538699
7. Rubin, R.H., *et al.* Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis, 1992. 15 Suppl 1: S216. https://www.ncbi.nlm.nih.gov/pubmed/1477233
8. Rubin, R.H., *et al.* General guidelines for the evaluation of new anti-infective drugs for the treatment of urinary tract infection. The European Society of Clinical Microbiology and Infectious diseases. Taukirchen, Germany., 1993: 240. [No abstract available].
9. U.S. Department of Health and Human Services, F.a.D.A., Center for Drug Evaluation and Research (CDER). Guidance for Industry Uncomplicated Urinary Tract Infections — Developing Antimicrobial Drugs for Treatment. 2019. https://www.fda.gov/media/129531/download
10. U.S. Department of Health and Human Services, F.a.D.A., Center for Drug Evaluation and Research (CDER). Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/complicated-urinary-tract-infections-developing-drugs-treatment

11. Johansen, T.E., *et al.* Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. Int J Antimicrob Agents, 2011. 38 Suppl: 64.
https://www.ncbi.nlm.nih.gov/pubmed/22018988
12. Singer, M., *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016. 315: 801.
https://www.ncbi.nlm.nih.gov/pubmed/26903338
13. Bell, B.G., *et al.* A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis, 2014. 14: 13.
https://www.ncbi.nlm.nih.gov/pubmed/24405683
14. WHO. Antimicrobial resistance: global report on surveillance 2014.
https://www.who.int/drugresistance/documents/surveillancereport/en/
15. Hulscher, M.E., *et al.* Antibiotic prescribing in hospitals: a social and behavioural scientific approach. Lancet Infect Dis, 2010. 10: 167.
https://www.ncbi.nlm.nih.gov/pubmed/20185095
16. Goff, D.A., *et al.* A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. Lancet Infect Dis, 2017. 17: e56.
https://www.ncbi.nlm.nih.gov/pubmed/27866945
17. Dellit, T.H., *et al.* Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis, 2007. 44: 159.
https://www.ncbi.nlm.nih.gov/pubmed/17173212
18. Davey, P., *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev, 2017. 2: CD003543.
https://www.ncbi.nlm.nih.gov/pubmed/23633313
19. Cefai, C., *et al.* Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. NICE Guidelines, 2015.
https://www.nice.org.uk/guidance/ng15
20. Schuts, E.C., *et al.* Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis, 2016. 16: 847.
https://www.ncbi.nlm.nih.gov/pubmed/26947617
21. Hermanides, H.S., *et al.* Development of quality indicators for the antibiotic treatment of complicated urinary tract infections: a first step to measure and improve care. Clin Infect Dis, 2008. 46: 703.
https://www.ncbi.nlm.nih.gov/pubmed/18230045
22. Spoorenberg, V., *et al.* Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay. Clin Infect Dis, 2014. 58: 164.
https://www.ncbi.nlm.nih.gov/pubmed/24158412
23. Lutay, N., *et al.* Bacterial control of host gene expression through RNA polymerase II. J Clin Invest, 2013. 123: 2366.
https://www.ncbi.nlm.nih.gov/pubmed/23728172
24. Hansson, S., *et al.* Untreated asymptomatic bacteriuria in girls: II--Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. BMJ, 1989. 298: 856.
https://www.ncbi.nlm.nih.gov/pubmed/2497823
25. Cai, T., *et al.* The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: To treat or not to treat? Clin Infect Dis, 2012. 55: 771.
https://www.ncbi.nlm.nih.gov/pubmed/22677710
26. Nicolle, L.E., *et al.* Infectious diseases society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis, 2005. 40: 643.
https://www.ncbi.nlm.nih.gov/pubmed/15714408
27. Kass, E.H. Asymptomatic infections of the urinary tract. Trans Assoc Am Physicians, 1956. 69: 56.
https://www.ncbi.nlm.nih.gov/pubmed/13380946
28. Gleckman, R., *et al.* Reliability of a single urine culture in establishing diagnosis of asymptomatic bacteriuria in adult males. J Clin Microbiol, 1979. 9: 596.
https://www.ncbi.nlm.nih.gov/pubmed/383746
29. Warren, J.W., *et al.* A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. J Infect Dis, 1982. 146: 719.
https://www.ncbi.nlm.nih.gov/pubmed/6815281
30. Kunin CM. Urinary tract infections: detection, prevention and management. 5th ed. Baltimore: Williams and Wilkins., 1997.

31. Koves, B., *et al.* Benefits and Harms of Treatment of Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. Eur Urol, 2017. https://www.ncbi.nlm.nih.gov/pubmed/28754533
32. Tencer, J. Asymptomatic bacteriuria--a long-term study. Scand J Urol Nephrol, 1988. 22: 31. https://www.ncbi.nlm.nih.gov/pubmed/3387908
33. Asscher, A.W., *et al.* The clinical significance of asymptomatic bacteriuria in the nonpregnant woman. J Infect Dis, 1969. 120: 17. https://www.ncbi.nlm.nih.gov/pubmed/5803281
34. Elder, H.A., *et al.* The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. Am J Obstet Gynecol, 1971. 111: 441. https://www.ncbi.nlm.nih.gov/pubmed/4937729
35. Elder, H.A., *et al.* Use of sulfasymazine in the treatment of bacteriuria of pregnancy. Antimicrob Agents Chemother (Bethesda), 1966. 6: 142. https://www.ncbi.nlm.nih.gov/pubmed/4862162
36. Gold, E.M., *et al.* Asymptomatic bacteriuria during pregnancy. Obstet Gynecol, 1966. 27: 206. https://www.ncbi.nlm.nih.gov/pubmed/5325600
37. Kass, E.H. Pyelonephritis and bacteriuria. A major problem in preventive medicine. Ann Intern Med, 1962. 56: 46. https://www.ncbi.nlm.nih.gov/pubmed/14454174
38. Kincaid-Smith, P., *et al.* Bacteriuria in Pregnancy. Lancet, 1965. 1: 395. https://www.ncbi.nlm.nih.gov/pubmed/14238090
39. Little, P.J. The incidence of urinary infection in 5000 pregnant women. Lancet, 1966. 2: 925. https://www.ncbi.nlm.nih.gov/pubmed/4162367
40. Mulla, N. Bacteriuria in pregnancy. Obstet Gynecol, 1960. 16: 89. https://www.ncbi.nlm.nih.gov/pubmed/14425118
41. Pathak, U.N., *et al.* Bacteriuria of pregnancy: results of treatment. J Infect Dis, 1969. 120: 91. https://www.ncbi.nlm.nih.gov/pubmed/5816817
42. Robertson, J.G., *et al.* The managment and complications of asymptomatic bacteriuria in pregnancy. Report of a study on 8,275 patients. J Obstet Gynaecol Br Commonw, 1968. 75: 59. https://www.ncbi.nlm.nih.gov/pubmed/5635245
43. Thomsen, A.C., *et al.* Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. Lancet, 1987. 1: 591. https://www.ncbi.nlm.nih.gov/pubmed/2881132
44. Williams, G.L., *et al.* Urinary concentrating ability in women with asymptomatic bacteriuria in pregnancy. Br Med J, 1969. 3: 212. https://www.ncbi.nlm.nih.gov/pubmed/5792611
45. Wren, B.G. Subclinical renal infection and prematurity. Med J Aust, 1969. 2: 596. https://www.ncbi.nlm.nih.gov/pubmed/5388374
46. Kazemier, B.M., *et al.* Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. Lancet Infect Dis, 2015. 15: 1324. https://www.ncbi.nlm.nih.gov/pubmed/26255208
47. Christopher, L.J., *et al.* A trial of hippramine in the treatment of bacteriuria of pregnancy. Ir J Med Sci, 1969. 8: 331. https://www.ncbi.nlm.nih.gov/pubmed/5806178
48. Reeves, D.S. Laboratory and clinical studies with sulfametopyrazine as a treatment for bacteriuria in pregnancy. J Antimicrob Chemother, 1975. 1: 171. https://www.ncbi.nlm.nih.gov/pubmed/1100589
49. Whalley, P.J., *et al.* Short-term versus continuous antimicrobial therapy for asymptomatic bacteriuria in pregnancy. Obstet Gynecol, 1977. 49: 262. https://www.ncbi.nlm.nih.gov/pubmed/320525
50. Bint, A., *et al.* A comparative trial of pivmecillinam and ampicillin in bacteriuria of pregnancy. Infection, 1979. 7: 290. https://www.ncbi.nlm.nih.gov/pubmed/232697
51. Harris, R.E., *et al.* Single-dose antimicrobial therapy for asymptomatic bacteriuria during pregnancy. Obstet Gynecol, 1982. 59: 546. https://www.ncbi.nlm.nih.gov/pubmed/7070725
52. Bailey, R.R., *et al.* Comparison of single dose with a 5-day course of co-trimoxazole for asymptomatic (covert) bacteriuria of pregnancy. Aust N Z J Obstet Gynaecol, 1983. 23: 139. https://www.ncbi.nlm.nih.gov/pubmed/6606421

53. Masterton, R.G., *et al.* Single-dose amoxycillin in the treatment of bacteriuria in pregnancy and the puerperium--a controlled clinical trial. Br J Obstet Gynaecol, 1985. 92: 498.
https://www.ncbi.nlm.nih.gov/pubmed/3888250
54. Pedler, S.J., *et al.* Comparative study of amoxicillin-clavulanic acid and cephalexin in the treatment of bacteriuria during pregnancy. Antimicrob Agents Chemother, 1985. 27: 508.
https://www.ncbi.nlm.nih.gov/pubmed/4004191
55. Campbell-Brown, M., *et al.* Is screening for bacteriuria in pregnancy worth while? Br Med J (Clin Res Ed), 1987. 294: 1579.
https://www.ncbi.nlm.nih.gov/pubmed/3113538
56. Pregazzi, R., *et al.* [Single-dose antibiotic therapy of asymptomatic bacteriuria in pregnancy. Results and complications]. Minerva Ginecol, 1987. 39: 289.
https://www.ncbi.nlm.nih.gov/pubmed/3601207
57. Gerstner, G.J., *et al.* Amoxicillin in the treatment of asymptomatic bacteriuria in pregnancy: a single dose of 3 g amoxicillin versus a 4-day course of 3 doses 750 mg amoxicillin. Gynecol Obstet Invest, 1989. 27: 84.
https://www.ncbi.nlm.nih.gov/pubmed/2659442
58. Olsen, L., *et al.* Single-dose versus six-day therapy with sulfamethizole for asymptomatic bacteriuria during pregnancy. A prospective randomised study. Dan Med Bull, 1989. 36: 486.
https://www.ncbi.nlm.nih.gov/pubmed/2680315
59. Thoumsin, H., *et al.* Single dose fosfomycin trometamol versus multiple dose nitrofurantoin in pregnant women with bacteriuria: preliminary results. Infection, 1990. 18 Suppl 2: S94.
https://www.ncbi.nlm.nih.gov/pubmed/2286469
60. Bayrak, O., *et al.* Is single-dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimester of pregnancy? Int Urogynecol J Pelvic Floor Dysf, 2007. 18: 525.
https://www.ncbi.nlm.nih.gov/pubmed/16941068
61. Estebanez, A., *et al.* Fosfomycin in a single dose versus a 7-day course of amoxicillin- clavulanate for the treatment of asymptomatic bacteriuria during pregnancy. Eur J Clin Microbiol Infect Dis, 2009. 28: 1457.
https://www.ncbi.nlm.nih.gov/pubmed/19768649
62. Lumbiganon, P., *et al.* One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: A randomized controlled trial. Obstet Gynecol, 2009. 113: 339.
https://www.ncbi.nlm.nih.gov/pubmed/19155904
63. Widmer, M., *et al.* Duration of treatment for asymptomatic bacteriuria during pregnancy. Cochrane Database Syst Rev, 2015: CD000491.
https://www.ncbi.nlm.nih.gov/pubmed/26560337
64. Zhanel, G.G., *et al.* Asymptomatic bacteriuria in patients with diabetes mellitus. Rev Infect Dis, 1991. 13: 150.
https://www.ncbi.nlm.nih.gov/pubmed/2017615
65. Harding, G.K., *et al.* Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. N Engl J Med, 2002. 347: 1576.
https://www.ncbi.nlm.nih.gov/pubmed/
66. Mody, L., *et al.* Urinary tract infections in older women: a clinical review. JAMA, 2014. 311: 844.
https://www.ncbi.nlm.nih.gov/pubmed/24570248
67. Boscia, J.A., *et al.* Therapy vs no therapy for bacteriuria in elderly ambulatory nonhospitalized women. JAMA, 1987. 257: 1067.
https://www.ncbi.nlm.nih.gov/pubmed/3806896
68. Abrutyn, E., *et al.* Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? Ann Intern Med, 1994. 120: 827.
https://www.ncbi.nlm.nih.gov/pubmed/7818631
69. Abrutyn, E., *et al.* Does treatment of asymptomatic bacteriuria in older ambulatory women reduce subsequent symptoms of urinary tract infection? J Am Geriatr Soc, 1996. 44: 293.
https://www.ncbi.nlm.nih.gov/pubmed/8600199
70. Nicolle, L.E., *et al.* Prospective randomized comparison of therapy and no therapy for asymptomatic bacteriuria in institutionalized elderly women. Am J Med, 1987. 83: 27.
https://www.ncbi.nlm.nih.gov/pubmed/3300325
71. Nicolle, L.E. Asymptomatic bacteriuria in the elderly. Infect Dis Clin North Am, 1997. 11: 647.
https://www.ncbi.nlm.nih.gov/pubmed/9378928
72. Silver, S.A., *et al.* Positive urine cultures: A major cause of inappropriate antimicrobial use in hospitals? Can J Infect Dis Med Microbiol, 2009. 20: 107.
https://www.ncbi.nlm.nih.gov/pubmed/21119801
73. Trautner, B.W. Asymptomatic bacteriuria: when the treatment is worse than the disease. Nat Rev Urol, 2011.
https://www.ncbi.nlm.nih.gov/pubmed/22143416

74. Nicolle, L.E., *et al.* Bacteriuria in elderly institutionalized men. N Engl J Med, 1983. 309: 1420.
https://www.ncbi.nlm.nih.gov/pubmed/6633618
75. Potts, L., *et al.* A double-blind comparative study of norfloxacin versus placebo in hospitalised elderly patients with asymptomatic bacteriuria. Arch Gerontol Geriatr, 1996. 23: 153.
https://www.ncbi.nlm.nih.gov/pubmed/15374159
76. Renneberg, J., *et al.* Single-day treatment with trimethoprim for asymptomatic bacteriuria in the elderly patient. J Urol, 1984. 132: 934.
https://www.ncbi.nlm.nih.gov/pubmed/6387184
77. Ouslander, J.G., *et al.* Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents? Ann Intern Med, 1995. 122: 749.
https://www.ncbi.nlm.nih.gov/pubmed/7717597
78. Moradi, M., *et al.* Effect of antibiotic therapy on asymptomatic bacteriuria in kidney transplant recipients. Urology Journal, 2005. 2: 32.
https://www.ncbi.nlm.nih.gov/pubmed/17629893
79. Amari, E.B.E., *et al.* Outcome of treated and untreated asymptomatic bacteriuria in renal transplant recipients. Nephrol Dial Transplant, 2011. 26: 4109.
https://www.ncbi.nlm.nih.gov/pubmed/21592976
80. Green, H., *et al.* Consequences of treated versus untreated asymptomatic bacteriuria in the first year following kidney transplantation: Retrospective observational study. Eur J Clin Microbiol Infect Dis, 2013. 32: 127.
https://www.ncbi.nlm.nih.gov/pubmed/22918514
81. Origuen, J., *et al.* Should asymptomatic bacteriuria be systematically treated in kidney transplant recipients? Results from a randomized controlled trial. Am J Transplant, 2016.
https://www.ncbi.nlm.nih.gov/pubmed/27088545
82. Nicolle, L.E. Urinary tract infections in patients with spinal injuries. Curr Infect Dis Rep, 2014. 16: 390.
https://www.ncbi.nlm.nih.gov/pubmed/24445675
83. Wullt, B., *et al.* Bladder, bowel and bugs--bacteriuria in patients with intestinal urinary diversion. World J Urol, 2004. 22: 186.
https://www.ncbi.nlm.nih.gov/pubmed/15309491
84. Darouiche, R.O., *et al.* Bacterial interference for prevention of urinary tract infection: a prospective, randomized, placebo-controlled, double-blind pilot trial. Clin Infect Dis, 2005. 41: 1531.
https://www.ncbi.nlm.nih.gov/pubmed/16231269
85. Sunden, F., *et al.* Escherichia coli 83972 bacteriuria protects against recurrent lower urinary tract infections in patients with incomplete bladder emptying. J Urol, 2010. 184: 179.
https://www.ncbi.nlm.nih.gov/pubmed/20473149
86. Bonkat, G., *et al.* Microbial biofilm formation and catheter-associated bacteriuria in patients with suprapubic catheterisation. World J Urol, 2013. 31: 565.
https://www.ncbi.nlm.nih.gov/pubmed/22926265
87. Tenke, P., *et al.* European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents, 2008. 31 Suppl 1: S68.
https://www.ncbi.nlm.nih.gov/pubmed/18006279
88. Cooper, F.P., *et al.* Policies for replacing long-term indwelling urinary catheters in adults. Cochrane Database Syst Rev, 2016. 7: CD011115.
https://www.ncbi.nlm.nih.gov/pubmed/27457774
89. Dasgupta, R., *et al.* Preoperative antibiotics before endourologic surgery: current recommendations. J Endourol, 2009. 23: 1567.
https://www.ncbi.nlm.nih.gov/pubmed/19785548
90. Sobel, J.D., *et al.* Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis, 2000. 30: 19.
https://www.ncbi.nlm.nih.gov/pubmed/10619727
91. Grabe, M., *et al.* The effect of a short antibiotic course in transurethral prostatic resection. Scand J Urol Nephrol, 1984. 18: 37.
https://www.ncbi.nlm.nih.gov/pubmed/6202000
92. Grabe, M., *et al.* Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. Eur J Clin Microbiol, 1987. 6: 11.
https://www.ncbi.nlm.nih.gov/pubmed/3569248
93. Cafferkey, M.T., *et al.* Antibiotics for the prevention of septicaemia in urology. J Antimicrob Chemother, 1982. 9: 471.
https://www.ncbi.nlm.nih.gov/pubmed/7107549

94. Murphy, D.M., *et al.* Bacteraemia during prostatectomy and other transurethral operations: influence of timing of antibiotic administration. J Clin Pathol, 1984. 37: 673.
https://www.ncbi.nlm.nih.gov/pubmed/6725613
95. Chong, J.T., *et al.* Pre-procedural antibiotics for endoscopic urological procedures: Initial experience in individuals with spinal cord injury and asymptomatic bacteriuria. Journal of Spinal Cord Medicine, 2015. 38: 187.
https://www.ncbi.nlm.nih.gov/pubmed/24621035
96. Cordero-Ampuero, J., *et al.* Are antibiotics necessary in hip arthroplasty with asymptomatic bacteriuria? Seeding risk with/without treatment. Clinical Orthopaedics and Related Research, 2013. 471: 3822.
https://www.ncbi.nlm.nih.gov/pubmed/23430723
97. Sousa, R., *et al.* Is asymptomatic bacteriuria a risk factor for prosthetic joint infection? Clin Infect Dis, 2014. 59: 41.
https://www.ncbi.nlm.nih.gov/pubmed/24723280
98. Foxman, B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Dis Mon, 2003. 49: 53.
https://www.ncbi.nlm.nih.gov/pubmed/12601337
99. Wagenlehner, F.M., *et al.* Uncomplicated urinary tract infections. Dtsch Arztebl Int, 2011. 108: 415.
https://www.ncbi.nlm.nih.gov/pubmed/21776311
100. Stamm, W.E., *et al.* Management of urinary tract infections in adults. N Engl J Med, 1993. 329: 1328.
https://www.ncbi.nlm.nih.gov/pubmed/8413414
101. Foxman, B., *et al.* Urinary tract infection among women aged 40 to 65: behavioral and sexual risk factors. J Clin Epidemiol, 2001. 54: 710.
https://www.ncbi.nlm.nih.gov/pubmed/11438412
102. van Buul, L.W., *et al.* The Development of a Decision Tool for the Empiric Treatment of Suspected Urinary Tract Infection in Frail Older Adults: A Delphi Consensus Procedure. J Am Med Dir Assoc, 2018. 19: 757.
https://www.ncbi.nlm.nih.gov/pubmed/29910137
103. Bent, S., *et al.* Does this woman have an acute uncomplicated urinary tract infection? JAMA, 2002. 287: 2701.
https://www.ncbi.nlm.nih.gov/pubmed/12020306
104. Bradbury, S.M. Collection of urine specimens in general practice: to clean or not to clean? J R Coll Gen Pract, 1988. 38: 363.
https://www.ncbi.nlm.nih.gov/pubmed/3256648
105. Lifshitz, E., *et al.* Outpatient urine culture: does collection technique matter? Arch Intern Med, 2000. 160: 2537.
https://www.ncbi.nlm.nih.gov/pubmed/10979067
106. Fihn, S.D. Clinical practice. Acute uncomplicated urinary tract infection in women. N Engl J Med, 2003. 349: 259.
https://www.ncbi.nlm.nih.gov/pubmed/12867610
107. Foxman, B., *et al.* Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am, 2003. 17: 227.
https://www.ncbi.nlm.nih.gov/pubmed/12848468
108. Falagas, M.E., *et al.* Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. J Infect, 2009. 58: 91.
https://www.ncbi.nlm.nih.gov/pubmed/19195714
109. Gagyor, I., *et al.* Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ, 2015. 351: h6544.
https://www.ncbi.nlm.nih.gov/pubmed/26698878
110. Vik, I., *et al.* Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-A double-blind, randomized non-inferiority trial. PLoS Med, 2018. 15: e1002569.
https://www.ncbi.nlm.nih.gov/pubmed/29763434
111. Kronenberg, A., *et al.* Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ, 2017. 359: j4784.
https://www.ncbi.nlm.nih.gov/pubmed/29113968
112. Wagenlehner, F.M., *et al.* Non-Antibiotic Herbal Therapy (BNO 1045) versus Antibiotic Therapy (Fosfomycin Trometamol) for the Treatment of Acute Lower Uncomplicated Urinary Tract Infections in Women: A Double-Blind, Parallel-Group, Randomized, Multicentre, Non-Inferiority Phase III Trial. Urol Int, 2018. 101: 327.
https://www.ncbi.nlm.nih.gov/pubmed/30231252
113. Gupta, K., *et al.* Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med, 2007. 167: 2207.
https://www.ncbi.nlm.nih.gov/pubmed/17998493
114. Lecomte, F., *et al.* Single-dose treatment of cystitis with fosfomycin trometamol (Monuril): analysis of 15 comparative trials on 2,048 patients. Giorn It Ost Gin, 1997. 19: 399.
https://www.sciencedirect.com/science/article/pii/S0399077X96802095

115. Nicolle, L.E. Pivmecillinam in the treatment of urinary tract infections. J Antimicrob Chemother, 2000. 46 Suppl 1: 35.
https://www.ncbi.nlm.nih.gov/pubmed/11051622
116. Huttner, A., *et al.* Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother, 2015. 70: 2456.
https://www.ncbi.nlm.nih.gov/pubmed/26066581
117. Gupta, K., *et al.* Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. Int J Antimicrob Agents, 2002. 19: 554.
https://www.ncbi.nlm.nih.gov/pubmed/12135847
118. Warren, J.W., *et al.* Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis, 1999. 29: 745.
https://www.ncbi.nlm.nih.gov/pubmed/10589881
119. Hooton, T.M., *et al.* Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA, 2012. 307: 583.
https://www.ncbi.nlm.nih.gov/pubmed/22318279
120. Hooton, T.M., *et al.* Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. Jama, 2005. 293: 949.
https://www.ncbi.nlm.nih.gov/pubmed/15728165
121. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. Quinolone and fluoroquinolone Article-31 referral, 2019.
https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf
122. Vazquez, J.C., *et al.* Treatments for symptomatic urinary tract infections during pregnancy. Cochrane Database Syst Rev, 2000: CD002256.
https://www.ncbi.nlm.nih.gov/pubmed/10908537
123. Wagenlehner, F.M., *et al.* Antimicrobials in urogenital infections. Int J Antimicrob Agents, 2011. 38 Suppl: 3.
https://www.ncbi.nlm.nih.gov/pubmed/22019184
124. Geerts, A.F., *et al.* Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. Eur J Clin Pharmacol, 2013. 69: 1701.
https://www.ncbi.nlm.nih.gov/pubmed/23660771
125. Hooton, T.M. Recurrent urinary tract infection in women. Int J Antimicrob Agents, 2001. 17: 259.
https://www.ncbi.nlm.nih.gov/pubmed/11295405
126. van Haarst, E.P., *et al.* Evaluation of the diagnostic workup in young women referred for recurrent lower urinary tract infections. Urology, 2001. 57: 1068.
https://www.ncbi.nlm.nih.gov/pubmed/11377307
127. Hooton, T.M., Prevention of recurrent urogenital tract infections in adult women, in EAU/International Consultation on Urological Infections. T, K.G. Naber, A.J. Schaeffer, C.F. Hynes & e. al., Editors. 2010, European Association of Urology: The Netherlands.
128. Beerepoot, M.A., *et al.* Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. J Urol, 2013. 190: 1981.
https://www.ncbi.nlm.nih.gov/pubmed/23867306
129. Wagenlehner, F.M., *et al.* Prevention of recurrent urinary tract infections. Minerva Urol Nefrol, 2013. 65: 9.
https://www.ncbi.nlm.nih.gov/pubmed/23538307
130. Raz, R., *et al.* A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med, 1993. 329: 753.
https://www.ncbi.nlm.nih.gov/pubmed/8350884
131. Bauer, H.W., *et al.* Prevention of recurrent urinary tract infections with immuno-active E. coli fractions: a meta-analysis of five placebo-controlled double-blind studies. Int J Antimicrob Agents, 2002. 19: 451.
https://www.ncbi.nlm.nih.gov/pubmed/12135831
132. Naber, K.G., *et al.* Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. Int J Antimicrob Agents, 2009. 33: 111.
https://www.ncbi.nlm.nih.gov/pubmed/18963856
133. Bauer, H.W., *et al.* A long-term, multicenter, double-blind study of an Escherichia coli extract (OM-89) in female patients with recurrent urinary tract infections. Eur Urol, 2005. 47: 542.
https://www.ncbi.nlm.nih.gov/pubmed/15774256
134. Schwenger, E.M., *et al.* Probiotics for preventing urinary tract infections in adults and children. Cochrane Database Syst Rev, 2015: CD008772.
https://www.ncbi.nlm.nih.gov/pubmed/26695595

135. Kontiokari, T., *et al.* Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. BMJ, 2001. 322: 1571.
https://www.ncbi.nlm.nih.gov/pubmed/11431298
136. Stothers, L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Can J Urol, 2002. 9: 1558.
https://www.ncbi.nlm.nih.gov/pubmed/12121581
137. Jepson, R.G., *et al.* Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev, 2012. 10: Cd001321.
https://www.ncbi.nlm.nih.gov/pubmed/23076891
138. Kranjcec, B., *et al.* D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol, 2014. 32: 79.
https://www.ncbi.nlm.nih.gov/pubmed/23633128
139. Damiano, R., *et al.* Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur Urol, 2011. 59: 645.
https://www.ncbi.nlm.nih.gov/pubmed/21272992
140. Madersbacher, H., *et al.* GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans--a review. Neurourol Urodyn, 2013. 32: 9.
https://www.ncbi.nlm.nih.gov/pubmed/22782909
141. Albert, X., *et al.* Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev, 2004: CD001209.
https://www.ncbi.nlm.nih.gov/pubmed/15266443
142. Rudenko, N., *et al.* Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol. Double blind, randomized, parallel group, placebo controlled study. Arzneimittelforschung, 2005. 55: 420.
https://www.ncbi.nlm.nih.gov/pubmed/16080282
143. Pfau, A., *et al.* Effective prophylaxis for recurrent urinary tract infections during pregnancy. Clin Infect Dis, 1992. 14: 810.
https://www.ncbi.nlm.nih.gov/pubmed/1576275
144. Schaeffer, A.J., *et al.* Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. J Urol, 1999. 161: 207.
https://www.ncbi.nlm.nih.gov/pubmed/10037399
145. Scholes, D., *et al.* Risk factors associated with acute pyelonephritis in healthy women. Ann Intern Med, 2005. 142: 20.
https://www.ncbi.nlm.nih.gov/pubmed/15630106
146. Hill, J.B., *et al.* Acute pyelonephritis in pregnancy. Obstet Gynecol, 2005. 105: 18.
https://www.ncbi.nlm.nih.gov/pubmed/15625136
147. Fulop, T. Acute Pyelonephritis Workup. 2012. (Updated june 2019).
https://emedicine.medscape.com/article/245559-workup
148. van Nieuwkoop, C., *et al.* Predicting the need for radiologic imaging in adults with febrile urinary tract infection. Clin Infect Dis, 2010. 51: 1266.
https://www.ncbi.nlm.nih.gov/pubmed/21034195
149. Cattrall, J.W.S., *et al.* A systematic review of randomised clinical trials for oral antibiotic treatment of acute pyelonephritis. Eur J Clin Microbiol Infect Dis, 2018. 37: 2285.
https://www.ncbi.nlm.nih.gov/pubmed/30191339
150. Gupta, K., *et al.* International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis, 2011. 52: e103.
https://www.ncbi.nlm.nih.gov/pubmed/21292654
151. Berti, F., *et al.* Short versus long course antibiotic therapy for acute pyelonephritis in adults: A systematic review and meta-analysis. Ital J Med, 2018. 12: 39.
https://www.italjmed.org/index.php/ijm/article/view/itjm.2018.840
152. Hooton, T.M. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med, 2012. 366: 1028.
https://www.ncbi.nlm.nih.gov/pubmed/22417256
153. Arakawa, S., *et al.* The efficacy and safety of tazobactam/ceftolozane in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection. J J Infect Chemother, 2019. 25: 104.
https://www.ncbi.nlm.nih.gov/pubmed/30420153
154. Armstrong, E.S., *et al.* Outcomes of high-dose levofloxacin therapy remain bound to the levofloxacin minimum inhibitory concentration in complicated urinary tract infections. BMC Infect Dis, 2016. 16: 710.
https://www.ncbi.nlm.nih.gov/pubmed/27887579

155. Huntington, J.A., *et al.* Efficacy of ceftolozane/tazobactam versus levofloxacin in the treatment of complicated urinary tract infections (cUTIs) caused by levofloxacinresistant pathogens: Results from the ASPECT-cUTI trial. J Antimicrobial Chemother, 2016. 71: 2014.
https://www.ncbi.nlm.nih.gov/pubmed/26994090
156. Carmeli, Y., *et al.* Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis, 2016. 16: 661.
https://www.ncbi.nlm.nih.gov/pubmed/27107460
157. Sims, M., *et al.* Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. J Infect Chemother, 2017. 72: 2616.
https://www.ncbi.nlm.nih.gov/pubmed/28575389
158. Wagenlehner, F.M., *et al.* Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. Clin Infect Dis, 2016. 63: 754.
https://www.ncbi.nlm.nih.gov/pubmed/27313268
159. Kaye, K.S., *et al.* Effect of meropenem-vaborbactam vs piperacillin-Tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection the TANGO I randomized clinical trial. JAMA, 2018. 319: 788.
https://www.ncbi.nlm.nih.gov/pubmed/29486041
160. Wunderink, R.G., *et al.* Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther, 2018. 7: 439.
https://www.ncbi.nlm.nih.gov/pubmed/30270406
161. Wagenlehner, F.M.E., *et al.* Once-Daily Plazomicin for Complicated Urinary Tract Infections. N Engl J Med, 2019. 380: 729.
https://www.ncbi.nlm.nih.gov/pubmed/30786187
162. Portsmouth, S., *et al.* Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis, 2018. 18: 1319.
https://www.ncbi.nlm.nih.gov/pubmed/30509675
163. Pitout, J.D. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs, 2010. 70: 313.
https://www.ncbi.nlm.nih.gov/pubmed/20166768
164. Mombelli, G., *et al.* Oral vs intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. Arch Intern Med, 1999. 159: 53.
https://www.ncbi.nlm.nih.gov/pubmed/9892331
165. Millar, L.K., *et al.* Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial. Obstet Gynecol, 1995. 86: 560.
https://www.ncbi.nlm.nih.gov/pubmed/7675380
166. Wing, D.A., *et al.* A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. Obstet Gynecol, 1998. 92: 249.
https://www.ncbi.nlm.nih.gov/pubmed/9699761
167. Ulleryd, P., *et al.* Ciprofloxacin for 2 or 4 weeks in the treatment of febrile urinary tract infection in men: a randomized trial with a 1 year follow-up. Scand J Infect Dis, 2003. 35: 34.
https://www.ncbi.nlm.nih.gov/pubmed/12685882
168. Reyner, K., *et al.* Urinary obstruction is an important complicating factor in patients with septic shock due to urinary infection. Am J Emerg Med, 2016. 34: 694.
https://www.ncbi.nlm.nih.gov/pubmed/26905806
169. Heyns, C.F. Urinary tract infection associated with conditions causing urinary tract obstruction and stasis, excluding urolithiasis and neuropathic bladder. World J Urol, 2012. 30: 77.
https://www.ncbi.nlm.nih.gov/pubmed/21720861
170. Spoorenberg, V., *et al.* [Better antibiotic use in complicated urinary tract infections; multicentre cluster randomised trial of 2 improvement strategies]. Ned Tijdschr Geneeskd, 2016. 160: D460.
https://www.ncbi.nlm.nih.gov/pubmed/27438395
171. Bader, M.S., *et al.* An update on the management of urinary tract infections in the era of antimicrobial resistance. Postgrad Med, 2017. 129: 242.
https://www.ncbi.nlm.nih.gov/pubmed/27712137

172. Geerlings, S.E., *et al.* SWAB Guidelines for Antimicrobial Therapy of Complicated Urinary Tract Infections in Adults. SWAB Guidelines, 2013.
https://www.ncbi.nlm.nih.gov/pubmed/17100128
173. Hooton, T.M., *et al.* Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis, 2010. 50: 625.
https://www.ncbi.nlm.nih.gov/pubmed/20175247
174. Peterson, J., *et al.* Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. Clin Ther, 2007. 29: 2215.
https://www.ncbi.nlm.nih.gov/pubmed/18042477
175. Bader, M.S., *et al.* Management of complicated urinary tract infections in the era of antimicrobial resistance. Postgrad Med, 2010. 122: 7.
https://www.ncbi.nlm.nih.gov/pubmed/21084776
176. Wagenlehner, F., *et al.* The Global Prevalence of Infections in Urology Study: A Long-Term, Worldwide Surveillance Study on Urological Infections. Pathogens, 2016. 5.
https://www.ncbi.nlm.nih.gov/pubmed/26797640
177. Popejoy, M.W., *et al.* Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae: A pooled analysis of Phase 3 clinical trials. J Antimicrob Chemother, 2017. 72: 268.
https://www.ncbi.nlm.nih.gov/pubmed/27707990
178. Sternbach, N., *et al.* Efficacy and safety of ceftazidime/avibactam: A systematic review and meta-analysis. J Antimicrob Chemother, 2018. 73: 2021.
https://www.ncbi.nlm.nih.gov/pubmed/29659836
179. van der Starre, W.E., *et al.* Risk factors for fluoroquinolone-resistant Escherichia coli in adults with community-onset febrile urinary tract infection. J Antimicrob Chemother, 2011. 66: 650.
https://www.ncbi.nlm.nih.gov/pubmed/21123286
180. Ren, H., *et al.* Treatment of complicated urinary tract infection and acute pyelonephritis by short-course intravenous levofloxacin (750 mg/day) or conventional intravenous/oral levofloxacin (500 mg/day): prospective, open-label, randomized, controlled, multicenter, non-inferiority clinical trial. Int Urol Nephrol, 2017. 49: 499.
https://www.ncbi.nlm.nih.gov/pubmed/28108978
181. Wagenlehner, F.M., *et al.* Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: A randomised, double-blind, phase 3 trial (ASPECT-cUTI). The Lancet, 2015. 385: 1949.
https://www.ncbi.nlm.nih.gov/pubmed/25931244
182. Rudrabhatla, P., *et al.* Stopping the effective non-fluoroquinolone antibiotics at day 7 vs continuing until day 14 in adults with acute pyelonephritis requiring hospitalization: A randomized non-inferiority trial. PLoS ONE, 2018. 13: e0197302.
https://www.ncbi.nlm.nih.gov/pubmed/29768465
183. Gould, C.V., *et al.* Guideline for prevention of catheter-associated urinary tract infections 2009. Infect Control Hosp Epidemiol, 2010. 31: 319.
https://www.ncbi.nlm.nih.gov/pubmed/20156062
184. Garibaldi, R.A., *et al.* Factors predisposing to bacteriuria during indwelling urethral catheterization. N Engl J Med, 1974. 291: 215.
https://www.ncbi.nlm.nih.gov/pubmed/4834750
185. Kunin, C.M., *et al.* Prevention of catheter-induced urinary-tract infections by sterile closed drainage. N Engl J Med, 1966. 274: 1155.
https://www.ncbi.nlm.nih.gov/pubmed/5934951
186. Hartstein, A.I., *et al.* Nosocomial urinary tract infection: a prospective evaluation of 108 catheterized patients. Infect Control, 1981. 2: 380.
https://www.ncbi.nlm.nih.gov/pubmed/6795141
187. Warren, J.W., *et al.* Fever, bacteremia, and death as complications of bacteriuria in women with long-term urethral catheters. J Infect Dis, 1987. 155: 1151.
https://www.ncbi.nlm.nih.gov/pubmed/3572035
188. Classen, D.C., *et al.* Prevention of catheter-associated bacteriuria: clinical trial of methods to block three known pathways of infection. Am J Infect Control, 1991. 19: 136.
https://www.ncbi.nlm.nih.gov/pubmed/1863002
189. Saint, S., *et al.* Preventing catheter-related bacteriuria: should we? Can we? How? Arch Intern Med, 1999. 159: 800.
https://www.ncbi.nlm.nih.gov/pubmed/10219925

190. Maki, D.G., *et al.* Engineering out the risk for infection with urinary catheters. Emerg Infect Dis, 2001. 7: 342. https://www.ncbi.nlm.nih.gov/pubmed/11294737
191. Jacobsen, S.M., *et al.* Complicated catheter-associated urinary tract infections due to Escherichia coli and Proteus mirabilis. Clin Microbiol Rev, 2008. 21: 26. https://www.ncbi.nlm.nih.gov/pubmed/18202436
192. Cek, M., *et al.* Healthcare-associated urinary tract infections in hospitalized urological patients--a global perspective: results from the GPIU studies 2003-2010. World J Urol, 2014. 32: 1587. https://www.ncbi.nlm.nih.gov/pubmed/24452449
193. Saint, S., *et al.* Preventing Catheter-Associated Urinary Tract Infections. N Engl J Med, 2016. 375: 1298. https://www.ncbi.nlm.nih.gov/pubmed/27682041
194. Marschall, J., *et al.* Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: Meta-analysis. BMJ, 2013. 346: f3147. https://www.ncbi.nlm.nih.gov/pubmed/23757735
195. Fang, Y.Q., *et al.* Antibiotic prophylaxis at time of catheter removal following laparoscopic radical prostatectomy: A prospective randomized study. Acta Med Mediter, 2014. 30: 161. http://www.actamedicamediterranea.com/archive/2014/medica-1/antibiotic-prophylaxis-at-time-of-catheter-removal-following-laparoscopic-radical-prostatectomy-a-prospective-randomized-study/pdf
196. Bone, R.C., *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest, 1992. 101: 1644. https://www.ncbi.nlm.nih.gov/pubmed/1303622
197. Levy, M.M., *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med, 2003. 31: 1250. https://www.ncbi.nlm.nih.gov/pubmed/12682500
198. Dellinger, R.P., *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med, 2013. 39: 165. https://www.ncbi.nlm.nih.gov/pubmed/23361625
199. Martin, G.S., *et al.* The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med, 2003. 348: 1546. https://www.ncbi.nlm.nih.gov/pubmed/12700374
200. Hotchkiss, R.S., *et al.* The pathophysiology and treatment of sepsis. N Engl J Med, 2003. 348: 138. https://www.ncbi.nlm.nih.gov/pubmed/12519925
201. Rosser, C.J., *et al.* Urinary tract infections in the critically ill patient with a urinary catheter. Am J Surg, 1999. 177: 287. https://www.ncbi.nlm.nih.gov/pubmed/10326844
202. Brun-Buisson, C., *et al.* EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med, 2004. 30: 580. https://www.ncbi.nlm.nih.gov/pubmed/14997295
203. Tandogdu, Z., *et al.* Antimicrobial resistance in urosepsis: outcomes from the multinational, multicenter global prevalence of infections in urology (GPIU) study 2003-2013. World J Urol, 2016. 34: 1193. https://www.ncbi.nlm.nih.gov/pubmed/26658886
204. Wilson, M.L., *et al.* Principles and procedures for blood cultures; Approved Guideline. Clin Lab Stand Inst, 2007. https://clsi.org/media/1448/m47a_sample.pdf
205. Howell, M.D., *et al.* Management of Sepsis and Septic Shock. JAMA, 2017. 317: 847. https://www.ncbi.nlm.nih.gov/pubmed/28114603
206. Brunkhorst, F.M., *et al.* Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. Intensive Care Med, 2000. 26 Suppl 2: S148. https://www.ncbi.nlm.nih.gov/pubmed/18470710
207. Angeletti, S., *et al.* Procalcitonin, MR-Proadrenomedullin, and Cytokines Measurement in Sepsis Diagnosis: Advantages from Test Combination. Dis Markers, 2015. 2015: 951532. https://www.ncbi.nlm.nih.gov/pubmed/26635427
208. Harbarth, S., *et al.* Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med, 2001. 164: 396. https://www.ncbi.nlm.nih.gov/pubmed/11500339
209. Mikkelsen, M.E., *et al.* Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med, 2009. 37: 1670. https://www.ncbi.nlm.nih.gov/pubmed/19325467
210. Carlet, J., *et al.* Guideliness for prevention of nosocomial infections in intensive care unit. Arnette Ed Paris 1994: 41. [No abstract available].

211. Riedl, C.R., *et al.* Bacterial colonization of ureteral stents. Eur Urol, 1999. 36: 53.
https://www.ncbi.nlm.nih.gov/pubmed/10364656
212. DeGroot-Kosolcharoen, J., *et al.* Evaluation of a urinary catheter with a preconnected closed drainage bag. Infect Control Hosp Epidemiol, 1988. 9: 72.
https://www.ncbi.nlm.nih.gov/pubmed/3343502
213. Rivers, E., *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med, 2001. 345: 1368.
https://www.ncbi.nlm.nih.gov/pubmed/11794169
214. Mouncey, P.R., *et al.* Trial of early, goal-directed resuscitation for septic shock. N Engl J Med, 2015. 372: 1301.
https://www.ncbi.nlm.nih.gov/pubmed/25776532
215. ARISE Investigators, *et al.* Goal-directed resuscitation for patients with early septic shock. N Engl J Med, 2014. 371: 1496.
https://www.ncbi.nlm.nih.gov/pubmed/25272316
216. ProCESS Investigators, *et al.* A randomized trial of protocol-based care for early septic shock. N Engl J Med, 2014. 370: 1683.
https://www.ncbi.nlm.nih.gov/pubmed/24635773
217. The PRISM Investigators. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. N Engl J Med, 2017. 376: 2223.
https://www.nejm.org/doi/full/10.1056/NEJMoa1701380
218. Monnet, X., *et al.* Prediction of fluid responsiveness: an update. Ann Intensive Care, 2016. 6: 111.
https://www.ncbi.nlm.nih.gov/pubmed/27858374
219. Dellinger, R.P., *et al.* Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med, 2004. 32: 858.
https://www.ncbi.nlm.nih.gov/pubmed/15090974
220. Zhang, N., *et al.* Are Ureaplasma spp. a cause of nongonococcal urethritis? A systematic review and meta-analysis. PLoS ONE, 2014. 9: e113771.
https://www.ncbi.nlm.nih.gov/pubmed/25463970
221. Horner, P.J., *et al.* 2016 European guideline on the management of non-gonococcal urethritis. Int J STD AIDS, 2016. 27: 928.
https://www.ncbi.nlm.nih.gov/pubmed/27147267
222. Workowski, K.A., *et al.* Sexually transmitted diseases treatment guidelines, 2015. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Cent Dis Contr, 2015. 64: 1.
https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm
223. Bartoletti, R., *et al.* Management of Urethritis: Is It Still the Time for Empirical Antibiotic Treatments? Eur Urol Focus, 2019. 5: 29.
https://www.ncbi.nlm.nih.gov/pubmed/30318465
224. Jensen, J.S., *et al.* 2016 European guideline on Mycoplasma genitalium infections. J Eur Acad Dermatol Venereol, 2016. 30: 1650.
https://www.ncbi.nlm.nih.gov/pubmed/27505296
225. Miller, J.M., *et al.* A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis, 2018. 67: e1.
https://www.ncbi.nlm.nih.gov/pubmed/29955859
226. Wagenlehner, F.M.E., *et al.* The Presentation, Diagnosis, and Treatment of Sexually Transmitted Infections. Dtsch Arztebl Int, 2016. 113: 11.
https://www.ncbi.nlm.nih.gov/pubmed/26931526
227. Sena, A.C., *et al.* Persistent and recurrent Trichomonas vaginalis infections: Epidemiology, treatment and management considerations. Exp Rev Anti-Infect Ther, 2014. 12: 673.
https://www.ncbi.nlm.nih.gov/pubmed/24555561
228. Shigemura, K., *et al.* History and epidemiology of antibiotic susceptibilities of Neisseria gonorrhoeae. Curr Drug Targ, 2015. 16: 272.
https://www.ncbi.nlm.nih.gov/pubmed/25410409
229. Hathorn, E., *et al.* The effectiveness of gentamicin in the treatment of Neisseria gonorrhoeae: A systematic review. Syst Revs, 2014. 3: 104.
https://www.ncbi.nlm.nih.gov/pubmed/25239090
230. Lau, A., *et al.* The efficacy of azithromycin for the treatment of genital mycoplasma genitalium: A systematic review and meta-analysis. Clin Infect Dis, 2015. 61: 1389.
https://www.ncbi.nlm.nih.gov/pubmed/26240201

231. Manhart, L.E., *et al.* Efficacy of Antimicrobial Therapy for Mycoplasma genitalium Infections. Clin Infect Dis, 2015. 61: S802.
https://www.ncbi.nlm.nih.gov/pubmed/26602619
232. Paez-Canro, C., *et al.* Antibiotics for treating urogenital Chlamydia trachomatis infection in men and non-pregnant women. Cochrane Database of Syst Rev, 2019. 2019: CD010871.
https://www.ncbi.nlm.nih.gov/pubmed/30682211
233. Atkinson, L.M., *et al.* 'The waiting game': are current chlamydia and gonorrhoea near-patient/point-of-care tests acceptable to service users and will they impact on treatment? Int J STD AIDS, 2016. 27: 650.
https://www.ncbi.nlm.nih.gov/pubmed/26092579
234. Harding-Esch, E.M., *et al.* Impact of deploying multiple point-of-care tests with a sample first' approach on a sexual health clinical care pathway. A service evaluation. Sex Transm Infect, 2017. 93: 424.
https://www.ncbi.nlm.nih.gov/pubmed/28159916
235. Mensforth, S., *et al.* Auditing the use and assessing the clinical utility of microscopy as a point-of-care test for Neisseria gonorrhoeae in a Sexual Health clinic. Int J STD AIDS, 2018. 29: 157.
https://www.ncbi.nlm.nih.gov/pubmed/28705094
236. Moi, H., *et al.* Microscopy of Stained Urethral Smear in Male Urethritis; Which Cutoff Should be Used? Sex Transm Infect, 2017. 44: 189.
https://www.ncbi.nlm.nih.gov/pubmed/28178118
237. Sarier, M., *et al.* Microscopy of Gram-stained urethral smear in the diagnosis of urethritis: Which threshold value should be selected? Andrologia, 2018. 50: e13143.
https://www.ncbi.nlm.nih.gov/pubmed/30238498
238. Falk, L., *et al.* Time to eradication of Mycoplasma genitalium after antibiotic treatment in men and women. J Antimicro Chemother, 2015. 70: 3134.
https://www.ncbi.nlm.nih.gov/pubmed/26283670
239. Khosropour, C.M., *et al.* Efficacy of standard therapies against Ureaplasma species and persistence among men with nongonococcal urethritis enrolled in a randomised controlled trial. Sex Transm Infect, 2015. 91: 308.
https://www.ncbi.nlm.nih.gov/pubmed/25616607
240. Kirkcaldy, R.D., *et al.* Neisseria gonorrhoeae Antimicrobial Susceptibility Surveillance - The Gonococcal Isolate Surveillance Project, 27 Sites, United States, 2014. Morbidity and mortality weekly report. MMWR Surveill Summ, 2016. 65: 1.
https://www.ncbi.nlm.nih.gov/pubmed/27414503
241. Ong, J.J., *et al.* Should female partners of men with non-gonococcal urethritis, negative for Chlamydia trachomatis and Mycoplasma genitalium, be informed and treated? Clinical outcomes from a partner study of heterosexual men with NGU. Sex Transm Dis, 2017. 44: 126.
https://www.ncbi.nlm.nih.gov/pubmed/28079749
242. Read, T.R.H., *et al.* Azithromycin 1.5g over 5 days compared to 1g single dose in urethral mycoplasma genitalium: Impact on treatment outcome and resistance. Clin Infect Dis, 2017. 64: 250.
https://www.ncbi.nlm.nih.gov/pubmed/28011607
243. Read, T.R.H., *et al.* Use of pristinamycin for Macrolide-Resistant mycoplasma genitalium infection. Emerg Infect Dis, 2018. 24: 328.
https://www.ncbi.nlm.nih.gov/pubmed/29350154
244. Salado-Rasmussen, K., *et al.* Mycoplasma genitalium testing pattern and macrolide resistance: A Danish nationwide retrospective survey. Clin Infect Dis, 2014. 59: 24.
https://www.ncbi.nlm.nih.gov/pubmed/24729494
245. Soda, M., *et al.* Evaluation of the microbiological efficacy of a single 2-gram dose of extended-release azithromycin by population pharmacokinetics and simulation in Japanese patients with gonococcal urethritis. Antimicrob Agents Chemother, 2018. 62: e01409.
https://www.ncbi.nlm.nih.gov/pubmed/29038284
246. Takahashi, S., *et al.* Clinical efficacy of a single two Gram dose of azithromycin extended release for male patients with urethritis. Antibiotics, 2014. 3: 109.
https://www.ncbi.nlm.nih.gov/pubmed/27025738
247. Unemo, M., *et al.* Five-day azithromycin treatment regimen for mycoplasma genitalium infection also effectively eradicates chlamydia trachomatis. Acta Derm-Venereol, 2015. 95: 730.
https://www.ncbi.nlm.nih.gov/pubmed/25823977
248. Yasuda, M., *et al.* A single 2 g oral dose of extended-release azithromycin for treatment of gonococcal urethritis. J Antimicrob Chemother, 2014. 69: 3116.
https://www.ncbi.nlm.nih.gov/pubmed/24948703
249. Yuan, Z., *et al.* Randomized controlled clinical trial on the efficacy of fosfomycin trometamol for uncomplicated gonococcal urethritis in men. Clin Microbiol Infect, 2016. 22: 507.
https://www.ncbi.nlm.nih.gov/pubmed/27064136

250. Berntsson, M., *et al.* Viral and bacterial aetiologies of male urethritis: findings of a high prevalence of Epstein-Barr virus. Int J STD AIDS, 2010. 21: 191.
https://www.ncbi.nlm.nih.gov/pubmed/20215624
251. Couldwell, D.L., *et al.* Ureaplasma urealyticum is significantly associated with non-gonococcal urethritis in heterosexual Sydney men. Int J STD AIDS, 2010. 21: 337.
https://www.ncbi.nlm.nih.gov/pubmed/20498103
252. Rietmeijer, C.A., *et al.* Recalibrating the Gram stain diagnosis of male urethritis in the era of nucleic acid amplification testing. Sex Transm Dis, 2012. 39: 18.
https://www.ncbi.nlm.nih.gov/pubmed/22183839
253. Centers for Disease, C., *et al.* Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae--2014. MMWR Recomm Rep, 2014. 63: 1.
https://www.ncbi.nlm.nih.gov/pubmed/24622331
254. Bissessor, M., *et al.* Macrolide resistance and azithromycin failure in a Mycoplasma genitalium-infected cohort and response of azithromycin failures to alternative antibiotic regimens. Clin Infect Dis, 2015. 60: 1228.
https://www.ncbi.nlm.nih.gov/pubmed/25537875
255. Kirkcaldy, R.D., *et al.* The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. Clin Infect Dis, 2014. 59: 1083.
https://www.ncbi.nlm.nih.gov/pubmed/25031289
256. Kojima, M., *et al.* Single-dose treatment of male patients with gonococcal urethritis using 2g spectinomycin: microbiological and clinical evaluations. Int J Antimicrob Agents, 2008. 32: 50.
https://www.ncbi.nlm.nih.gov/pubmed/18539003
257. Lanjouw, E., *et al.* 2015 European guideline on the management of Chlamydia trachomatis infections. Int J STD AIDS, 2016. 27: 333.
https://www.ncbi.nlm.nih.gov/pubmed/26608577
258. Lau, C.Y., *et al.* Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sex Transm Dis, 2002. 29: 497.
https://www.ncbi.nlm.nih.gov/pubmed/12218839
259. Moran, J.S., *et al.* Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis, 1995. 20 Suppl 1: S47.
https://www.ncbi.nlm.nih.gov/pubmed/7795109
260. Unemo, M., *et al.* Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution, and future. Clin Microbiol Rev, 2014. 27: 587.
https://www.ncbi.nlm.nih.gov/pubmed/24982323
261. Alexander, R.B., *et al.* Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. Urology, 1998. 52: 744.
https://www.ncbi.nlm.nih.gov/pubmed/9801092
262. Alexander, R.B., *et al.* Chronic prostatitis: results of an Internet survey. Urology, 1996. 48: 568.
https://www.ncbi.nlm.nih.gov/pubmed/8886062
263. Zermann, D.H., *et al.* Neurourological insights into the etiology of genitourinary pain in men. J Urol, 1999. 161: 903.
https://www.ncbi.nlm.nih.gov/pubmed/10022711
264. Perletti, G., *et al.* Antimicrobial therapy for chronic bacterial prostatitis. Cochrane Database Syst Rev, 2013: CD009071.
https://www.ncbi.nlm.nih.gov/pubmed/23934982
265. Dadashpour. M, *et al.* Acute Prostatitis After Transrectal Ultrasound-guided Prostate Biopsy: Comparing Two Different Antibiotic Prophylaxis Regimen. Biomed Pharmacol J, 2016. 9: 593.
http://biomedpharmajournal.org/vol9no2/acute-prostatitis/
266. Schaeffer, A.J., *et al.* Treatment of chronic bacterial prostatitis with levofloxacin and ciprofloxacin lowers serum prostate specific antigen. J Urol, 2005. 174: 161.
https://www.ncbi.nlm.nih.gov/pubmed/15947609
267. Skerk, V., *et al.* Comparative analysis of azithromycin and ciprofloxacin in the treatment of chronic prostatitis caused by Chlamydia trachomatis. Int J Antimicrob Agents, 2003. 21: 457.
https://www.ncbi.nlm.nih.gov/pubmed/12727080
268. Vickovic, N., *et al.* Metronidazole 1.5 gram dose for 7 or 14 days in the treatment of patients with chronic prostatitis caused by Trichomonas vaginalis: A randomized study. J Chemother, 2010. 22: 364.
https://www.ncbi.nlm.nih.gov/pubmed/21123162
269. Cai, T., *et al.* Serenoa repens associated with Urtica dioica (ProstaMEV) and curcumin and quercitin (FlogMEV) extracts are able to improve the efficacy of prulifloxacin in bacterial prostatitis patients: results from a prospective randomised study. Int J Antimicrob Agents, 2009. 33: 549.
https://www.ncbi.nlm.nih.gov/pubmed/19181486

270. Aliaev Iu, G., *et al.* [Wardenafil in combined treatment of patients with chronic bacterial prostatitis]. Urologiia, 2008: 52.
https://www.ncbi.nlm.nih.gov/pubmed/19256057
271. Lipsky, B.A., *et al.* Treatment of bacterial prostatitis. Clin Infect Dis, 2010. 50: 1641.
https://www.ncbi.nlm.nih.gov/pubmed/20459324
272. Wise, G.J., *et al.* Atypical infections of the prostate. Curr Prostate Reps, 2008. 6: 86.
https://link.springer.com/article/10.1007/s11918-008-0014-2
273. Turner, J.A., *et al.* Validity and responsiveness of the national institutes of health chronic prostatitis symptom index. J Urol, 2003. 169: 580.
https://www.ncbi.nlm.nih.gov/pubmed/12544311
274. Zegarra Montes, L.Z., *et al.* Semen and urine culture in the diagnosis of chronic bacterial prostatitis. Int Braz J Urol, 2008. 34: 30.
https://www.ncbi.nlm.nih.gov/pubmed/18341719
275. Budia, A., *et al.* Value of semen culture in the diagnosis of chronic bacterial prostatitis: a simplified method. Scand J Urol Nephrol, 2006. 40: 326.
https://www.ncbi.nlm.nih.gov/pubmed/16916775
276. Skerk, V., *et al.* The role of unusual pathogens in prostatitis syndrome. Int J Antimicrob Agents, 2004. 24 Suppl 1: S53.
https://www.ncbi.nlm.nih.gov/pubmed/15364308
277. Schneider, H., *et al.* The 2001 Giessen Cohort Study on patients with prostatitis syndrome--an evaluation of inflammatory status and search for microorganisms 10 years after a first analysis. Andrologia, 2003. 35: 258.
https://www.ncbi.nlm.nih.gov/pubmed/14535851
278. Naber, K.G., *et al.*, Prostatitits, epididymitis and orchitis, In: Infectious diseases, D. Armstrong & J. Cohen, Editors. 1999, Mosby: London.
279. Badalyan, R.R., *et al.* Chlamydial and ureaplasmal infections in patients with nonbacterial chronic prostatitis. Andrologia, 2003. 35: 263.
https://www.ncbi.nlm.nih.gov/pubmed/14535852
280. Berger, R.E., Epididymitis., In: Sexually transmitted diseases, K.K. Holmes, P.-A. Mardh, P.F. Sparling & P.J. Wiesner, Editors. 1984, McGraw-Hill: New York.
281. Robinson, A.J., *et al.* Acute epididymitis: why patient and consort must be investigated. Br J Urol, 1990. 66: 642.
https://www.ncbi.nlm.nih.gov/pubmed/2265337
282. Schaeffer, A.J. Prostatitis: US perspective. Int J Antimicrob Agents, 1999. 11: 205.
https://www.ncbi.nlm.nih.gov/pubmed/10394972
283. Krieger, J.N., *et al.* NIH consensus definition and classification of prostatitis. Jama, 1999. 282: 236.
https://www.ncbi.nlm.nih.gov/pubmed/10422990
284. Workshop Committee of the national institute of diabetes and digestive and kidney diease (NIDDK), Chronic prostatitis workshop. 1995: Bethesda, Maryland.
285. Krieger, J.N., *et al.* Chronic pelvic pains represent the most prominent urogenital symptoms of “chronic prostatitis”. Urology, 1996. 48: 715.
https://www.ncbi.nlm.nih.gov/pubmed/8911515
286. Nickel, J.C. Effective office management of chronic prostatitis. Urol Clin North Am, 1998. 25: 677.
https://www.ncbi.nlm.nih.gov/pubmed/10026774
287. Etienne, M., *et al.* Performance of the urine leukocyte esterase and nitrite dipstick test for the diagnosis of acute prostatitis. Clin Infect Dis, 2008. 46: 951.
https://www.ncbi.nlm.nih.gov/pubmed/18288905
288. Meares, E.M., *et al.* Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol, 1968. 5: 492.
https://www.ncbi.nlm.nih.gov/pubmed/4870505
289. Nickel, J.C., *et al.* How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol, 2006. 176: 119.
https://www.ncbi.nlm.nih.gov/pubmed/16753385
290. Doble, A., *et al.* Ultrasonographic findings in prostatitis. Urol Clin North Am, 1989. 16: 763.
https://www.ncbi.nlm.nih.gov/pubmed/2683305
291. Papp, J.R., *et al.* Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae — 2014. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control, 2014. 63: 1.
https://www.ncbi.nlm.nih.gov/pubmed/24622331
292. Polascik, T.J., *et al.* Prostate specific antigen: a decade of discovery--what we have learned and where we are going. J Urol, 1999. 162: 293.
https://www.ncbi.nlm.nih.gov/pubmed/10411025

293. Wagenlehner, F.M., *et al.* Bacterial prostatitis. World J Urol, 2013. 31: 711.
https://www.ncbi.nlm.nih.gov/pubmed/23519458
294. Gill, B.C., *et al.* Bacterial prostatitis. Curr Opin Infect Dis, 2016. 29: 86.
https://www.ncbi.nlm.nih.gov/pubmed/26555038
295. Wagenlehner, F.M., *et al.* Prostatitis: the role of antibiotic treatment. World J Urol, 2003. 21: 105.
https://www.ncbi.nlm.nih.gov/pubmed/12687400
296. Krieger, J.N. Recurrent lower urinary tract infections in men. J New Rem Clin, 1998. 47: 4. [No abstract available].
297. Litwin, M.S., et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol, 1999. 162: 369.
https://www.ncbi.nlm.nih.gov/pubmed/10411041
298. Schaeffer, A.J., *et al.* Summary consensus statement: diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol 2003. 43: 1.
https://www.ncbi.nlm.nih.gov/pubmed/12521576
299. Bjerklund Johansen, T.E., *et al.* The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. Eur Urol, 1998. 34: 457.
https://www.ncbi.nlm.nih.gov/pubmed/9831786
300. Cai, T., *et al.* Clinical and microbiological efficacy of prulifloxacin for the treatment of chronic bacterial prostatitis due to Chlamydia trachomatis infection: results from a prospective, randomized and open-label study. Methods Find Exp Clin Pharmacol, 2010. 32: 39.
https://www.ncbi.nlm.nih.gov/pubmed/20383345
301. Smelov, V., *et al.* Chlamydia trachomatis survival in the presence of two fluoroquinolones (lomefloxacin versus levofloxacin) in patients with chronic prostatitis syndrome. Andrologia, 2005. 37: 61.
https://www.ncbi.nlm.nih.gov/pubmed/16026425
302. Ohkawa, M., *et al.* Antimicrobial treatment for chronic prostatitis as a means of defining the role of Ureaplasma urealyticum. Urol Int, 1993. 51: 129.
https://www.ncbi.nlm.nih.gov/pubmed/8249222
303. Jimenez-Cruz, J.F., *et al.* Treatment of chronic prostatitis: intraprostatic antibiotic injections under echography control. J Urol, 1988. 139: 967.
https://www.ncbi.nlm.nih.gov/pubmed/3283385
304. Mayersak, J.S. Transrectal ultrasonography directed intraprostatic injection of gentamycin-xylocaine in the management of the benign painful prostate syndrome. A report of a 5 year clinical study of 75 patients. Int Surg, 1998. 83: 347.
https://www.ncbi.nlm.nih.gov/pubmed/10096759
305. Hua, L.X., *et al.* [The diagnosis and treatment of acute prostatitis: report of 35 cases]. Zhonghua Nan Ke Xue, 2005. 11: 897.
https://www.ncbi.nlm.nih.gov/pubmed/16398358
306. Yoon, B.I., *et al.* Acute bacterial prostatitis: how to prevent and manage chronic infection? J Infect Chemother, 2012. 18: 444.
https://www.ncbi.nlm.nih.gov/pubmed/22215226
307. Ludwig, M., *et al.* Diagnosis and therapeutic management of 18 patients with prostatic abscess. Urology, 1999. 53: 340.
https://www.ncbi.nlm.nih.gov/pubmed/9933051
308. Chou, Y.H., *et al.* Prostatic abscess: transrectal color Doppler ultrasonic diagnosis and minimally invasive therapeutic management. Ultrasound Med Biol, 2004. 30: 719.
https://www.ncbi.nlm.nih.gov/pubmed/15219951
309. Çek, M., *et al.* Acute and Chronic Epididymitis in EAU-EBU Update Series. Eur Urol Suppl 2017. 16: 124.
https://www.sciencedirect.com/science/article/pii/S1569905617300568
310. Harnisch, J.P., *et al.* Aetiology of acute epididymitis. Lancet, 1977. 1: 819.
https://www.ncbi.nlm.nih.gov/pubmed/67333
311. Street, E., *et al.* The 2016 European guideline on the management of epididymo-orchitis. Int J STD AIDS, 2016. 28: 744.
https://www.ncbi.nlm.nih.gov/pubmed/28632112
312. Abbara, A., *et al.* Etiology and management of genitourinary tuberculosis. Nat Rev Urol, 2011. 8: 678.
https://www.ncbi.nlm.nih.gov/pubmed/22157940
313. Street, E., *et al.* BASHH 2010 United Kingdom national guideline for the management of epididymo-orchitis. Int J STD AIDS, 2011. 22: 361.
https://www.ncbi.nlm.nih.gov/pubmed/21729951
314. Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines - Epididymitis. 2015.
https://www.cdc.gov/std/tg2015/default.htm

315. Banyra, O., *et al.* Acute epididymo-orchitis: staging and treatment. Cent Eur J Urol, 2012. 65: 139.
https://www.ncbi.nlm.nih.gov/pubmed/24578950
316. Haddadeen, C., *et al.* Comparative regional audit of urology and genito-urinary departments in the management of acute epididymo-orchitis. HIV Med, 2010. 11: 45.
https://www.ncbi.nlm.nih.gov/pubmed/70186144
317. Nicholson, A., *et al.* Management of epididymo-orchitis in primary care: Results from a large UK primary care database. Brit J General Pract, 2010. 60: e407.
https://www.ncbi.nlm.nih.gov/pubmed/20883615
318. Pilatz, A., *et al.* Impact of bacterial epididymitis on semen quality after antibiotic treatment. J Urol, 2012. 1): e443.
https://www.ncbi.nlm.nih.gov/pubmed/70720788
319. Pilatz, A., *et al.* Acute Epididymitis Revisited: Impact of Molecular Diagnostics on Etiology and Contemporary Guideline Recommendations. Eur Urol, 2015. 68: 428.
https://www.ncbi.nlm.nih.gov/pubmed/25542628
320. Andersen, B., *et al.* Impact of intensified testing for urogenital Chlamydia trachomatis infections: a randomised study with 9-year follow-up. Sex Transm Infect, 2011. 87: 156.
https://www.ncbi.nlm.nih.gov/pubmed/21097811
321. Eickhoff, J.H., *et al.* A double-blind, randomized, controlled multicentre study to compare the efficacy of ciprofloxacin with pivampicillin as oral therapy for epididymitis in men over 40 years of age. BJU Int, 1999. 84: 827.
https://www.ncbi.nlm.nih.gov/pubmed/10532980
322. Chennamsetty, A., *et al.* Contemporary diagnosis and management of Fournier's gangrene. Ther Adv Urol, 2015. 7: 203.
https://www.ncbi.nlm.nih.gov/pubmed/26445600
323. Eke, N. Fournier's gangrene: a review of 1726 cases. Br J Surg, 2000. 87: 718.
https://www.ncbi.nlm.nih.gov/pubmed/10848848
324. Subrahmanyam, U., *et al.* Honey dressing beneficial in treatment of fournier's gangrene. Indian J Surg, 2004. 66: 75.
https://pdfs.semanticscholar.org/ce8f/3708e4096a4d61dc74cd5089245c1d26558d.pdf
325. Jallali, N., *et al.* Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. Am J Sur, 2005. 189: 462.
https://www.ncbi.nlm.nih.gov/pubmed/15820462
326. Karian, L.S., *et al.* Reconstruction of Defects After Fournier Gangrene: A Systematic Review. Eplasty, 2015. 15: e18.
https://www.ncbi.nlm.nih.gov/pubmed/26171090
327. Furr, J., *et al.* Contemporary Trends in the Inpatient Management of Fournier's Gangrene: Predictors of Length of Stay and Mortality Based on Population-based Sample. Urology, 2017. 102: 79.
https://www.ncbi.nlm.nih.gov/pubmed/27693572
328. Kim, S.Y., *et al.* A Contemporary Analysis of Fournier Gangrene Using the National Surgical Quality Improvement Program. Urology, 2015.
https://www.ncbi.nlm.nih.gov/pubmed/25770725
329. Sorensen, M.D., *et al.* Fournier's Gangrene: Epidemiology and Outcomes in the General US Population. Urol Int, 2016. 97: 249.
https://www.ncbi.nlm.nih.gov/pubmed/27172977
330. Roghmann, F., *et al.* Is there a need for the Fournier's gangrene severity index? Comparison of scoring systems for outcome prediction in patients with Fournier's gangrene. BJU Int, 2012. 110: 1359.
https://www.ncbi.nlm.nih.gov/pubmed/22494217
331. Lauerman, M., *et al.* Less is More? Antibiotic duration and outcomes in fournier's gangrene. J Trauma Acute Care Surg, 2017.
https://www.ncbi.nlm.nih.gov/pubmed/28538648
332. Li, C., *et al.* Hyperbaric oxygen therapy as an adjuvant therapy for comprehensive treatment of Fournier's gangrene. Urol Int, 2015. 94: 453.
https://www.ncbi.nlm.nih.gov/pubmed/25677386
333. Stevens, D.L., *et al.* Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis, 2014. 59: 147.
https://www.ncbi.nlm.nih.gov/pubmed/24947530
334. European Centre for Disease Prevention and Control. Healthcare-associated infections in intensive care units - Annual Epidemiological Report for 2016.
https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-intensive-care-units-annual-epidemiological-0

335. CDC. Procedure-associated Module 9: Surgical Site Infection (SSI) Event. 2017. https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf
336. Tanner, J., *et al.* Surgical hand antisepsis to reduce surgical site infection. Cochrane Database Syst Rev, 2016: CD004288. https://www.ncbi.nlm.nih.gov/pubmed/26799160
337. Webster, J., *et al.* Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. Cochrane Database Syst Rev, 2015: CD004985. https://www.ncbi.nlm.nih.gov/pubmed/25927093
338. Tanner, J., *et al.* Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev, 2011: CD004122. https://www.ncbi.nlm.nih.gov/pubmed/22071812
339. Arnold, A., *et al.* Preoperative Mechanical Bowel Preparation for Abdominal, Laparoscopic, and Vaginal Surgery: A Systematic Review. J Minim Invasive Gynecol, 2015. 22: 737. https://www.ncbi.nlm.nih.gov/pubmed/25881881
340. Guenaga, K.F., *et al.* Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev, 2011: CD001544. https://www.ncbi.nlm.nih.gov/pubmed/21901677
341. Dumville, J.C., *et al.* Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Cochrane Database Syst Rev, 2015: CD003949. https://www.ncbi.nlm.nih.gov/pubmed/25897764
342. Webster, J., *et al.* Use of plastic adhesive drapes during surgery for preventing surgical site infection. Cochrane Database Syst Rev, 2015: CD006353. https://www.ncbi.nlm.nih.gov/pubmed/25901509
343. Bonkat, G., *et al.* Non-molecular Methods to Detect Bacteriuria Prior to Urological Interventions: A Diagnostic Accuracy Systematic Review. Eur Urol Focus, 2017. 3: 535. https://www.ncbi.nlm.nih.gov/pubmed/29627196
344. ECDC. Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis. 2013. https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Perioperative%20antibiotic%20prophylaxis%20-%20June%202013.pdf
345. Antibacterial prophylaxis in surgery: 2 - Urogenital, obstetric and gynaecological surgery. Drug Therapeut Bull, 2004. 42: 9. https://www.ncbi.nlm.nih.gov/pubmed/15067952
346. Foon, R., *et al.* Prophylactic antibiotics to reduce the risk of urinary tract infections after urodynamic studies [Systematic Review]. Cochrane Database of Syst Rev, 2012. 10: 10. https://www.ncbi.nlm.nih.gov/pubmed/23076941
347. Gurbuz, C., et al. Are prophylactic antibiotics necessary for urodynamic study? Kaohsiung J Med Sci, 2013. 29: 325. https://www.ncbi.nlm.nih.gov/pubmed/20377490
348. Hirakauva Ey, *et al.*Incidence of urinary infection in women after urodynamic study (UDS). Int Urogynecol J Pelvic Floor Dysf, 2011. 22. [No abstract availanle].
349. Carey, M.M., *et al.* Should We Use Antibiotic Prophylaxis for Flexible Cystoscopy? A Systematic Review and Meta-Analysis. Urol Int, 2015. 95: 249. https://www.ncbi.nlm.nih.gov/pubmed/26138144
350. Garcia-Perdomo, H.A., *et al.* Efficacy of antibiotic prophylaxis in patients undergoing cystoscopy: A randomized clinical trial. World J Urol, 2013. 31: 1433. https://www.ncbi.nlm.nih.gov/pubmed/23412704
351. Lu, Y., *et al.* Antibiotic prophylaxis for shock wave lithotripsy in patients with sterile urine before treatment may be unnecessary: A systematic review and meta-analysis. J Urol, 2012. 188: 441. https://www.ncbi.nlm.nih.gov/pubmed/52059642
352. Mrkobrada, M., *et al.* CUA Guidelines on antibiotic prophylaxis for urologic procedures. Can Urol Assoc J, 2015. 9: 13. https://www.ncbi.nlm.nih.gov/pubmed/25737749
353. Hsieh, C.H., *et al.* The Effectiveness of Prophylactic Antibiotics with Oral Levofloxacin against Post-Shock Wave Lithotripsy Infectious Complications: A Randomized Controlled Trial. Surg Infect, 2016. 17: 346. https://www.ncbi.nlm.nih.gov/pubmed/26910613
354. Liker, Y., *et al.* The role of antibiotics in patients with increased risk of infection during extracorporeal shock wave lithotripsy (ESWL) treatment. Marmara Med J, 1996. 9: 174. https://www.ncbi.nlm.nih.gov/pubmed/26377368

355. Bootsma, A.M.J., et al. Antibiotic Prophylaxis in Urologic Procedures: A Systematic Review. Eur Urol, 2008. 54: 1270.
https://www.ncbi.nlm.nih.gov/pubmed/50098356
356. Dahm, P., *et al.* Evidence-based Urology. BMJ Books London, 2010: 50.
357. Lo, C.W., *et al.* Effectiveness of Prophylactic Antibiotics against Post-Ureteroscopic Lithotripsy Infections: Systematic Review and Meta-Analysis. Surg Infect, 2015. 16: 415.
https://www.ncbi.nlm.nih.gov/pubmed/26207401
358. Seyrek, M., *et al.* Perioperative prophylaxis for percutaneous nephrolithotomy: Randomized study concerning the drug and dosage. J Endourol, 2012. 26: 1431.
https://www.ncbi.nlm.nih.gov/pubmed/22612061
359. Tuzel, E., *et al.* Prospective comparative study of two protocols of antibiotic prophylaxis in percutaneous nephrolithotomy. J Endourol, 2013. 27: 172.
https://www.ncbi.nlm.nih.gov/pubmed/22908891
360. Tekdogan, U., *et al.* The efficiency of prophylactic antibiotic treatment in patients without risk factor who underwent transrectal. Turk Uroloji Dergisi, 2006. 32: 261.
https://www.ncbi.nlm.nih.gov/pubmed/289651865
361. Wang, H., *et al.* [Investigation of infection risk and the value of antibiotic prophylaxis during transrectal biopsy of the prostate by endotoxin determination]. Zhonghua Nan Ke Xue, 2004. 10: 496. [No abstract available].
362. Lindert, K.A., *et al.* Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. J Urol, 2000. 164: 76.
https://www.ncbi.nlm.nih.gov/pubmed/10840428
363. Abughosh, Z., *et al.* A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. J Urol, 2013. 189: 1326.
https://www.ncbi.nlm.nih.gov/pubmed/23041343
364. Ghafoori, M., *et al.* Decrease in infection rate following use of povidone-iodine during transrectal ultrasound guided biopsy of the prostate: a double blind randomized clinical trial. Iranian J Radiol, 2012. 9: 67.
https://www.ncbi.nlm.nih.gov/pubmed/23329966
365. Kanjanawongdeengam, P., *et al.* (2009) Reduction in bacteremia rates after rectum sterilization before transrectal, ultrasound-guided prostate biopsy: a randomized controlled trial. Chotmaihet thangphaet [J Med Ass Thailand] 92, 1621.
https://www.ncbi.nlm.nih.gov/pubmed/20043564
366. Melekos, M.D. Efficacy of prophylactic antimicrobial regimens in preventing infectious complications after transrectal biopsy of the prostate. Int Urol Nephrol, 1990. 22: 257.
https://www.ncbi.nlm.nih.gov/pubmed/2210982
367. Sharpe, J.R., *et al.* Urinary tract infection after transrectal needle biopsy of the prostate. J Urol, 1982. 127: 255.
https://www.ncbi.nlm.nih.gov/pubmed/7062377
368. Brown, R.W., *et al.* (1981) Bacteremia and bacteriuria after transrectal prostatic biopsy. Urology 18, 145.
https://www.ncbi.nlm.nih.gov/pubmed/7269016
369. Taher, Y., *et al.* MP48-11 Prospective randomized controlled study to assess the effect of perineal region cleansing with povidone iodine before transrectal needle biopsy of the prostate on infectious complications. J Urol, 2015. 193: e598
https://www.auajournals.org/doi/full/10.1016/j.juro.2015.02.1685
370. Yu, L., *et al.* Impact of insertion timing of iodophor cotton ball on the control of infection complications after transrectal ultrasound guided prostate biopsy. Nat Med J China, 2014. 94: 609.
https://www.ncbi.nlm.nih.gov/pubmed/24762693
371. Bonkat, G., *et al.* EAU Guidelines on Urological Infection. In: EAU Guidelines, edition presented at the annual EAU Congress Copenhagen. In: EAU Guidelines, edition presented at the annual EAU Congress Copenhagen 2018. ISBN 978-94-92671-01-1.
372. Cerruto, M.A., *et al.* Transrectal versus transperineal 14-core prostate biopsy in detection of prostate cancer: a comparative evaluation at the same institution. Arch Ital Urol Androl, 2014. 86: 284.
https://www.ncbi.nlm.nih.gov/pubmed/25641452
373. Chae, Y., *et al.* The Comparison between Transperineal and Transrectal Ultrasound-Guided Prostate Needle Biopsy. Korean J Urol, 2009. 50: 119.
https://synapse.koreamed.org/search.php?where=aview&id=10.4111/kju.2009.50.2.119&code=0020KJU&vmode=PUBREADER
374. Guo, L.H., *et al.* Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial. Sci Rep, 2015. 5: 16089.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630643/

375. Hara, R., *et al.* Prostatic biopsy at Kawasaki Medical School: A prospective study of the results of transperineal biopsy over the past 13 years and the results of systematic 12-site biopsy using the transperineal and transrectal methods. Nishinihon J Urol, 2006. 68: 403.
https://www.researchgate.net/publication/289682762_Prostatic_biopsy_at_Kawasaki_Medical_School_A_prospective_study_of_the_results_of_transperineal_biopsy_over_the_past_13_years_and_the_results_of_systematic_12-site_biopsy_using_the_transperineal_and_t
376. Singh, S., *et al.* Comparison of infective complications in transperineal versus transrectal ultrasound guided prostatic biopsy in patients suspected to have prostate cancer. Indian J Urol, 2017. 33. [No abstract available].
377. Udeh, E.I., *et al.* Transperineal versus transrectal prostate biopsy: our findings in a tertiary health institution. Nigerian J Clin Pract, 2015. 18: 110.
https://www.ncbi.nlm.nih.gov/pubmed/25511354
378. Wegelin, O., *et al.* Complications and Adverse Events of Three Magnetic Resonance Imaging-based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. Eur Urol Oncol, 2019.
https://www.ncbi.nlm.nih.gov/pubmed/31519516
379. Yang, L., *et al.* Clinical significance of antibiotic prophylaxis for transrectal prostate biopsy. Zhonghua wai ke za zhi [Chin J Surg], 2001. 39: 940.
https://www.ncbi.nlm.nih.gov/pubmed/16201177
380. Aron, M., *et al.* Antibiotic prophylaxis for transrectal needle biopsy of the prostate: A randomized controlled study. BJU Int, 2000. 85: 682.
https://www.ncbi.nlm.nih.gov/pubmed/10759665
381. Isen, K., *et al.* Isen, K., *et al.* Antibiotic prophylaxis for transrectal biopsy of the prostate: A prospective randomized study of the prophylactic use of single dose oral fluoroquinolone versus trimethoprim-sulfamethoxazole. Int Urol Nephrol, 1999. 31: 491.
https://www.ncbi.nlm.nih.gov/pubmed/10668944
382. Kapoor, D.A., *et al.* Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology, 1998. 52: 552.
https://www.ncbi.nlm.nih.gov/pubmed/9763070
383. Meyer, W.H., *et al.* Transrectal prostatic biopsy: The incidence of fever and sepsis after treatment with antibiotics. Aktuelle Urol, 1987. 18: 22. [No abstract available].
384. Thompson, P.M., *et al.* The problem of infection after prostatic biopsy: The case for the transperineal approach. British J Urol, 1982. 54: 736.
https://www.ncbi.nlm.nih.gov/pubmed/7150932
385. Ruebush, I.T.K., *et al.* A double-blind study of trimethoprim-sulfamethoxazole prophylaxis in patients having transrectal needle biopsy of the prostate. J Urol, 1979. 122: 492.
https://www.ncbi.nlm.nih.gov/pubmed/384025
386. Pilatz, A., *et al.* Antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy: A Systematic Review and Meta-analysis. J Urol, 2020. [In press].
https://abdn.pure.elsevier.com/en/publications/antibiotic-prophylaxis-for-the-prevention-of-infectious-complicat
387. Carignan, A., *et al.* Effectiveness of fosfomycin tromethamine prophylaxis in preventing infection following transrectal ultrasound-guided prostate needle biopsy: Results from a large Canadian cohort. J Glob Antimicrob Resist, 2019. 17: 112.
https://www.ncbi.nlm.nih.gov/pubmed/30553114

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, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

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