Guidelines on Urological Infections

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1. INTRODUCTION

1.1 Background

Urinary tract infections (UTIs) are among the most prevailing infectious diseases with a substantial financial burden on society. In the USA, UTIs are responsible for over 7 million physician visits annually (1). Approximately 15% of all community-prescribed antibiotics in the USA are dispensed for UTI (2) and data from some European countries suggest a similar rate (3). In the US, UTIs account for more than 100,000 hospital admissions annually, most often for pyelonephritis (1). These data do not account for complicated UTI associated with urological patients, the prevalence of which is not known. Urinary tract infections represent at least 40% of all hospital acquired infections and are, in the majority of cases, catheter associated (4). Bacteriuria develops in up to 25% of patients who require a urinary catheter for one week or more with a daily risk of 5-7% (5,6). The recent Global Prevalence Infection in Urology (GPIU) studies have shown that 10-12% of patients hospitalised in urological wards have a healthcare-associated infection (HAI). The strains retrieved from these patients are even more resistant (7).

1.2 Bacterial resistance development

The present state of microbial resistance development is alarming (8). The use of antibiotics in different European countries mirrors the global increase in resistant strains (9). The presence of extended-spectrum β-lactamase (ESBL) producing bacteria showing resistance to most antibiotics, except for the carbapenem group, is steadily increasing in the population (10). Even more alarming are the recent reports from all continents of faecal bacteria carrying the $ESBL_{CARBA}$ enzyme (i.e New-Dehli metallo-β-lactamase NDM-1) making them resistant to all available antibiotics including the carbapenem group.

Particularly troublesome is the increasing resistance to broad-spectrum antibiotics such as fluoroquinolones and cephalosporins due to an overconsumption of these two groups and the parallel development of co-resistance to other antibiotics (collateral damage) (11). This development is a threat to patients undergoing urological surgery in general and men subjected to prostate biopsy in particular.

An urgent and strong grip on this threatening development is thus required. With only a few new antibiotics expected in the coming 5 to 10 years, prudent use of available antibiotics is the only option to delay the development of resistance (9) and the urological community has a responsibility to participate in this combat. It is essential to consider the local microbial environment and resistance pattern as well as risk factors for harbouring resistant microbes in individual patients.

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

1.3 The aim of the guidelines

The current guidelines aim to provide both urologists and physicians from other medical specialities with evidence-based guidance regarding the treatment and prophylaxis of UTI. These guidelines cover male and female UTIs, male genital infections and special fields such as UTI in paediatric urology, immunosuppression, renal insufficiency and kidney transplant recipients. Much attention is given to antibiotic prophylaxis, aiming to reduce the overuse of peri-operative prophylactic antibiotics. High quality clinical research using strict internationally recognised definitions and classifications as presented in this section are encouraged.

1.4 Pathogenesis of UTIs

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

Haematogenous infection of the urinary tract is restricted to a few relatively uncommon microbes,

such as *Staphylococcus aureus, Candida* sp., *Salmonella* sp. and *Mycobacterium tuberculosis*, which cause primary infections elsewhere in the body. Candida albicans readily causes a clinical UTI via the haematogenous route, but is also an infrequent cause of an ascending infection if an indwelling catheter is present, or following antibiotic therapy.

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

1.5 Microbiological and other laboratory findings

The number of bacteria is considered relevant for the diagnosis of a UTI. In 1960, Kass developed the concept of significant bacteriuria ($\geq 10^5$ cfu/mL) in the context of pyelonephritis in pregnancy (12). Although this concept introduced quantitative microbiology into the diagnosis of infectious diseases, and is therefore still of general importance, it has recently become clear that there is no fixed bacterial count that is indicative of significant bacteriuria, which can be applied to all kinds of UTIs and in all circumstances. As described in Appendix 16.1, the following bacterial counts are clinically relevant:

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

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

It is obvious that methods of urine collection and culture, as well as the quality of laboratory investigations, may vary. Two levels of standard must therefore be used for the management of patients. A basic standard level is necessary for routine assessment, whereas a higher standard level is required for scientific assessment and in special clinical circumstances, e.g. fever of unknown origin in immunocompromised patients. In research, the need for a precise definition of sampling methods, such as the time that urine is kept in the bladder, must be recognised, and these parameters carefully recorded.

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

- clinical symptoms;
- results of selected laboratory tests (blood, urine or expressed prostatic secretion [EPS]);
- evidence of the presence of microorganisms by culturing or other specific tests;
- most of these investigations can today be performed in any laboratory.

It has to be considered, however, that microbiological methods and definitions applied must follow accepted standards with regard to specimen transport, pathogen identification, and antimicrobial susceptibility testing. These methods and microbiological definitions may vary between countries and institutions. One example is the breakpoints for classification of pathogen susceptibility. It is important to report not only the results, but also which methods and standards were applied, such as the European Committee for Antimicrobial Susceptibility Testing (EUCAST) (13,14), or the National Committee for Clinical Laboratory Standards (NCCLS) (15). Mixing results obtained by different methods, e.g. rates of bacterial resistance, can be problematic and requires careful interpretation. Histological investigation sometimes shows the presence of non-specific inflammation. Only in some cases, such findings (e.g. prostatitis in patients who have elevated levels of prostate-specific antigen [PSA]) might help determine the appropriate treatment, whereas in more specific inflammation, such as tuberculosis and actinomycosis, histology can be diagnostic. In general, however, histological findings usually contribute very little to the treatment decisions.

1.6 Methodology

The EAU Urological Infections guidelines panel consists of a group of urologists, specialised in the treatment of UTIs. It must be emphasised that clinical guidelines present the best evidence available to the experts at the time of writing. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when treatment decisions for individual patients are being taken. Guidelines help to focus decisions. Clinical decisions must also take into account patients' personal values and preferences and their individual circumstances.

1.6.1 Level of evidence and grade of guideline recommendations

References used in the text have been assessed according to their level of scientific evidence (Table 1). Guideline recommendations have been graded (Table 2) in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence (LE) (16). The aim of grading recommendations (GR) is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

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

**Modified from Sackett et al. (16).*

It should be noted that when recommendations are graded, the link between the LE and GR is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a GR: A where there are methodological limitations or disparity in published results.

Conversely, an absence of high LE does not necessarily preclude a GR: A, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (17-19).

The EAU Guidelines Office, do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

Table 2: Grade of recommendation*

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

**Modified from Sackett et al. (16).*

1.6.2 Publication history

A first version of the guidelines on the management of UTI and male genital infections was published in the EAU guidelines 2001 and in European Urology (20). A second updated version was included in the EAU guidelines 2006. The EAU/ICUD textbook on Urogenital Infections (21) has become the book of reference for the Guidelines and the recent update 2011. Guidelines on special conditions of the urogenital tract have also been published elsewhere (22-24).

Standard procedure for EAU publications includes an annual assessment of newly published literature in this

field, guiding future updates. An ultra-short reference document is being published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

1.7 References

1. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002 Jul;113 Suppl 1A:5S-13S. http://www.ncbi.nlm.nih.gov/pubmed/12113866
2. Mazzulli T. Resistance trends in urinary tract pathogens and impact on management. J Urol 2002 Oct;168(4 Pt 2):1720-2. http://www.ncbi.nlm.nih.gov/pubmed/12352343
3. UVI - nedre urinvägsinfektioner hos kvinnor [UTI - lower urinary tract infections in females]. The Medical Products Agency, Sweden 2007;18 (2).
4. Rüden H, Gastmeier P, Daschner FD, et al. Nosocomial and community-acquired infections in Germany. Summary of the results of the First National Prevalence Study (NIDEP). Infection 1997 Jul-Aug;25(4):199-202. http://www.ncbi.nlm.nih.gov/pubmed/9266256
5. Maki DG, Tambyah PA. Engineering out the risk for infection with urinary catheters. Emerg Infect Dis 2001 Mar-Apr;7(2):342-7. http://www.ncbi.nlm.nih.gov/pubmed/11294737
6. Tambyah P, Olyszyna D P, Tenke P, Koves P. Urinary catheters and drainage systems: definition, epidemiology and risk factors. In Naber K G, Schaeffer AJ, Heyns C, Matsumoto T et al (eds). Urogenital Infections. European Association of Urology, Arnhem, The Netherlands 2010, p 523-31.
7. Bjerklund Johansen TE, Cek M, Naber KG, et al; PEP and PEAP-study investigators and the board of the European Society of Infections in Urology. Prevalence of Hospital-Acquired Urinary Tract Infections in Urology departments. Eur Urol 2007 Apr;51(4):1100-11;discussion 1112. http://www.ncbi.nlm.nih.gov/pubmed/17049419
8. Carlet J, Collignon P, Goldmann D, et al. Society's failure to protect a precious resource: antibiotics. Lancet 2011 Jul;378(9788):369-71. http://www.ncbi.nlm.nih.gov/pubmed/21477855
9. Gyssens IC. Antibiotic policy. Int J Antimicrob Agents 2011 Dec;38 Suppl:11-20. http://www.ncbi.nlm.nih.gov/pubmed/22018989
10. Oteo J, Pérez-Vázquez M, Campos J. Extended-spectrum [beta]-lactamas producing Escherichia coli: changing epidemiology and clinical impact. Curr Opin Infect Dis 2010 Aug; 23(4): 320-6. http://www.ncbi.nlm.nih.gov/pubmed/20614578
11. Cassier P, Lallechère S, Aho S, et al. Cephalosporin and fluoroquinolone combination are highly associated with CTX-M β-lactamase-producing Escherichia coli: a case control study in a French teaching hospital. Clin Microbiol Infect 2011;17(11):1746-51. http://www.ncbi.nlm.nih.gov/pubmed/20840333
12. Kass EH. Bacteriuria and pyelonephritis of pregnancy. Arch Intern Med 1960 Feb;105:194-8. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/14404662
13. European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Dieases (ESCMID). EUCAST Definitive Document E.DEF 3.1, June 2000: Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution. Clin Microbiol Infect 2000 Sep;6(9):509-15. http://www.eucast.org http://www.ncbi.nlm.nih.gov/pubmed/11168187
14. European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Dieases (ESCMID). EUCAST Definitive Document E. Def 1.2, May 2000: Terminology relating to methods for the determination of susceptibility of bacteria to antimicrobial agents. Clin Microbiol Infect 2000 Sep;6(9):503-8. http://www.eucast.org http://www.ncbi.nlm.nih.gov/pubmed/11168186
15. National Committee for Clinical Laboratory Standards (NCCLS). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved Standard 4th Edition M7-A5 (2002) and M100-S12, 2004. Wayne, PA.
16. Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. [Access date February 2014] http://www.cebm.net/index.aspx?o=1025

17. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004 Jun;328(7454):1490. http://www.ncbi.nlm.nih.gov/pubmed/15205295
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 May;336(7650):924-6. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2335261/
19. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. BMJ 2008 May;336(7652):1049-51. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376019/
20. Naber KG, Bergman B, Bishop MC, et al; Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). EAU guidelines for the management of urinary and male genital tract infections. Eur Urol 2001 Nov;40(5):576-88. http://www.ncbi.nlm.nih.gov/pubmed/11752870
21. Naber K G, Schaeffer A J, Heyns C F, Matsumoto T et al (eds). Urogenital Infections. European Association of Urology - International Consultations on Urological Diseases 2010. Arnhem, The Netherlands. ISBN:978-90-79754-41-0. http://www.icud.info/urogenitalinfections.html
22. Schneede P, Tenke P, Hofstetter AG; Urinary Tract Infection Working Group of the Health Care Office of the European Association of Urology. Sexually transmitted diseases (STDs) - a synoptic overview for urologists. Eur Urol 2003 Jul;44(1):1-7. http://www.ncbi.nlm.nih.gov/pubmed/12814668.
23. Çek M, Lenk S, Naber KG, et al; Members of the Urinary Tract Infection (UTI) Working Group of the European Association of Urology (EAU) Guidelines Office. EAU guidelines for the management of genitourinary tuberculosis. Eur Urol 2005 Sep;48(3):353-62. http://www.ncbi.nlm.nih.gov/pubmed/15982799
24. Bichler KH, Savatovsky I; the Members of the Urinary Tract Infection (UTI) Working Group of the Guidelines Office of the European Association of Urology (EAU): Naber KG, Bischop MC, Bjerklund-Johansen TE, Botto H, Çek M, Grabe M, Lobel B, Redorta JP, Tenke P. EAU guidelines for the management of urogenital schistosomiasis. Eur Urol 2006 Jun;49(6):998-1003. http://www.ncbi.nlm.nih.gov/pubmed/16519990

2. CLASSIFICATION OF UTIs

2.1 Introduction

The following guidelines cover UTI and male accessory gland infections (MAGI), both infections are closely associated in males. Chapters 3-9 cover UTIs and Chapters 10-12 cover MAGI. Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings. Practically, UTIs have been divided in uncomplicated and complicated UTIs, and sepsis. The following classification model is a working instrument useful for daily assessment and for clinical research.

A critical review of present classifications was undertaken for the EAU/ICUD Urogenital Infections initiative (1) in Appendix 16.1. The overall aim is to provide the clinician and researcher with a standardised tool and nomenclature for UTI. The present guidelines give a short summary of a tentative improved system of classification of UTI based on:

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

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

2.2 Anatomical level of infection

The symptoms, as presented in the Appendix 16.1, focus on the anatomical level of infection, defined as:

- urethra: urethritis (UR);
- urinary bladder: cystitis (CY);
- kidney: pyelonephritis (PN);

- blood stream: sepsis (US).

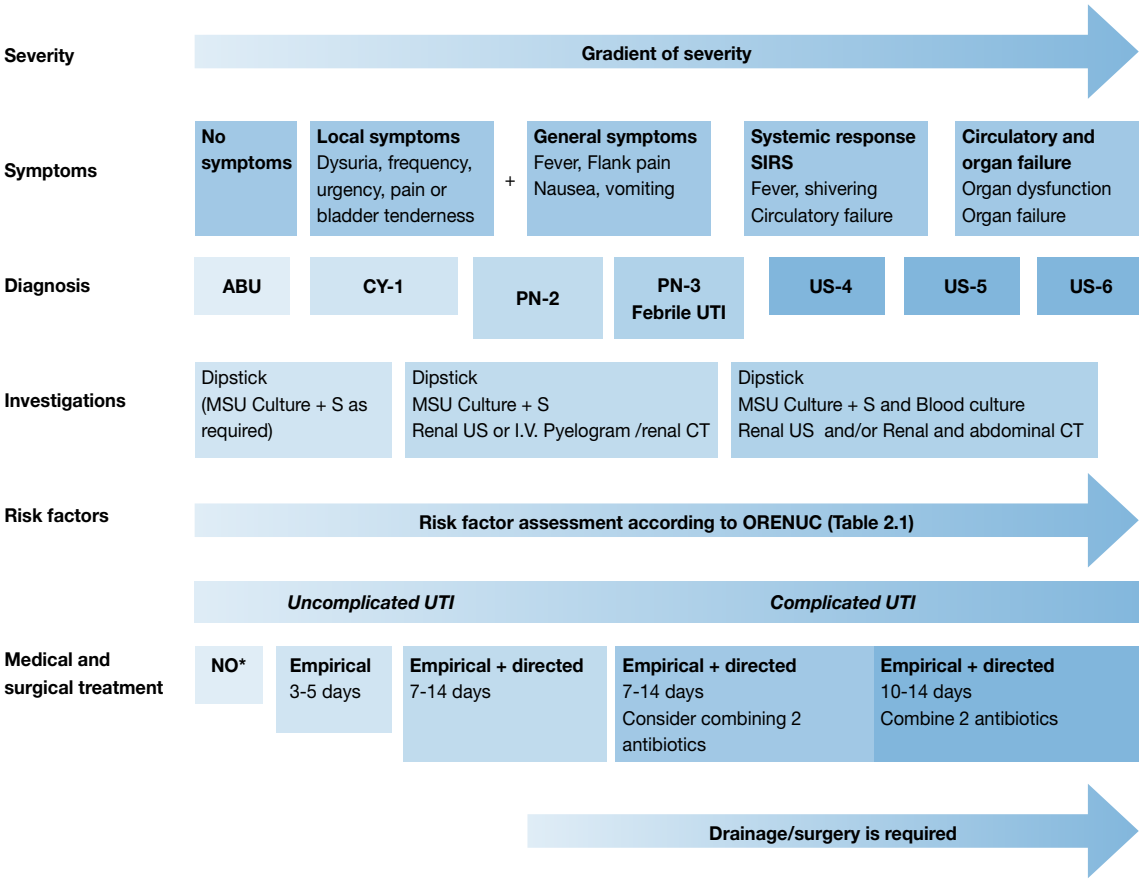
Figure 2.1 illustrates the basic diagnostic and treatment strategy for UTI. Urethritis, being poorly understood, is for the time being not included. Also MAGI, orchitis, epididymitis and prostatitis are not included.

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

2.3 Grade of severity

The grade of severity is set on a scale of 1-6 that is related to the risk of fatal outcome (Figure 2.1).

Figure 2.1: Classification of UTI as proposed by the EAU European Section of Infection in Urology (ESIU) (1)



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

Table 2.1: Host risk factors in UTI

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

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

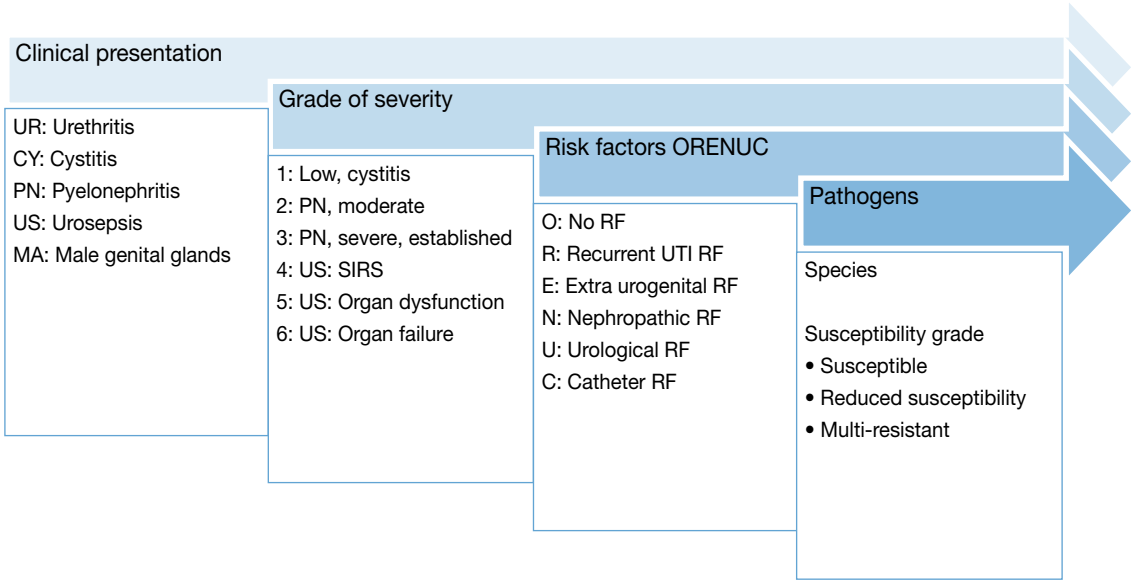
2.4 Pathogens

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

2.5 Classification of UTI

Figure 2.2 shows a summary of the additive parameters that make up an individual class of UTI.

Figure 2.2: Additive parameters of UTI classification and severity assessment



By cumulating the different parameters, a UTI can be classified as follows (1):

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

2.6 Reference

1. Bjerklund-Johansen TE, Botto H, Cek M, et al. Critical review of current definitions of urinary tract infections and proposal of an ESU/ESIU classification system. Internat J Antimicrob Agents 2011 Dec;38S:64-70.
http://www.ncbi.nlm.nih.gov/pubmed/22018988

3. UNCOMPLICATED UTIS IN ADULTS

3.1 Summary and recommendations

This chapter is by itself the summary of the EAU/ICUD initiative on urogenital infections, Chapter 3 on uncomplicated UTI (1).

3.2 Definition

Acute, uncomplicated UTIs in adults include sporadic, community-acquired episodes of acute cystitis and acute pyelonephritis in otherwise healthy individuals. These UTIs are seen mostly in women without structural and functional abnormalities within the urinary tract, kidney diseases, or comorbidity that could lead to more serious outcomes and therefore require additional attention (2).

*3.2.1 **Aetiological spectrum***

The spectrum of aetiological agents is similar in uncomplicated upper and lower UTIs, with *E. coli* the causative pathogen in 70-95% of cases and *Staphylococcus saprophyticus* in 5-10%. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* sp., are isolated (3) (LE: 2a).

3.3 Acute uncomplicated sporadic cystitis in premenopausal, non-pregnant women

*3.3.1 **Diagnosis***

3.3.1.1 Clinical diagnosis

The diagnosis of acute uncomplicated cystitis can be made with a high probability based on a focused history of urinary irritative symptomatology (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation, in those women who have no other risk factors for complicated UTIs (4) (LE: 2a, GR: B).

3.3.1.2 Laboratory diagnosis

Urine dipstick testing, as opposed to urinary microscopy, is a reasonable alternative to urinalysis for diagnosis of acute uncomplicated cystitis (5,6) (LE: 2a, GR: B).

Urine cultures are recommended for those with: (i) suspected acute pyelonephritis; (ii) symptoms that do not resolve or recur within 2-4 weeks after the completion of treatment; and (iii) those women who present with atypical symptoms (7,8) (LE: 4, GR: B).

A colony count of $\geq 10^3$ cfu/mL of uropathogens is microbiologically diagnostic in women who present with symptoms of acute uncomplicated cystitis (9) (LE: 3, GR: B).

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

*3.3.2 **Therapy***

Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo (10) (LE: 1a, GR: A).

The choice of an antibiotic for therapy should be guided by:

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

- adverse ecological effects;
- cost;
- availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg bid for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available (11-13) (LE: 1a, GR: A) (Table 3.1). Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% (14,15) (LE: 1b, GR: B). However, adverse effects including the negative ecological effects and selection of resistance have to be considered (Table 3.1).
Aminopenicillins are no more suitable for empirical therapy because of the worldwide high *E. coli* resistance. Aminopenicillins in combination with a betalactamase inhibitor such as ampicillin/sulbactam or amoxicillin/slavulanic acid and oral cephalosporins are in general not so effective as short-term therapy and are not recommended for empirical therapy because of ecological collateral effects, but can be used in selected cases (16,17).

Table 3.1: Recommended antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy premenopausal women

Antibiotics	Daily dose	Duration of therapy
Fosfomycin trometamol°	3 g SD	1 day
Nitrofurantoin	50 mg q6h	7 days
Nitrofurantoin macrocrystal	100 mg bid	5-7 days
Pivmecillinam*	400 mg bid	3 days
Pivmecillinam*	200 mg tid	5 days
Alternatives		
Ciprofloxacin	250 mg bid	3 days
Levofloxacin	250 mg qd	3 days
Norfloxacin	400 mg bid	3 days
Ofloxacin	200 mg bid	3 days
*If local resistance pattern is known (*E. coli *resistance < 20%)*		
Trimethoprim-sulphamethoxazole	160/800mg bid	3 days
Trimethoprim	200 mg bid	5 days

°not available in all countries.
**available only in Scandinavia, the Netherlands, Austria, and Canada.*

*3.3.3 **Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated (18) (LE: 2b, GR: B). In women whose symptoms do not resolve by the end of treatment, and in those whose symptoms resolve but recur within 2 weeks, urine culture and antimicrobial susceptibility tests should be performed (LE: 4, GR: B). For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a 7-day regimen using another agent should be considered (LE: 4, GR: C).

3.4 Acute uncomplicated pyelonephritis in premenopausal, non-pregnant women

*3.4.1 **Diagnosis***

3.4.1.1 Clinical diagnosis

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness, and it can occur in the absence of symptoms of cystitis (19).

3.4.1.2 Laboratory diagnosis

Urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis (20) (LE: 4, GR: C).

Colony counts ≥ 10^4 cfu/mL of uropathogens are considered to be indicative of clinically relevant bacteriuria (21) (LE: 2b, GR: C).

3.4.1.3 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound should be performed to rule out urinary obstruction or

renal stone disease (LE: 4, GR: C).

Additional investigations, such as an unenhanced helical computed tomography (CT), excretory urography, or dimercaptosuccinic acid (DMSA) scanning, should be considered if the patients remain febrile after 72 h of treatment (LE: 4, GR: C).

*3.4.2 **Therapy***

As a result of the lack of suitable surveillance studies, the spectrum and susceptibility patterns of uropathogens that cause uncomplicated cystitis can be used as a guide for empirical therapy (3) (LE: 4, GR: B). However, S. saprophyticus is less frequent in acute pyelonephritis as compared to acute cystitis (LE: 4, GR: B).

3.4.2.1 Mild and moderate cases of acute uncomplicated pyelonephritis (Table 3.2)

In mild and moderate cases of acute uncomplicated pyelonephritis, oral therapy of 10-14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still < 10% (22) (LE: 1b, GR: A). If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days (23,24) (LE: 1b, GR: B). However, increasing numbers of fluoroquinolone-resistant *E. coli* in the community have already been found in some parts of the world, thus restricting the empirical use of fluoroquinolones.

A third-generation oral cephalosporin, such as cefpodoxime proxetil or ceftibuten, could be an alternative (25,26) (LE: 1b, GR: B). However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin.

As a result of increasing *E. coli* resistance rates >10%, cotrimoxazole is not suitable for empirical therapy in most areas, but it can be used after sensitivity has been confirmed through susceptibility testing (27) (LE: 1b, GR: B).

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

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

3.4.2.2 Severe cases of acute uncomplicated pyelonephritis (Table 3.2)

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

	LE	**GR**
A parenteral fluoroquinolone, in communities with *E. coli* fluoroquinolone-resistance rates < 10%.	1b	B
A third-generation cephalosporin, in communities with ESBL-producing *E. coli* resistance rates < 10%.	1b	B
An aminopenicillin plus a b-lactamase-inhibitor in cases of known susceptible Gram-positive pathogens.	4	B
An aminoglycoside or carbapenem in communities with fluoroquinolone and/or ESBL-producing *E. coli* resistance rates > 10%.	1b	B

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

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

Table 3.2: Recommended initial empirical antimicrobial therapy in acute uncomplicated pyelonephritis in otherwise healthy premenopausal women

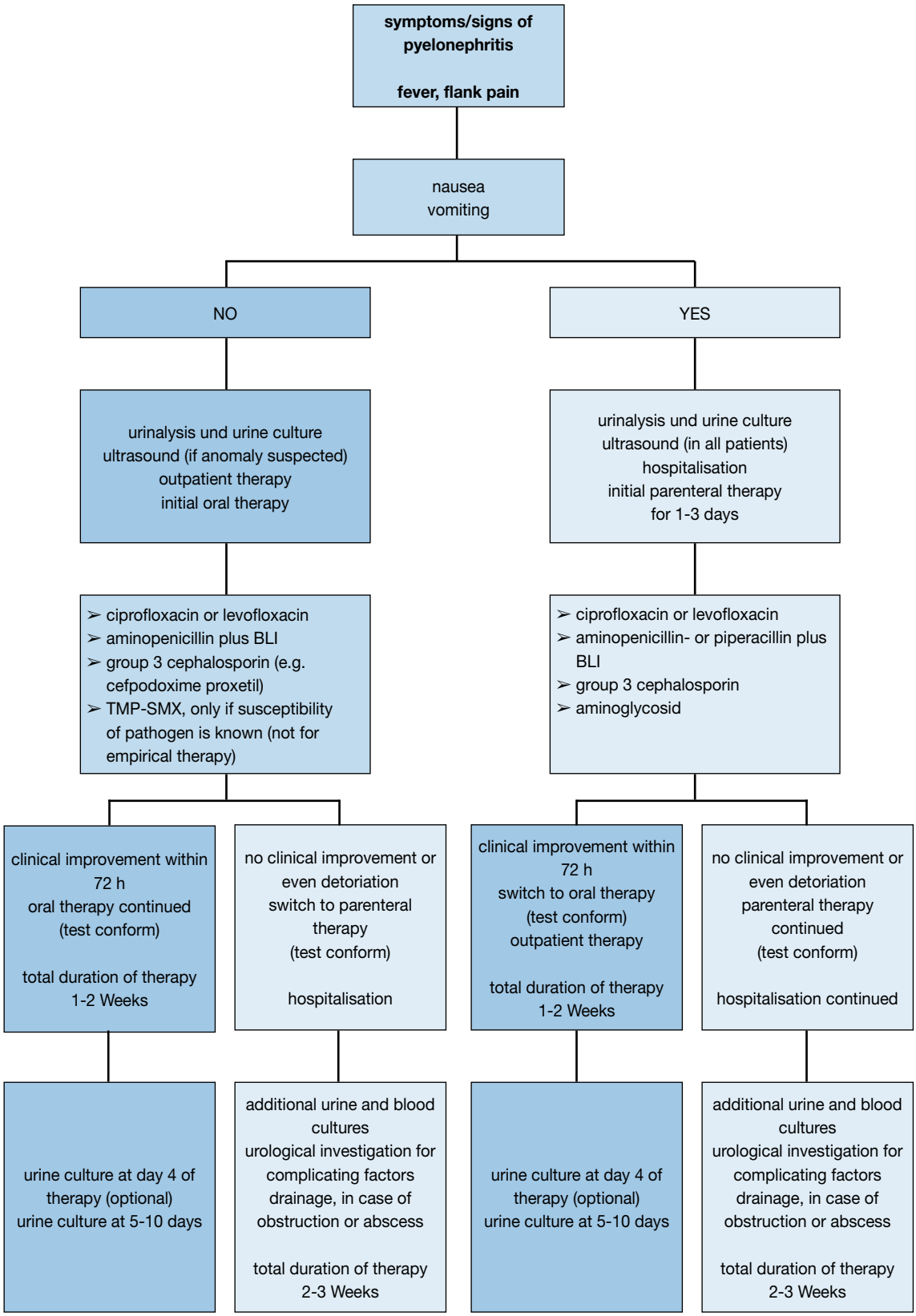
I. Oral therapy in mild and moderate cases			
Antibiotics	Daily dose	Duration of therapy	Reference
Ciprofloxacin[1]	500-750 mg bid	7-10 days	(22)
Levofloxacin[1]	250-500 mg qd	7-10 days	(28)
Levofloxacin	750 mg qd	5 days	(23,24)
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones):			
Cefpodoxime proxetil	200 mg bid	10 days	(25)
Ceftibuten	400 mg qd	10 days	(24)
Only if the pathogen is known to be susceptible (not for initial empirical therapy):			
Trimethoprim-sulphamethoxazole	160/800 mg bid	14 days	(21)
Co-amoxiclav[2,3]	0.5/0.125 g tid	14 days	

[1]lower dose studied, but higher dose recommended by experts.
[2]not studied as monotherapy for acute uncomplicated pyelonephritis.
[3]mainly for Gram-positive pathogens.

II. Initial parenteral therapy in severe cases		
After improvement, the patient can be switched to an oral regimen using one of the above-mentioned antibacterials (if active against the infecting organism) to complete the 1-2-week course of therapy. Therefore, only daily dose and no duration of therapy are indicated.		
Antibiotics	**Daily dose**	**Reference**
Ciprofloxacin	400 mg bid	(22)
Levofloxacin[1]	250-500 mg qd	(28)
Levofloxacin	750 mg qd	(23)
Alternatives:		
Cefotaxime[2]	2 g tid	
Ceftriaxone[1,4]	1-2 g qd	(29)
Ceftazidime[2]	1-2 g tid	(30)
Cefepime[1,4]	1-2 g bid	(31)
Co-amoxiclav[2,3]	1.5 g tid	
Piperacillin/tazobactam[1,4]	2.5-4.5 g tid	(32)
Gentamicin[2]	5 mg/kg qd	
Amikacin[2]	15 mg/kg qd	
Ertapenem[4]	1 g qd	(29)
Imipenem/cilastatin[4]	0.5/0.5 g tid	(32)
Meropenem[4]	1 g tid	(30)
Doripenem[4]	0.5 g tid	(33)

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

Figure 3.1: Clinical management of acute pyelonephritis



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

3.4.3 ***Follow-up***

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C).

In women whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation,

such as renal ultrasound, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

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

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

An algorithm of the clinical management of acute pyelonephritis is shown in Figure 3.1.

3.5 Recurrent uncomplicated UTIs in premenopausal women

3.5.1 ***Diagnosis***

Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts (34) (LE: 2a).

Recurrent UTIs need to be diagnosed by urine culture (LE: 4, GR: A). Imaging of the upper urinary tract and cystoscopy are not routinely recommended for evaluation of women with recurrent UTIs (35) (LE: 1b, GR: B) but should be performed without delay in atypical cases. Also, residual urine should be excluded (LE:4, GR:B)

3.5.2 ***Antimicrobial treatment and prevention***

Before any antimicrobial prophylaxis is initiated, eradication of a previous UTI should be confirmed by a negative urine culture 1-2 weeks after treatment (LE: 4, GR: A). Continuous or post-coital antimicrobial prophylaxis (36) for prevention of recurrent UTI should be considered only after counselling and behavioural modification has been attempted, and when non-antimicrobial measures have been unsuccessful (LE: 4, GR: B). Significant residual urine should be treated optimally, which also includes Clean Intermittent Catheterisation (CIC) when valued necessary. In post-menopausal women, hormonal replacement therapy should be considered (see chapter 3.7).

In appropriate women with recurrent uncomplicated cystitis, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered (37) (LE: 2b, GR: A). The choice of antibiotics is the same as for sporadic uncomplicated UTI (Table 3.1).

3.5.2.1 Antimicrobial prophylaxis

Antimicrobial prophylaxis can be given continuously (daily, weekly) for longer periods of time (3-6 months), or as a single post-coital dose. Drug regimens used in clinical trials are shown in Tables 3.3 and 3.4.

Table 3.3: Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs (34)

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg once daily	0-0.2
TMP-SMX 40/200 mg thrice weekly	0.1
Trimethoprim 100 mg once daily	0-1.5**
Nitrofurantoin 50 mg once daily	0-0.6
Nitrofurantoin 100 mg once daily	0-0.7
Cefaclor 250 mg once daily	0.0
Cephalexin 125 mg once daily	0.1
Cephalexin 250 mg once daily	0.2
Norfloxacin 200 mg once daily	0.0
Ciprofloxacin 125 mg once daily	0.0
Fosfomycin 3 g every 10 days	0.14

**Trimethoprim-sulfamethoxazole*

***high recurrence rates observed with trimethoprim use associated with trimethoprim resistance*

Table 3.4: Postcoital antimicrobial prophylaxis regimens for women with recurrent UTIs (34)

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg	0.30
TMP-SMX 80/400 mg	0.00
Nitrofurantoin 50 or 100 mg	0.10
Cephalexin 250 mg	0.03
Ciprofloxacin 125 mg	0.00
Norfloxacin 200 mg	0.00
Ofloxacin 100 mg	0.06

**Trimethoprim-sulfamethoxazole*

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

- Because of ecological collateral effects, oral fluoroquinolones and cephalosporins are no longer recommended routinely, except in specific clinical situations
- The worldwide increase of *E. coli* resistance against trimethoprim casts doubts on trimethoprim with or without a sulphonamide to be an effective prophylactic agent still
- There are recent warnings by governmental agencies for the long-term prophylactic use of nitrofurantoin because of the rare but severe pulmonary and hepatic adverse effects (38).

Altogether it demonstrates that antimicrobial prophylaxis of a recurrent UTI needs to be reconsidered in each individual case and effective alternative measures would be highly appreciated.

*3.5.3 **Non-antimicrobial prophylaxis***

There are many non-antimicrobial measures recommended for recurrent UTI but only a few result from well-designed studies and are therefore able to make evidence-based recommendations (39).

3.5.3.1 Immunoactive prophylaxis

OM-89 (Uro-Vaxom®) is sufficiently well documented and has been shown to be more effective than placebo in several randomised trials. Therefore, it can be recommended for immunoprophylaxis in female patients with recurrent uncomplicated UTI (40,41) (LE: 1a, GR: B). Its efficacy in other groups of patients, and its efficacy relative to antimicrobial prophylaxis remain to be established.

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

For other immunotherapeutic products, such as Urostim® and Urvakol®, no controlled studies are available. Therefore, no recommendations are possible.

3.5.3.2 Prophylaxis with probiotics (Lactobacillus sp)

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

When commercially available, it is reasonable to consider the use of intravaginal probiotics that contain L. rhamnosus GR-1 and L. reuteri RC-14 for the prevention of recurrent UTI (42), and these products can be used once or twice weekly (LE: 4, GR: C). Vaginal application of Lactobacillus crispatus reduced the rate of recurrent UTI in pre-menopausal women in one study, and can also be used if available (43) (LE: 1b, GR: B).

Daily use of the oral product with strains GR-1 and RC-14 is worth testing given that it can restore the vaginal lactobacilli, compete with urogenital pathogens, and prevent bacterial vaginosis, a condition that increases the risk of UTI (39) (LE: 1b, GR: C).

3.5.3.3 Prophylaxis with cranberry

Previous limited studies have suggested that cranberry (Vaccinium macrocarpon) is useful in reducing the rate of lower UTIs in women (44,45) (LE: 1b, GR: C). However, one recent larger study has not been able to confirm any significant effect (46). A recent meta-analysis including 24 studies and comprising 4,473 participants showed cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or for any of the following sub-groups: children with recurrent UTIs, older people, women with recurrent UTIs, pregnant

women, cancer patients, or people with neuropathic bladder or spinal injury (47). Due to these contradictory results, any recommendation of the daily consumption of cranberry products cannot be made.

3.6 UTIs in pregnancy

Urinary tract infections and asymptomatic bacteriuria are common during pregnancy. Most women are prone to or acquire asymptomatic bacteriuria before pregnancy, and 20-40% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy.

*3.6.1 **Diagnosis of UTIs in pregnant women***

Diagnostic criteria of acute cystitis and pyelonephritis in otherwise healthy pregnant women are similar to that of non-pregnant women (3.3.1 and 3.4.1). However, physical examination and urinalysis including urine culture are highly recommended in cystitis. In addition, in case of suspicion of pyelonephbritis, ultrasound of the kidneys and urinary tract is necessary.

*3.6.2 **Definition of bacteriuria***

In a pregnant woman, asymptomatic bacteriuria is diagnosed in case of two consecutive voided urine specimens with grow of $\geq 10^5$ cfu/mL of the same bacterial species; or a single catheterised specimen with grow of $\geq 10^5$ cfu/mL of a uropathogen (18) (LE: 2a, GR: A).
In a pregnant woman with symptoms compatible with UTI, bacteriuria is considered relevant if a voided or catheterised urine specimen grows $\geq 10^3$ cfu/mL of a uropathogen (LE: 4, GR: B).

*3.6.3 **Screening***

Pregnant women should be screened for bacteriuria during the first trimester (48) (LE: 1a, GR: A).

*3.6.4 **Treatment of asymptomatic bacteriuria and acute cystitis***

Asymptomatic bacteriuria detected during pregnancy should be eradicated with antimicrobial therapy (48) (LE: 1a, GR: A). Acute cystitis should be adequately treated. Recommended antibiotic regimens are listed in Table 3.5.

Table 3.5: Treatment regimens for asymptomatic bacteriuria and cystitis in pregnancy (44)

Antibiotics	Duration of therapy	Comments
Nitrofurantoin (Macrobid®) 100 mg	q12 h, 3-5 days	Avoid in G6PD deficiency
Amoxicillin 500 mg	q8 h, 3-5 days	Increasing resistance
Co-amoxicillin/clavulanate	500 mg q12 h, 3-5 days	
Cephalexin (Keflex®) 500 mg	q8 h, 3-5 days	Increasing resistance
Fosfomycin 3 g	Single dose	
Trimethoprim	q12 h, 3-5 days	Avoid trimethoprim in first trimester/term

G6PD = glucose-6-phosphate dehydrogenase

*3.6.5 **Duration of therapy***

Short courses of antimicrobial therapy (3 days) should be considered for the treatment of asymptomatic bacteriuria and cystitis in pregnancy (49) (LE: 1a, GR: A).

*3.6.6 **Follow-up***

Urine cultures should be obtained 1-2 weeks after completion of therapy for asymptomatic bacteriuria and symptomatic UTI in pregnancy (LE: 4, GR: A).

*3.6.7 **Prophylaxis***

Postcoital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI (50) (LE: 2b, GR: B).

*3.6.8 **Treatment of pyelonephritis***

Outpatient management with appropriate antibiotics should be considered in women with pyelonephritis in pregnancy, provided symptoms are mild and close follow-up is feasible (51) (LE: 1b, GR: A). Recommended parenteral antibiotic regimens are shown in Table 3.6 (51,52). After clinical improvement parenteral therapy can be switched to oral therapy for a total treatment duration of 7-10 days (LE: 4; GR:B).

Table 3.6: Treatment regimens for pyelonephritis in pregnancy

Antibiotics	Dose
Ceftriaxone	1-2 g IV or IM q24 h
Aztreonam	1 g IV q8-12 h
Piperacillin-tazobactam	3.375-4.5 g IV q6 h
Cefepime	1 g IV q12 h
Imipenem-cilastatin	500 mg IV q6 h
Ampicillin +	2 g IV q6 h
Gentamicin	3-5 mg/kg/day IV in 3 divided doses

*3.6.9 **Complicated UTI***

For diagnostics of complicating factors within the urinary tract, ultrasound or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus (LE: 4; GR: B). Treatment follows the same general principles as outlined in 4.4. Appropriate antimicrobial therapy for 7-10 days and the management of any urological abnormality are mandatory. Hospitalisation is usually required and supportive care as required.

3.7 UTIs in postmenopausal women

3.7.1 Risk factors

	Reference	LE
In older institutionalised women, urine catheterisation and functional status deterioration appear to be the most important risk factors associated with UTI.	53	2a
Atrophic vaginitis.	53	2a
Incontinence, cystocele and post-voiding residual urine.	53	2a
UTI before menopause.	53	2a
Non-secretor status of blood group antigens.	53	2a

*3.7.2 **Diagnosis***

Diagnosis of UTI in postmenopausal women should always consider the following:

	Reference	LE	GR
History, physical examination and urinalysis, including culture.		4	B
Genitourinary symptoms are not necessarily related to UTI and an indication for antimicrobial treatment.	54	1b	B

*3.7.3 **Treatment***

	Reference	LE	GR
Treatment of acute cystitis in postmenopausal women is similar to that in premenopausal women, however, short-term therapy is not so well-established as in premenopausal women.	55	1b	C
Treatment of pyelonephritis in postmenopausal women is similar to that in premenopausal women.		4	C
Asymptomatic bacteriuria in elderly women should not be treated with antibiotics.	18	2b	A
Optimal antimicrobials, doses and duration of treatment in elderly women appear to be similar to those recommended for younger postmenopausal women.		4	C
Oestrogen (especially vaginal) can be administered for prevention of UTI, but results are contradictory.	56	1b	C
Alternative methods, such as cranberry and probiotic lactobacilli, can contribute but they are not sufficient to prevent recurrent UTI.	57	1b	C
If complicating factors, such as urinary obstruction and neurogenic bladder, are ruled out, antimicrobial prophylaxis should be carried out as recommended for premenopausal women.		4	C

3.8 Acute uncomplicated UTIs in young men

3.8.1 ***Men with acute uncomplicated UTI***

	Reference	LE	GR
Only a small number of 15-50-year-old men suffer from acute uncomplicated UTI.	58		
Such men should receive, as minimum therapy, a 7-day antibiotic regimen.		4	B

3.8.2 Men with UTI and concomitant prostate infection

	Reference	LE	GR
Most men with febrile UTI have a concomitant infection of the prostate, as measured by transient increases in serum PSA and prostate volume.	59	2a	
Urological evaluation should be carried out routinely in adolescents and men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected.		4	A
A minimum treatment duration of 2 weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent.	60	2a	B

3.9 Asymptomatic bacteriuria

3.9.1 ***Diagnosis***

	Reference	LE	GR
For women, a count of $\geq 10^5$ cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.	18	2b	B
For men, a count of $\geq 10^3$ cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.	61	2a	B
For men with specimens collected using an external condom catheter, $\geq 10^5$ cfu/ mL is an appropriate quantitative diagnostic criterion.	62	2a	B
For patients with indwelling urethral catheters, a count of $\geq 10^5$ cfu/mL is diagnostic of bacteriuria.	18	2b	B
For a urine specimen collected by in and out catheter, a count of $\geq$ 100 cfu/mL is consistent with bacteriuria.	18	2a	B
Pyuria in the absence of signs or symptoms in a person with bacteriuria should not be interpreted as symptomatic infection or as an indication for antimicrobial therapy.	18	2b	B

3.9.2 ***Screening***

Screening for and treatment of asymptomatic bacteriuria is recommended:

	Reference	LE	GR
For pregnant women.	48	1a	A
Before an invasive genitourinary procedure for which there is a risk of mucosal bleeding.	18	1b	A

Screening for or treatment of asymptomatic bacteriuria is not recommended for:

	Reference	LE	GR
Premenopausal, non-pregnant women.	18	1a	A
Postmenopausal women.	18	1b	A
Women with diabetes.	63	1b	A
Healthy men.	64	2b	B
Residents of long-term care facilities.	18	1a	A
Patients with an indwelling urethral catheter.	18	1b	
Patients with nephrostomy tubes or ureteric stents.		4	C
Patients with spinal cord injury.	65	2a	B
Patients with candiduria.	66	1b	A

Screening for or treatment of asymptomatic bacteriuria in renal transplant patients beyond the first 6 months is not recommended (LE: 2b, GR: B).

No recommendation can be made with respect to screening for or treatment of bacteriuria in patients with neutropenia (LE: 4).

3.10 References

1. Naber KG (chair), Schaeffer AJ, Hynes CF, et al. (Eds) (2010). EAU/International Consultation on Urological Infections. The Netherlands, European Association of Urology.
2. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am 1997 Sep;11(3):551-81. http://www.ncbi.nlm.nih.gov/pubmed/9378923
3. Naber KG, Schito G, Botto H, et al. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. Eur Urol 2008 Nov;54(5):1164-75. http://www.ncbi.nlm.nih.gov/pubmed/18511178
4. Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med 1993 Oct; 329(18):1328-34. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/8413414
5. Bradbury SM. Collection of urine specimens in general practice: to clean or not to clean? J R Coll Gen Pract 1988 Aug;38(313):363-5. http://www.ncbi.nlm.nih.gov/pubmed/3256648
6. Lifshitz E, Kramer L. Outpatient urine culture: does collection technique matter? Arch Intern Med 2000 Sep;160(16):2537-40. http://www.ncbi.nlm.nih.gov/pubmed/10979067
7. Foxman B, Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am 2003 Jun;17(2):227-41. http://www.ncbi.nlm.nih.gov/pubmed/12848468
8. Fihn SD. Clinical practice. Acute uncomplicated urinary tract infection in women. N Engl J Med 2003 Jul;349(3):259-66. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/12867610
9. Kunin C. Urinary tract infections. In: Detection, prevention and management. 5th edition.1997, Philadelphia: Lea & Febiger.
10. Falagas ME, Kotsantis IK, Vouloumanou EK, et al. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. J Infect 2009 Feb;58(2):91-102. http://www.ncbi.nlm.nih.gov/pubmed/19195714
11. Lecomte F, Allaert FA. Single-dose treatment of cystitis with fosfomycin trometamol (Monuril): analysis of 15 comparative trials on 2,048 patients. Giorn It Ost Gin 1997;19:399-404.
12. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. J Antimicrob Chemother 2000 Sep;46 Suppl 1:35-9;discussion 63-5. http://www.ncbi.nlm.nih.gov/pubmed/11051622
13. Gupta, K, Hooton TM, Roberts PL, et al. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med 2007 Nov;167(20):2207-12. http://www.ncbi.nlm.nih.gov/pubmed/17998493
14. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999 Oct;29(4):745-58. http://www.ncbi.nlm.nih.gov/pubmed/10589881
15. Gupta K, Stamm WE. Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. Int J Antimicrob Agents 2002 Jun;19(6):554-6. http://www.ncbi.nlm.nih.gov/pubmed/12135847
16. Hooton TM, Scholes D, Gupta K, et al. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA 2005 Feb;293 (8):949-55. http://www.ncbi.nlm.nih.gov/pubmed/15728165
17. Hooton TM, Roberts PL, Stapelton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA 2012 Feb;307(6):583-9. http://www.ncbi.nlm.nih.gov/pubmed/22318279
18. Nicolle LE, Bradley S, Colgan R, et al; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005 Mar;40(5):643-54. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/15714408

19. Scholes D, Hooton TM, Roberts PL, et al. Risk factors associated with acute pyelonephritis in healthy women. Ann Intern Med 2005 Jan;142(1):20-7.
http://www.ncbi.nlm.nih.gov/pubmed/15630106
20. Fulop T. Acute Pyelonephritis Workup. Aug 22, 2012. [Access date February 2014]
http://emedicine.medscape.com/article/245559-workup#aw2aab6b5b3
21. Rubin US, Andriole VT, Davis RJ, et al. Evaluation of new anti-infective drugs for the treatment of UTI. Clin Infect Di 1992;15:216.
http://cid.oxfordjournals.org/content/15/Supplement_1/S216.short
22. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprimsulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA 2000 Mar;283(12):1583-90.
http://www.ncbi.nlm.nih.gov/pubmed/10735395
23. Klausner HA, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Curr Med Res Opin 2007 Nov;23(11):2637-45.
http://www.ncbi.nlm.nih.gov/pubmed/17880755
24. Peterson J, Kaul S, Khashab M, et al. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology 2008 Jan;71(1):17-22.
http://www.ncbi.nlm.nih.gov/pubmed/18242357
25. Cronberg S, Banke S, Bergman B, et al. Fewer bacterial relapses after oral treatment with norfloxacin than with ceftibuten in acute pyelonephritis initially treated with intravenous cefuroxime. Scand J Infect Dis 2001;33(5):339-43.
http://www.ncbi.nlm.nih.gov/pubmed/11440218
26. Naber KG, Schoenwald S, Hauke W. [Cefpodoxime proxetil in patients with acute uncomplicated pyelonephritis. International, prospective, randomized comparative study versus ciprofloxacin in general practice.] Chemotherapie Journal 2001;10:29-34. [Article in German]
27. Stamm WE, McKevitt M, Counts GW. Acute renal infection in women: treatment with trimethoprimsulfamethoxazole or ampicillin for two or six weeks. A randomized trial. Ann Intern Med 1987 Mar;106(3):341-5.
http://www.ncbi.nlm.nih.gov/pubmed/3492950
28. Richard GA, Klimberg IN, Fowler CL, et al. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. Urology 1998 Jul;52(1):51-5.
http://www.ncbi.nlm.nih.gov/pubmed/9671870
29. Wells WG, Woods GL, Jiang Q, et al. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by an appropriate oral therapy. J Antimicrob Chemother 2004 Jun;53 Suppl 2: ii67-74.
http://www.ncbi.nlm.nih.gov/pubmed/15150185
30. Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. Meropenem Study Group. J Antimicrob Chemother 1995 Jul;36 Suppl A:145-56.
http://www.ncbi.nlm.nih.gov/pubmed/8543490
31. Giamarellou H. Low-dosage cefepime as treatment for serious bacterial infections. J Antimicrob Chemother 1993 Nov;32 Suppl B:123-32.
http://www.ncbi.nlm.nih.gov/pubmed/8150755
32. Naber KG, Savov O, Salmen HC. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/ cilastatin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents 2002 Feb;19(2):95-103.
http://www.ncbi.nlm.nih.gov/pubmed/11850161
33. Naber KG, Llorens L, Kaniga K, et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for the treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother 2009 Sep;53(9):3782-92.
http://www.ncbi.nlm.nih.gov/pubmed/19581455
34. Hooton, TM. Recurrent urinary tract infection in women. Int J Antimicrob Agents 2001 Apr;17(4): 259-68.
http://www.ncbi.nlm.nih.gov/pubmed/11295405
35. Fowler JE Jr, Pulaski ET. Excretory urography, cystography, and cystoscopy in the evaluation of women with urinary-tract infection: a prospective study. N Engl J Med 1981 Feb;304(8):462-5. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/7453771

36. Albert X, Huertas I, Pereiró II, et al. Antibiotics for preventing recurrent urinary tract infection in nonpregnant women. Cochrane Database Syst Rev 2004(3):CD001209. http://www.ncbi.nlm.nih.gov/pubmed/15266443
37. Schaeffer AJ, Stuppy BA. Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. J Urol 1999 Jan;161(1):207-11. http://www.ncbi.nlm.nih.gov/pubmed/10037399
38. Agence francaise de securtite sanitaire des produits de santé (afssaps). [Nitrofurantoïne et risque de survenue d'effets indésirables indésirables hépatiques et pulmonaires lors de traitements prolongés]. Pharmacovigilance 2011 Feb. [Article in French] http://www.infectiologie.com/site/medias/_documents/consensus/lp-110311-nitrofurantoine.pdf
39. Wagenlehner FM, Vahlensieck W, Bauer HW, et al. Prevention of recurrent urinary tract infections. Minerva Urol Nefrol 2013 Mar;65(1):9-20. http://www.ncbi.nlm.nih.gov/pubmed/23538307
40. Bauer HW, Rahlfs VW, Lauener PA, et al. Prevention of recurrent urinary tract infections with immunoactive E. coli fractions: a meta-analysis of five placebo-controlled double-blind studies. Int J Antimicrob Agents 2002 Jun;19(6):451-6. http://www.ncbi.nlm.nih.gov/pubmed/12135831
41. Naber KG, Cho YH, Matsumoto T, et al. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. Int J Antimicrob Agents 2009 Feb;33(2):111-9. http://www.ncbi.nlm.nih.gov/pubmed/18963856
42. Anukam KC, Osazuwa E, Osemene GI, et al. Clinical study comparing probiotic Lactobacillus GR-1 and RC-14 with metronidazole vaginal gel to treat symptomatic bacterial vaginosis. Microbes Infect 2006 Oct;8(12-13):2772-6. http://www.ncbi.nlm.nih.gov/pubmed/17045832
43. Stapleton AE, Au-Yeung M, Hooton TM, et al. Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infections. Clin Infect Dis 2011 May;52(10):1212-7. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079401/
44. Kontiokari T, Sundqvist K, Nuutinen M, et al. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. BMJ 2001 Jun;322(7302):1571. http://www.ncbi.nlm.nih.gov/pubmed/11431298
45. 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 Jun; 9(3):1558-62. http://www.ncbi.nlm.nih.gov/pubmed/12121581
46. Barbosa-Cesnik C, Brown MB, Buxton M, et al. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomised placebo-controlled trial. Clin Infect Dis 2011 Jan;52(1):23-30. http://www.ncbi.nlm.nih.gov/pubmed/21148516
47. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Sys Rev 2012 Oct;10:CD001321. http://www.ncbi.nlm.nih.gov/pubmed/23076891
48. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2007 Apr 18;(2):CD000490. http://www.ncbi.nlm.nih.gov/pubmed/17443502
49. Vazquez JC, Villar J. Treatments for symptomatic urinary tract infections during pregnancy. Cochrane Database Syst Rev 2000;(3):CD002256. http://www.ncbi.nlm.nih.gov/pubmed/10908537
50. Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary tract infections during pregnancy. Clin Infect Dis 1992 Apr 14;(4): 810-4. http://www.ncbi.nlm.nih.gov/pubmed/1576275
51. Millar LK, Wing DA, Paul RH, et al. Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial. Obstet Gynecol 1995 Oct; 86(4 Pt 1):560-4. http://www.ncbi.nlm.nih.gov/pubmed/7675380
52. Wing DA, Hendershott CM, Debuque L, et al. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. Obstet Gynecol 1998 Aug;92(2):249-53. http://www.ncbi.nlm.nih.gov/pubmed/9699761
53. Nicolle LE. Asymptomatic bacteriuria in the elderly. Infect Dis Clin North Am 1997 Sep;11(3):647-62. http://www.ncbi.nlm.nih.gov/pubmed/9378928

54. Foxman B, Somsel P, Tallman P, et al. Urinary tract infection among women aged 40 to 65: behavioural and sexual risk factors. J Clin Epidemiol 2001 Jul;54(7):710-8.
http://www.ncbi.nlm.nih.gov/pubmed/11438412
55. Vogel T, Verreault R, Gourdeau M, et al. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. CMAJ 2004 Feb;170(4):469-73.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC332712/
56. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med 1993 Sep;329(11):753-6.
http://www.ncbi.nlm.nih.gov/pubmed/8350884
57. Avorn J, Monane M, Gurwitz JH, et al. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA 1994 Mar;271(10):751-4.
http://www.ncbi.nlm.nih.gov/pubmed/8093138
58. Stamm WE. Urinary tract infections in young men. In: Bergan T (ed). Urinary tract infections. Basel, Switzerland: Karger, 1997 vol 1;pp. 46-7. [No abstract available]
http://content.karger.com/ProdukteDB/produkte.asp?Doi=61396
59. Ulleryd P. Febrile urinary tract infection in men. Int J Antimicrob Agents 2003 Oct;22 Suppl 2:89-93.
http://www.ncbi.nlm.nih.gov/pubmed/14527778
60. Ulleryd P, Sandberg T. 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(1):34-9.
http://www.ncbi.nlm.nih.gov/pubmed/12685882
61. Gleckman R, Esposito A, Crowley M, et al. Reliability of a single urine culture in establishing diagnosis of asymptomatic bacteriuria in adult males. J Clin Microbiol 1979 May;9(5):596-7.
http://www.ncbi.nlm.nih.gov/pubmed/383746
62. Nicolle LE, Harding GK, Kennedy J, et al. Urine specimen collection with external devices for diagnosis of bacteriuria in elderly incontinent men. J Clin Microbiol 1988 Jun;26(6):1115-9.
http://www.ncbi.nlm.nih.gov/pubmed/3384923
63. Harding GK, Zhanel GG, Nicolle LE, et al; Manitoba Diabetes Urinary Tract Infection Study Group. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. N Engl J Med 2002 Nov; 347(20):1576-83.
http://www.ncbi.nlm.nih.gov/pubmed/12432044
64. Mims AD, Norman DC, Yamamura RH, et al. Clinically inapparent (asymptomatic) bacteriuria in ambulatory elderly men: epidemiological, clinical, and microbiological findings. J Am Geriatr Soc 1990 Nov;38(11):1209-14.
http://www.ncbi.nlm.nih.gov/pubmed/2246458
65. Lewis RI, Carrion HM, Lockhart JL, et al. Significance of asymptomatic bacteriuria in neurogenic bladder disease. Urology 1984 Apr;23(4):343-7.
http://www.ncbi.nlm.nih.gov/pubmed/6369712
66. Sobel JD, Kauffman CA, McKinsey 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 Jan;30(1):19-24.
http://www.ncbi.nlm.nih.gov/pubmed/10619727

4. COMPLICATED UTIs DUE TO UROLOGICAL DISORDERS

4.1 Summary and recommendations

A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defence mechanisms, which increase the risks of acquiring infection or of failing therapy. Examples of risk factors are listed in both Tables 4.1 and 2.1.

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

Enterobacteriaceae are the predominant pathogens, with *E. coli* being the most common pathogen. However, non-fermenters (e.g. *Pseudomonas aeruginosa*) and Gram-positive cocci (e.g. staphylococci and

enterococci) may also play an important role, depending on the underlying conditions.

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

If empirical therapy is necessary, the antibacterial spectrum of the antibiotic agent should include the most relevant pathogens (GR: A). A fluoroquinolone with mainly renal excretion, an aminopenicillin plus a β-lactamase inhibitor (BLI), a Group 2 or 3a cephalosporin or, in the case of parenteral therapy, an aminoglycoside, are recommended alternatives (LE: 1b, GR: B).

In case of failure of initial therapy, or in case of clinically severe infection, a broader-spectrum antibiotic should be chosen that is also active against *Pseudomonas* (LE: 1b, GR: B), e.g. a fluoroquinolone (if not used for initial therapy), an acylaminopenicillin (piperacillin) plus a BLI, a Group 3b cephalosporin, or a carbapenem, with or without combination with an aminoglycoside (LE: 1b, GR: B).

The duration of therapy is usually 7-14 days (LE: 1b, GR: A), but sometimes has to be prolonged for up to 21 days (LE: 1b, GR: A).

Until predisposing factors are completely removed, true cure without recurrent infection is usually not possible. Therefore, a urine culture should be carried out 5-9 days after completion of therapy and also 4-6 weeks later (GR: B).

4.2 Definitions and classification

A complicated UTI is an infection associated with a condition, such as structural or functional abnormalities of the genitourinary tract or the presence of an underlying disease, which increases the risks of acquiring an infection or of failing therapy (1-3). Two criteria are mandatory to define a complicated UTI: a positive urine culture and one or more of the factors listed in Table 4.1.

Table 4.1: Factors that suggest a potential complicated UTI

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

Host related risk factors for UTI in general and complicated UTI in particular are listed in Table 4.1. Complicated UTI can arise in a heterogeneous group of patients. However, neither patient age nor sex *per se* are part of the definition of a complicated UTI. With regard to prognosis and clinical studies, it is advisable to stratify complicated UTIs due to urological disorders into at least two groups (4):

- Patients in whom the complicating factors could be eliminated by therapy, e.g. stone extraction, removal of an indwelling catheter.
- Patients in whom the complicating factor could not be or is not removed satisfactorily during therapy, e.g. permanent indwelling catheter, stone residues after treatment or neurogenic bladder.

*4.2.1 **Clinical presentation***

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

Apart from urological abnormalities, concomitant medical conditions, such as diabetes mellitus (10%) and renal failure, which can be related to urological abnormalities (5), are often present in a complicated UTI. These are discussed in more detail in Sections 8.1.3 and 8.1.4 on UTIs in renal insufficiency, transplant recipients, diabetes mellitus and immunosuppression.

4.2.2 *Urine cultures*

Significant bacteriuria in a complicated UTI is defined by counts of $\geq 10^5$ cfu/mL and $\geq 10^4$ cfu/mL, in the mid-stream urine (MSU) of women and men, respectively (1,2). If a straight catheter urine sample is taken, $\geq 10^4$ cfu/mL can be considered relevant. For an asymptomatic patient, two consecutive urine cultures (at least 24 h apart) yielding $\geq 10^5$ cfu/mL of the same microorganism are required. The requirement for pyuria is ≥ 10 white blood cells (WBC) per high-power field (x400) in the resuspended sediment of a centrifuged aliquot of urine or per mm^3 in unspun urine. A dipstick method can also be used for routine assessment, including a leukocyte esterase test, haemoglobin and probably a nitrite reaction.

4.3 Microbiology

4.3.1 *Spectrum and antibiotic resistance*

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

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

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than with an uncomplicated UTI and the bacteria are more likely to be antibiotic-resistant (especially in a treatment-related complicated UTI) than those isolated in an uncomplicated UTI. *E. coli, Proteus, Klebsiella*, Pseudomonas and *Serratia* sp. and enterococci are the usual strains found in cultures. Enterobacteriaceae predominate (60-75%) (6-8), with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another.

4.3.2 *Complicated UTIs associated with urinary stones*

In the subset of complicated UTIs related to urinary stones, the frequency of *E. coli* and enterococci infection seem less important pathogens. In contrast, a greater portion of *Proteus* and *Pseudomonas* sp. (9) is found.

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

Among patients with staghorn calculus disease, 88% were found to have a UTI at the time of diagnosis, with 82% of patients infected with urease-producing organisms (10). The enzyme, urease, splits urea into carbon dioxide and ammonia. The resultant increase in ammonia in the urine injures the glycosaminoglycan layer, which in turn increases bacterial adherence (11) and enhances the formation of struvite crystals. These aggregate to form renal stones and incrustations on urinary catheters (12).

The pathogenic potential of coagulase-negative staphylococci and non-group D streptococci is controversial (13,14). Under certain circumstances, such as the presence of a stone or foreign bodies, staphylococci can be relevant pathogens. Otherwise, staphylococci are not so common in complicated UTIs (0-11%), according to published reports (6,15).

4.3.3 *Complicated UTIs associated with urinary catheters*

In catheter-associated UTIs, the distribution of microorganisms is similar (16), and biofilm has to be considered. Antimicrobial therapy may only be effective in the early stages of the infection (15). For more details see Chapter 6 on catheter-associated UTIs.

4.4 Treatment

4.4.1 *General principles*

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

4.4.2 *Choice of antibiotics*

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

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

Many therapeutic trials have been published on the use of specific antimicrobial therapies in complicated UTIs. Unfortunately, most reports are of limited use for the practical management of the patient in

a day-to-day situation because of limitations such as:

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

Intense use of any antimicrobial, especially when used on an empirical basis in this group of patients with a high likelihood of recurrent infection, will lead to the emergence of resistant microorganisms in subsequent infections. Whenever possible, empirical therapy should be replaced by a therapy adjusted for the specific infective organisms identified in the urine culture. Therefore, a urine specimen for culture must be obtained before initiation of therapy, and the selection of an antimicrobial agent should be re-evaluated once culture results are available (7). To date, it has not been shown that any agent or class of agents is superior in cases in which the infective organism is susceptible to the drug administered.

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

If empirical treatment is necessary, fluoroquinolones with mainly renal excretion are usually recommended because they have a large spectrum of antimicrobial activity that covers most of the expected pathogens, and they reach high concentration levels both in the urine and the urogenital tissues. Fluoroquinolones can be used orally as well as parenterally. An aminopenicillin plus a BLI, a Group 2 or 3a cephalosporin, or, in the case of parenteral therapy, an aminoglycoside, are alternatives. A new Group 1 oral carbapenem, ertapenem, in a prospective randomised trial, has been shown to be as effective as ceftriaxone (16).

In most countries, *E. coli* shows a high rate of resistance against TMP-SMX (18-25% in the latest evaluation in the USA) (17) and should therefore be avoided as a first-line treatment. Fosfomycin trometamol is licensed only for a single-dose therapy of uncomplicated cystitis (18). The aminopenicillins, ampicillin or amoxicillin, are no longer sufficiently active against *E. coli*.

In the case of failure of initial therapy, or if microbiological results are not yet available, or as initial therapy in the case of clinically severe infection, treatment should be switched to an antibiotic with a broader spectrum that is also active against *Pseudomonas*, such as a fluoroquinolone (if not used for initial therapy), an acylaminopenicillin (piperacillin) plus a BLI, a Group 3b cephalosporin, or a carbapenem, eventually in combination with an aminoglycoside. Similarly, many experts concur that empirical therapy for the institutionalised or hospitalised patients with a serious UTI should include an intravenous antipseudomonal agent because of an increased risk of urosepsis (19).

Patients can generally be treated as outpatients. In more severe cases (e.g. hospitalised patients), antibiotics have to be given parenterally. A combination of an aminoglycoside with a BLI or a fluoroquinolone is widely used for empirical therapy. After a few days of parenteral therapy and clinical improvement, patients can be switched to oral treatment. Therapy has to be reconsidered when the infective strains have been identified and their susceptibilities are known.

The successful treatment of a complicated UTI always combines effective antimicrobial therapy, optimal management of the underlying urological abnormalities or other diseases, and sufficient life-supporting measures. The antibacterial treatment options are summarised in Table 4.2 and Appendix 16.2 (Recommendations for antimicrobial therapy in urology).

4.4.3 ***Duration of antibiotic therapy***

Treatment for 7-14 days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality (1). Sometimes, a prolongation for up to 21 days, according to the clinical situation, is necessary (2).

4.4.4 ***Complicated UTIs associated with urinary stones***

If a nidus of a stone or an infection remains, stone growth will occur. Complete removal of the stones and adequate antimicrobial therapy are both needed. Eradication of the infection will probably eliminate the growth of struvite calculi (20). Long-term antimicrobial therapy should be considered if complete removal of the stone cannot be achieved (21).

4.4.5 ***Complicated UTIs associated with indwelling catheters***

Current data do not support the treatment of asymptomatic bacteriuria, either during short-term catheterisation (< 30 days) or during long-term catheterisation, because it will promote the emergence of resistant strains (22,23). In short-term catheterisation, antibiotics may delay the onset of bacteriuria, but do not reduce complications (24).

A symptomatic complicated UTI associated with an indwelling catheter is treated with an agent with

as narrow a spectrum as possible, based on culture and sensitivity results. The optimal duration is not well established. Treatment durations that are too short as well as too long may cause the emergence of resistant strains. A 7-day course could be a reasonable compromise.

*4.4.6 **Complicated UTIs in patients with spinal cord injury***

In case of persistent UTIs and suspicion of urinary retention, a full urodynamic assessment to appraise bladder function is to be carried out. Priority is to ensure proper drainage of the bladder to protect the urinary tract. For further details, see the EAU guidelines on Neurogenic Lower Urinary Tract Dysfunction (25).

It is generally accepted that asymptomatic bacteriuria in patients with spinal cord injury should not be treated (26), even in cases of intermittent catheterisation. For symptomatic episodes of infection in patients with spinal cord injury, only a few studies have investigated the most appropriate agent and duration of therapy. Currently, 7-10 days of therapy is most commonly used. There is no superiority of one agent or class of antimicrobials in this group of patients.

Antimicrobial treatment options are summarised in Table 4.2.

Table 4.2: Antimicrobial treatment options for empirical therapy

Antibiotics recommended for initial empirical treatment
Fluoroquinolones
Aminopenicillin plus a BLI
Cephalosporin (Groups 2 or 3a)
Aminoglycoside
Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases
Fluoroquinolone (if not used for initial therapy)
Ureidopenicillin (piperacillin) plus BLI
Cephalosporin (Group 3b)
Carbapenem
Combination therapy:
- Aminoglycoside + BLI
- Aminoglycoside + fluoroquinolone
Antibiotics not recommended for empirical treatment
Aminopenicillins, e.g. amoxicillin, ampicillin
Trimethoprim-sulphamethoxazole (only if susceptibility of pathogen is known)
Fosfomycin trometamol

BLI = β-lactam inhibitor

*4.4.7 **Follow-up after treatment***

The greater likelihood of the involvement of resistant microorganisms in complicated UTIs is another feature of these infectious diseases. This is not a priori related to the urinary abnormality, but is related more to the fact that patients with a complicated UTI tend to have recurrent infection (7). For these reasons, before and after the completion of the antimicrobial treatment, urine cultures must be obtained for the identification of the microorganisms and the evaluation of susceptibility testing.

4.5 References

1. Rubin RH, Shapiro ED, Andriole VT, 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 Nov;15 Suppl 1:S216-S227. http://www.ncbi.nlm.nih.gov/pubmed/1477233
2. Rubin RH, Shapiro ED, Andriole VT, et al, with modifications by a European Working Party. General guidelines for the evaluation of new anti-infective drugs for the treatment of UTI. Taufkirchen, Germany: The European Society of Clinical Microbiology and Infectious Diseases, 1993, pp. 240-310.
3. Kumazawa J, Matsumoto T. Complicated UTIs. In: Bergan T, ed. UTIs. *Infectiology*. Vol 1. Basel: Karger, 1997, pp. 19-26.

4. Naber KG. Experience with the new guidelines on evaluation of new anti-infective drugs for the treatment of urinary tract infections. Int J Antimicrob Agents 1999 May;11(3-4):189-96. http://www.ncbi.nlm.nih.gov/pubmed/10394969
5. Sharifi R, Geckler R, Childs S. Treatment of urinary tract infections: selecting an appropriate broadspectrum antibiotic for nosocomial infections. Am J Med 1996 Jun;100(6A):76S-82S. http://www.ncbi.nlm.nih.gov/pubmed/8678101
6. Frankenschmidt A, Naber KG, Bischoff W, et al. Once-daily fleroxacin versus twice-daily ciprofloxacin in the treatment of complicated urinary tract infections. J Urol 1997 Oct;158(4):1494-9. http://www.ncbi.nlm.nih.gov/pubmed/9302150
7. Nicolle LE. A practical guide to the management of complicated urinary tract infection. Drugs 1997 Apr;53(4):583-92. http://www.ncbi.nlm.nih.gov/pubmed/9098661
8. Cox CE, Holloway WJ, Geckler RW. A multicenter comparative study of meropenem and imipenem/cilastatin in the treatment of complicated urinary tract infections in hospitalized patients. Clin Infect Dis 1995 Jul;21(1):86-92. http://www.ncbi.nlm.nih.gov/pubmed/7578765
9. Dobardzic AM, Dobardzic R. Epidemiological features of complicated UTI in a district hospital of Kuwait. Eur J Epidemiol 1997 Jun;13(4):465-70. http://www.ncbi.nlm.nih.gov/pubmed/9258554
10. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. Clin Microbiol Rev 1993 Oct;6(4):428-42. http://www.ncbi.nlm.nih.gov/pubmed/8269394
11. Parsons CL, Stauffer C, Mulholland SG, et al. Effect of ammonium on bacterial adherence to bladder transitional epithelium. J Urol 1984 Aug;132(2):365-6. http://www.ncbi.nlm.nih.gov/pubmed/6376829
12. Dumanski AJ, Hedelin H, Edin-Liljergen A, et al. Unique ability of the Proteus mirabilis capsule to enhance mineral growth in infectious urinary calculi. Infect Immun 1994 Jun;62(7):2998-3003. http://www.ncbi.nlm.nih.gov/pubmed/8005688
13. Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med 1993 Oct;329(18):1328-34. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/8413414
14. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry. Complicated urinary tract infections and pyelonephritis-developing antimicrobial drugs for treatment. Clin-Anti. Rockville, MD: Drug Information Branch. Division of Communications Management, 1998. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070981.pdf
15. Reid G. Biofilms in infectious disease and on medical devices. Int J Antimicrob Agents 1999 May; 11(3-4):223-6. http://www.ncbi.nlm.nih.gov/pubmed/10394974
16. Wells WG, Woods GL, Jiang Q, et al. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by an appropriate oral therapy. J Antimicrob Chemother 2004 Jun;53 Suppl 2:ii67-74. http://www.ncbi.nlm.nih.gov/pubmed/15150185
17. Sahm DF, Thornsberry C, Mayfield DC, et al. Multidrug-resistant urinary tract isolates of Escherichia coli: prevalence and patient demographics in the United States in 2000. Antimicrob Agents Chemother 2001 May;45(5):1402-6. http://www.ncbi.nlm.nih.gov/pubmed/11302802
18. Lerner SA, Price S, Kulkarni S. Microbiological studies of fosfomycin trometamol against urinary isolates in vitro. In: *New trends in urinary tract infections*. Williams N, ed. Basel: Karger, 1988, pp. 121-129.
19. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. Drugs 2004;64(12):1359-73. http://www.ncbi.nlm.nih.gov/pubmed/15200349
20. Griffith DP, Osborne CA. Infection (urease) stones. Miner Electrolyte Metab 1987;13(4):278-85. http://www.ncbi.nlm.nih.gov/pubmed/3306321
21. Beck EM, Riehle RA Jr. The fate of residual fragments after extracorporeal shock wave lithotripsy monotherapy of infection stones. J Urol 1991 Jun;145(1):6-9. http://www.ncbi.nlm.nih.gov/pubmed/1984100

22. Alling B, Brandberg A, Seeberg S, et al. Effect of consecutive antibacterial therapy on bacteriuria in hospitalized geriatric patients. Scand J Infect Dis 1975;7(3):201-7. http://www.ncbi.nlm.nih.gov/pubmed/809837
23. Warren JW, Anthony WC, Hoopes JM, et al. Cephalexin for susceptible bacteriuria in afebrile, long term catheterized patients. JAMA 1982 Jul;248(4):454-8. http://www.ncbi.nlm.nih.gov/pubmed/7045440
24. Yoshikawa TT, Nicolle LE, Norman DC. Management of complicated urinary tract infection in older patients. J Am Geriatr Soc 1996 Oct;44(10):1235-41. http://www.ncbi.nlm.nih.gov/pubmed/8856005
25. Stöhrer M, Blok B, Castro-Diaz D, et al. EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction. Eur Urol 2009 Jul;56(1):81-8. http://www.ncbi.nlm.nih.gov/pubmed/19403235
26. National Institute on Disability and Rehabilitation Research. The prevention and management of urinary tract infections among people with spinal cord injuries. National Institute on Disability and Rehabilitation Research Consensus Statement. January 27-29, 1992. J Am Paraplegia Soc 1992 Jul;15(3):194-204. http://www.ncbi.nlm.nih.gov/pubmed/1500945

5. SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

5.1 Summary and recommendations

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

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

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

5.2 Background

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

Severe sepsis has a mortality rate of 20-42% (1) with most reports in the literature related to pulmonary (50%) or abdominal (24%) infections, with UTIs accounting for only 5% (2). Sepsis is more common in men than in women (3). In recent years, the incidence of sepsis has increased by 8.7% per year (1), but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000 (4). Globally (this is not true for urosepsis), the rate of sepsis due to fungal organisms has increased while Gram-positive bacteria have become the predominant pathogen in sepsis, even if Gram-negative bacteria remain predominant in urosepsis.

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include: elderly patients; diabetics; immunosuppressed patients, such as transplant recipients; patients receiving cancer chemotherapy or corticosteroids; and patients with AIDS. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can

be affected by bacterial species that are capable of inducing inflammation within the urinary tract. Moreover, it is now recognised that SIRS may be present without infection (e.g. pancreatitis, burns, or non-septic shock) (5).

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

5.3 Definition and clinical manifestation of sepsis in urology

The clinical evidence of UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. The following definitions apply (Table 5.1):

- Sepsis is a systemic response to infection. The symptoms of SIRS which were initially considered to be 'mandatory' for the diagnosis of sepsis (5), are now considered to be alerting symptoms (6). Many other clinical or biological symptoms must be considered.
- Severe sepsis is associated with organ dysfunction.
- Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation.
- Refractory septic shock is defined by an absence of response to therapy.

Table 5.1: Clinical diagnostic criteria of sepsis and septic shock (5,6)

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient.
Systematic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following conditions: - Temperature > 38°C or < 36°C - Heart rate > 90 bpm - Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg (< 4.3 kPa) - WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms
Sepsis	Activation of the inflammatory process due to infection.
Hypotension	Systolic blood pressure < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes of hypotension.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or acute alteration of mental status.
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Refractory septic shock	Septic shock that lasts for > 1 h and does not respond to fluid administration or pharmacological intervention.

5.4 Physiology and biochemical markers

Microorganisms reach the urinary tract by way of the ascending, haematogenous, or lymphatic routes. For urosepsis to be established, the pathogens have to reach the bloodstream. The risk of bacteraemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis, and is facilitated by obstruction of the urinary tract. *E. coli* remains the most prevalent microorganism. In several countries, some bacterial strains can be resistant to quinolones or third-generation cephalosporins. Some microorganisms are multi-resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and *Serratia* sp. and

therefore difficult to treat. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection. A fatal outcome is described in 20-40% of all patients.

*5.4.1 **Cytokines as markers of the septic response***

Cytokines are involved in the pathogenesis of sepsis syndrome. They are peptides that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. When they become bound to specific receptors on other cells, cytokines change their behaviour in the inflammatory response. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Other cytokines that are associated with sepsis are interleukins (ILs) (IL-1, -6, -8) and tumour necrosis factor (TNF)-α. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood (2).

*5.4.2 **Procalcitonin is a potential marker of sepsis***

Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise to > 100 ng/mL. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. The exact site of procalcitonin production during sepsis is not known. Procalcitonin monitoring may be useful in patients likely to develop a SIRS of infectious origin. High procalcitonin levels, or an abrupt increase in levels in these patients, should prompt a search for the source of infection. Procalcitonin may be useful in differentiating between infectious and non-infectious causes of severe inflammatory status (7,8).

5.5 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for a combination of treatment of the cause (obstruction of the urinary tract), adequate life-supporting care, and appropriate antibiotic therapy (2). In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

*5.5.1 **Preventive measures of proven or probable efficacy (9,10)***

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections:

- Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. It is well known that long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting (11). Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective, disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

*5.5.2 **Appropriate perioperative antimicrobial prophylaxis***

For appropriate perioperative antimicrobial prophylaxis, see Chapter 15. The potential side effects of antibiotics must be considered before their administration in a prophylactic regimen.

*5.5.3 **Preventive measures of debatable efficacy***

- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.

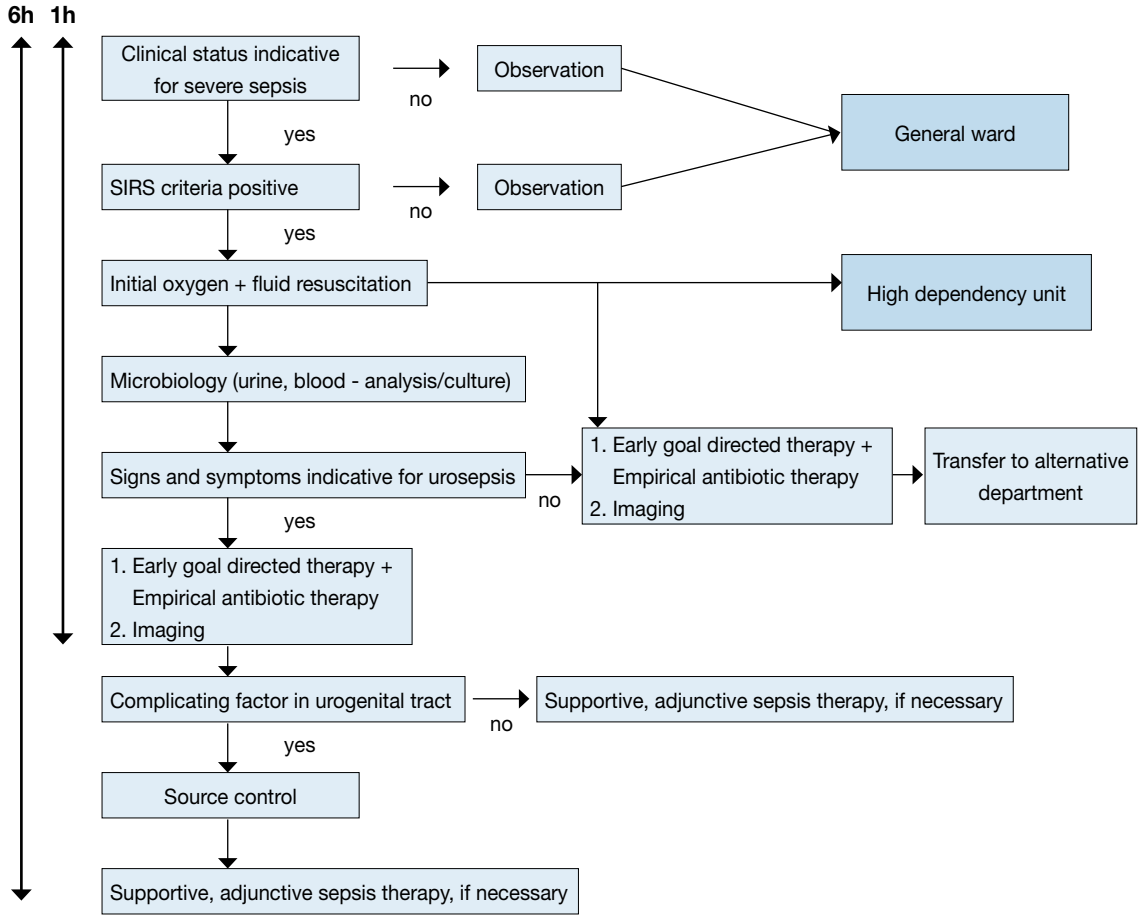
- Use of urinary catheters coated with antibiotics or silver.

5.5.4 ***Ineffective or counterproductive measures***

- Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase the risk of infection with resistant bacteria (9,12).
- Routine administration of antimicrobial drugs to catheterised patients, which reduces the incidence of bacteriuria only for a few days and increases the risk of infection with multi-resistant bacteria (9,12). Its use may be reserved for immunosuppressed patients.

5.6 Algorithm for the management of urosepsis

Figure 5.1: Clinical algorithm for the management of urosepsis



5.7 Treatment

5.7.1 ***Clinical algorithm for management of urosepsis***

Table 5.2: Early goal directed therapy

Early goal directed therapy	
Central venous pressure (CVP)	8-12 mmHg
Mean arterial pressure (MAP)	65-90 mmHg
Central venous oxygen (CVO2)	≥ 70%
Haematocrit (HKT)	> 30 %
Urine output	> 40 mL/h

Table 5.3: Levels of therapy in sepsis

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

*5.7.2 **Relief of obstruction***

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

*5.7.3 **Antimicrobial therapy***

Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the basis of culture results. The dosage of the antibiotic substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure. Antimicrobials must be administered no later than 1 h after clinical assumption of sepsis (see Figure 5.1). The antibacterial treatment options are summarised in Appendix 16.1 and 16.2.

*5.7.4 **Adjunctive measures (12,13)***

The management of fluid and electrolyte balance is a crucial aspect of patient care in sepsis syndrome; particularly when the clinical course is complicated by shock. The use of human albumin is debatable. Early goal-directed therapy has been shown to reduce mortality (14). Volaemic expansion and vasopressor therapy have a considerable impact on the outcome. Early intervention with appropriate measures to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilisation of arterial pressure, and providing sufficient oxygen transport capacity are highly effective.

Hydrocortisone (with a debate on dosage) is useful in patients with relative insufficiency in the pituitary gland-adrenal cortex axis (adrenocorticotropin test) (15).

Tight blood glucose control by administration of insulin doses up to 50 U/h is associated with a reduction in mortality (16).

Current evidence does not support the use of human recombinant activated protein C in adults and children with severe sepsis and septic shock (17).

The best strategy has been summarised and graded according to a careful evidence-based methodology in the recently published ‘Surviving Sepsis Guidelines’ (18).

5.8 Conclusion

Sepsis syndrome in urology remains a severe situation with a mortality rate as high as 20-40%. A recent campaign, ‘Surviving Sepsis Guidelines’, aims to reduce mortality by 25% in the next few years (18). Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patient survival. The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using antibiotic prophylaxis and therapy in a prudent and well-accepted manner.

5.9 Acknowledgement

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5.10 References

1. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003 Apr;348(16):1546-54. http://www.ncbi.nlm.nih.gov/pubmed/12700374
2. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003 Jan;348(2):138-50. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/12519925

3. Rosser CJ, Bare RL, Meredith JW. Urinary tract infections in the critically ill patient with a urinary catheter. Am J Surg 1999 Apr;177(4):287-90.
http://www.ncbi.nlm.nih.gov/pubmed/10326844
4. Brun-Buisson C, Meshaka P, Pinton P, et al; EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 2004 Apr;30(4):580-8.
http://www.ncbi.nlm.nih.gov/pubmed/14997295
5. Bone RC, Balk RA, Cerra FB, 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 Jun;101(6):1644-55.
http://www.ncbi.nlm.nih.gov/pubmed/1303622
6. Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003 Apr;31(4):1250-6.
http://www.ncbi.nlm.nih.gov/pubmed/12682500
7. Brunkhorst FM, Wegscheider K, Forycki ZF, et al. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis and septic shock. Intensive Care Med 2000 Mar;26 Suppl 2:S148-52.
http://www.ncbi.nlm.nih.gov/pubmed/18470710
8. Harbarth S, Holeckova K, Froidevaux C, et al; Geneva Sepsis Network. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001 Aug;164(3):396-402.
http://www.ncbi.nlm.nih.gov/pubmed/11500339
9. Carlet J, Dumay MF, Gottot S, et al. [Guideliness for prevention of nosocomial infections in intensive care unit.] Arnette Ed Paris 1994:41-53. [Article in French]
10. Riedl CR, Plas E, Hübner WA, et al. Bacterial colonization of ureteral stents. Eur Urol 1999;36(1):53-9.
http://www.ncbi.nlm.nih.gov/pubmed/10364656
11. DeGroot-Kosolcharoen J, Guse R, Jones JM. Evaluation of a urinary catheter with a preconnected closed drainage bag. Infect Control Hosp Epidemiol 1988 Feb;9(2):72-6.
http://www.ncbi.nlm.nih.gov/pubmed/3343502
12. Persky L, Liesen D, Yangco B. Reduced urosepsis in a veterans' hospital. Urology 1992 May;39(5):443-5.
http://www.ncbi.nlm.nih.gov/pubmed/1580035
13. Glück T, Opal SM. Advances in sepsis therapy. Drugs 2004;64(8):837-59.
http://www.ncbi.nlm.nih.gov/pubmed/15059039
14. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001 Nov;345(19):1368-77.
http://www.ncbi.nlm.nih.gov/pubmed/11794169
15. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002 Aug;288(7):862-71.
http://www.ncbi.nlm.nih.gov/pubmed/12186604
16. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001 Nov;345(19):1359-67.
http://www.ncbi.nlm.nih.gov/pubmed/11794168
17. Marti-Carvajal AJ, Solà I, Lathyris D, et al. Human recombinant activated protein C for severe sepsis. Cochrane Database Syst Rev 2011 Apr;(4):CD004388.
http://www.ncbi.nlm.nih.gov/pubmed/21491390
18. Dellinger RP, Carlet JM, Masur H, et al; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004 Mar;32:858-73.
http://www.ncbi.nlm.nih.gov/pubmed/15090974

6. CATHETER-ASSOCIATED UTIs

Based on the EAU guidelines published in 2007 (ISBN-13:978-90-70244-59-0), the following text presents the findings of a comprehensive update produced as a collaborative effort by the ESIU (a full EAU section office), the Urological Association of Asia, the Asian Association of UTI/STD, the Western Pacific Society for Chemotherapy, the Federation of European Societies for Chemotherapy and Infection, and the International Society of Chemotherapy for Infection and Cancer. This text was recently published as "The European and Asian guidelines on management and prevention of catheter-associated urinary tract infections" (1). Since the complete document is available online, only the abstract and a summary of the recommendations are presented here.

6.1 Abstract

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

The survey found that the urinary tract is the commonest source of nosocomial infection, particularly when the bladder is catheterised (LE: 2a). Most CAUTIs are derived from the patient's own colonic flora (LE: 2b) and the catheter predisposes to UTI in several ways. The most important risk factor for the development of catheter-associated bacteriuria is the duration of catheterisation (LE: 2a). Most episodes of short-term catheter-associated bacteriuria are asymptomatic and are caused by a single organism (LE: 2a). Further organisms tend to be acquired by patients who are catheterised for > 30 days.

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

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

6.2 Summary of recommendations

Recommendation		GR
General aspects		
1.	Written catheter care protocols are necessary.	B
2.	Health care workers should observe protocols on hand hygiene and the need to use disposable gloves between catheterised patients.	A
Catheter insertion and choice of catheter		
3.	An indwelling catheter should be introduced under antiseptic conditions.	B
4.	Urethral trauma should be minimised by the use of adequate lubricant and the smallest possible catheter calibre.	B
5.	Antibiotic-impregnated catheters may decrease the frequency of asymptomatic bacteriuria within 1 week. There is, however, no evidence that they decrease symptomatic infection. Therefore, they cannot be recommended routinely.	B
6.	Silver alloy catheters significantly reduce the incidence of asymptomatic bacteriuria, but only for < 1 week. There was some evidence of reduced risk for symptomatic UTI. Therefore, they may be useful in some settings.	B
Prevention		
7.	The catheter system should remain closed.	A
8.	The duration of catheterisation should be minimal.	A
9.	Topical antiseptics or antibiotics applied to the catheter, urethra or meatus are not recommended.	A
10.	Benefits from prophylactic antibiotics and antiseptic substances have never been established, therefore, they are not recommended.	A
11.	Removal of the indwelling catheter after non-urological operation before midnight might be beneficial.	B
12.	Long-term indwelling catheters should be changed at intervals adapted to the individual patient, but must be changed before blockage is likely to occur, however, there is no evidence for the exact intervals of changing catheters.	B
13.	Chronic antibiotic suppressive therapy is generally not recommended.	A
14.	The drainage bag should always be kept below the level of the bladder and the connecting tube.	B
Diagnostics		
15.	Routine urine culture in asymptomatic catheterised patients is not recommended.	B
16.	Urine, and in septic patients, also blood for culture must be taken before any antimicrobial therapy is started.	C
17.	Febrile episodes are only found in < 10% of catheterised patients living in a long-term facility. It is therefore extremely important to rule out other sources of fever.	A
Treatment		
18.	While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended, except in certain circumstances, especially before traumatic urinary tract interventions.	A
19.	In case of asymptomatic candiduria, neither systemic nor local antifungal therapy is indicated, but removal of the catheter or stent should be considered.	A/C
20.	Antimicrobial treatment is recommended only for symptomatic infection.	B
21.	In case of symptomatic CAUTI, it might be reasonable to replace or remove the catheter before starting antimicrobial therapy if the indwelling catheter has been in place for > 7 days.	B
22.	For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns.	C
23.	After culture results are available, antibiotic therapy should be adjusted according to pathogen sensitivity.	B

24.	In case of candiduria associated with urinary symptoms, or if candiduria is the sign of systemic infection, systemic therapy with antifungals is indicated.	B
25.	Elderly female patients may need treatment if bacteriuria does not resolve spontaneously after catheter removal.	C
Alternative drainage systems		
26.	There is limited evidence that postoperative intermittent catheterisation reduces the risk of bacteriuria compared with indwelling catheters. No recommendation can be made.	C
27.	In appropriate patients, a suprapubic, condom drainage system or intermittent catheter is preferable to an indwelling urethral catheter.	B
28.	There is little evidence to suggest that antibiotic prophylaxis decreases bacteriuria in patients using intermittent catheterisation, therefore, it is not recommended.	B
Long-term follow up		
29.	Patients with urethral catheters in place for ≥ 10 years should be screened for bladder cancer.	C

6.3 Reference

1. Tenke P, Kovacs B, Bjerklund Johansen TE, et al. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 2008 Feb;31 Suppl 1:S68-78.
http://www.ncbi.nlm.nih.gov/pubmed/18006279

7. UTIs IN CHILDREN

7.1 Summary and recommendations

Urinary tract infection in children is a frequent health problem, with the incidence only a little lower than that of upper respiratory and digestive infections.

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

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

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

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

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

7.2 Background

The urinary tract is a common source of infection in children and infants. It represents the most common bacterial infection in children < 2 years of age (1) (LE: 2a). The outcome of a UTI is usually benign, but in early infancy, it can progress to renal scarring, especially when associated with congenital anomalies of the urinary tract. Delayed sequelae related to renal scarring include hypertension, proteinuria, renal damage and even chronic renal failure, which requires dialysis treatment in a significant number of adults (2) (LE: 2a).

The risk of UTI during the first decade of life is 1% in males and 3% in females (3). It has been suggested that 5% of schoolgirls and up to 0.5% of schoolboys undergo at least one episode of UTI during their school life. The incidence is different for children < 3 months of age, when it is more common in boys. The incidence of asymptomatic bacteriuria is 0.7-3.4% in neonates, 0.7-1.3% in infants < 3 months of age, and 0.2-0.8% in preschool boys and girls (3). The incidence of symptomatic bacteriuria is 0.14% in neonates, with a further increase to 0.7% in boys and 2.8% in girls aged < 6 months. The overall recurrence rate for the neonatal period has been reported to be 25% (3,4).

7.3 Aetiology

The common pathogenic sources are Gram-negative, mainly enteric, bacteria. Of these, *E. coli* is responsible for 90% of UTI episodes (5). Gram-positive bacteria (particularly enterococci and staphylococci) represent 5-7% of cases. Hospital-acquired infections show a wider pattern of aggressive bacteria, such as *Klebsiella, Serratia* and *Pseudomonas* sp. Groups A and B streptococci are relatively common in new-born infants (6). There is an increasing trend towards the isolation of *S. saprophyticus* in UTIs in children, although the role of this bacterium is still debatable (7).

7.4 Pathogenesis and risk factors

The urinary tract is a sterile space with an impermeable lining. Retrograde ascent is the most common mechanism of infection. Nosocomial infection and involvement as part of a systemic infection are less common (8).

Obstruction and dysfunction are among the most common causes of urinary infection. Phimosis predisposes to UTI (9,10) (LE: 2a). Enterobacteria derived from intestinal flora colonise the preputial sac, glandular surface and the distal urethra. Among these bacteria are strains of *E. coli* that express P fimbriae, which adhere to the inner layer of the preputial skin and to uroepithelial cells (11).

A wide variety of congenital urinary tract abnormalities can cause UTIs through obstruction, e.g. urethral valves, ureteropelvic junction obstruction or non-obstructive urinary stasis (e.g. prune belly syndrome, or VUR). More mundane but significant causes of UTIs include labial adhesion and chronic constipation (7).

Dysfunctional voiding in an otherwise normal child may result in infrequent bladder emptying aided by delaying manoeuvres, e.g. crossing legs, sitting on heels (12). Neuropathic bladder dysfunction (e.g. spina bifida, or sphincter dyssynergia) may lead to post-void residual urine and secondary VUR (4).

The link between renal damage and UTIs is controversial. The mechanism in obstructive nephropathy is self-evident, but more subtle changes occur when there is VUR. Almost certainly, the necessary components include VUR, intrarenal reflux and UTI. These must all work together in early childhood when the growing kidney is likely to be susceptible to parenchymal infection. Later on in childhood, the presence of bacteriuria seems irrelevant to the progression of existing scars or the very unusual formation of new scars. Another confounding factor is that many so-called scars are dysplastic renal tissue which develop *in utero* (13).

7.5 Signs and symptoms

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

A UTI in neonates may be non-specific and with no localisation. In small children, a UTI may present with gastrointestinal signs, such as vomiting and diarrhoea. In the first weeks of life, 13.6% of patients with fever have a UTI (14). Rarely, septic shock is the presentation. Signs of UTI may be vague in small children, but later on, when they are older than 2 years, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain may appear with or without fever.

7.6 Classification

UTIs may be classified as a first episode or recurrent, or according to severity (simple or severe).
Recurrent UTI may be subclassified into three groups (8):

- *Unresolved infection*: subtherapeutic level of antimicrobial, non-compliance with treatment, malabsorption, resistant pathogens.
- *Bacterial persistence*: may be due to a nidus for persistent infection in the urinary tract. Surgical correction or medical treatment for urinary dysfunction may be needed.
- *Reinfection*: each episode is a new infection acquired from periurethral, perineal or rectal flora.

From the clinical point of view, severe and simple forms of UTIs should be differentiated because to some extent the severity of symptoms dictates the degree of urgency with which investigation and treatment are to be undertaken (Table 7.1).

Table 7.1: Clinical classification of UTIs in children

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

7.6.1 ***Severe UTI***

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

7.6.2 ***Simple UTI***

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

7.7 Diagnosis

7.7.1 ***Physical examination***

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

7.7.2 ***Laboratory tests***

The definitive diagnosis of infection in children requires a positive urine culture (8,15). Urine must be obtained under bacteriologically reliable conditions when undertaking a urine specimen culture (16). A positive urine culture is defined as the presence of > 100,000 cfu/mL of one pathogen. The urine specimen may be difficult to obtain in a child < 4 years old, and different methods are advised because there is a high risk of contamination (17,18).

7.7.2.1 Collection of the urine

7.7.2.1.1 Suprapubic bladder aspiration

Suprapubic bladder aspiration is the most sensitive method, even though urine may be obtained in 23-99% of cases (8,18).

7.7.2.1.2 Bladder catheterisation

Bladder catheterisation is also a very sensitive method, even though there is the risk of introduction of nosocomial pathogens (8,19).

7.7.2.1.3 Plastic bag attached to the genitalia

Prospective studies have shown a high incidence of false-positive results, ranging from 85 to 99% (8,18). It is helpful when the culture is negative (8,18) and has a positive predictive value of 15% (16). To obtain a urine sample in the best condition in children < 2 years of age (girls and uncircumcised boys without sphincteric control), it is better to use suprapubic bladder aspiration or bladder catheterisation. In older children with sphincteric control, MSU collection is possible and reliable (18).

7.7.2.2 Quantification of bacteriuria

The final concentration of bacteria in urine is directly related to the method of collection, diuresis, and method of storage and transport of the specimen (15). The classical definition of significant bacteriuria of > 10^5 cfu/mL is still used and depends on the clinical environment (15,17).

The presence of pyuria (> 5 leukocytes per field) and bacteriuria in a fresh urine sample reinforce the clinical diagnosis of UTI (17).

In boys, when the urine is obtained by bladder catheterisation, the urine culture is considered positive with > 10^4 cfu/mL. Even though Hoberman (20) has identified a microorganism in 65% of cases with colony counts between 10,000 and 50,000 cfu/mL, there was a mixed growth pattern suggesting contamination. In these cases, it is better to repeat the culture or to evaluate the presence of other signs, such as pyuria, nitrites or other biochemical markers (15). The collection of MSU or in a collecting bag of ≥10^5 cfu/mL is considered positive (16) (Table 7.2).

Table 7.2: Criteria for UTI in children

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

7.7.2.3 Other biochemical markers

The presence of other biochemical markers in a urine sample are useful to establish the diagnosis of UTI (8). The most frequent markers are nitrite and leukocyte esterase usually combined in a dipstick test.

7.7.2.3.1 Nitrite

Nitrite is the degradation product of nitrate in bacterial metabolism, particularly in Gram-negative bacteria. When an infection is caused by Gram-positive bacteria, the test may be negative (8,16). Limitations of the nitrite test include:

- not all uropathogens reduce nitrate to nitrite, e.g. *P. aeruginosa*, or enterococci;
- even nitrite-producing pathogens may show a negative test result, due to the short transit time in the bladder in cases of high diuresis and urine dilution, e.g. neonates;
- the nitrite test has a sensitivity of only 45-60%, but a very good specificity of 85-98% (8,17,21).

7.7.2.3.2 Leukocyte esterase

Leukocyte esterase is produced by the activity of leukocytes. The test for leukocyte esterase has a sensitivity of 48-86% and a specificity of 17-93% (8,17,20,21).

A combination of nitrite and leukocyte esterase testing improves sensitivity and specificity, but carries the risk of false-positive results (21).

The dipstick test has become useful to exclude rapidly and reliably the presence of a UTI, provided both nitrite and leukocyte esterase tests are negative. If the tests are positive, it is better to confirm the results in combination with the clinical symptoms and other tests (17,21).

Bacteriuria without pyuria may be found:

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

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

Bacteriuria without pyuria is found in 0.5% of specimens. This figure corresponds well with the estimated rate of asymptomatic bacteriuria in childhood (20,22) (LE: 2a).

Pyuria without bacteriuria may be due to:

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

Thus, either bacteriuria or pyuria may not be considered reliable parameters to diagnose or exclude UTI. Their assessment can be influenced by other factors, such as the degree of hydration, method of specimen collection, mode of centrifugation, volume in which sediment is resuspended and subjective interpretation of results (23). However, according to Landau et al. (24), pyuria in febrile children is indicative of acute pyelonephritis.

For all of these reasons, in neonates and children < 6 months of age, either pyuria, bacteriuria or the nitrite test, separately, have minimal predictive value for UTI (25,26) (LE: 3). In contrast, the positive predictive value of significant Gram staining with pyuria is 85% (20) (LE: 2b). In older children, pyuria with a positive nitrite test is more reliable for the diagnosis of UTI, with a positive predictive value of 98%.

Combining bacteriuria and pyuria in febrile children, the findings of $\geq$ 10 WBC/mm^3 and $\geq$ 50,000 cfu/mL in a specimen collected by catheterisation are significant for a UTI, and discriminate between infection and contamination (20,25).

7.7.2.3.3 C-reactive protein

Although non-specific in febrile children with bacteriuria, C-reactive protein seems to be useful in distinguishing between acute pyelonephritis and other causes of bacteriuria. It is considered significant at a concentration > 20 µg/mL.

7.7.2.3.4 Urinary N-acetyl-β-glucosaminidase

Urinary N-acetyl-β-glucosaminidase is a marker of tubular damage. It is increased in febrile UTI and may become a reliable diagnostic marker for UTIs, although it is also elevated in VUR (27).

7.7.2.3.5 IL-6

The clinical use of urinary concentrations of IL-6 in UTIs (28) is still at the research stage.

7.7.3 ***Imaging of the urinary tract***

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

7.7.3.1 Ultrasound

Ultrasound (US) has become very useful in children because of its safety, speed and high accuracy in identifying the anatomy and size of the renal parenchyma and collecting system (29). It is subjective and therefore operator-dependent, and gives no information on renal function. However, scars can be identified, although not as well as with Tc-99m DMSA scanning (29,30) (LE: 2a). This technique has been shown to be very sensitive and excretory urography must be reserved only for when images need to be morphologically clarified (31) (LE: 2a).

7.7.3.2 Radionuclide studies

Tc-99m DMSA is a radiopharmaceutical that is bound to the basement membrane of proximal renal tubular cells; half of the dose remains in the renal cortex after 6 h. This technique is helpful in determining functional renal mass and ensures an accurate diagnosis of cortical scarring by showing areas of hypoactivity, which indicates lack of function. A UTI interferes with the uptake of this radiotracer by the proximal renal tubular cells, and may show areas of focal defect in the renal parenchyma. A star-shaped defect in the renal parenchyma may indicate an acute episode of pyelonephritis. A focal defect in the renal cortex usually indicates a chronic lesion or a renal scar (32-34) (LE: 2a).

Focal scarring or a smooth uniform loss of renal substance as demonstrated by Tc-99m DMSA is generally regarded as being associated with VUR (reflux nephropathy) (35,36). However, Rushton et al. (37) have stated that significant renal scarring may develop, regardless of the existence or absence of VUR. Ransley and Risdon (38) have reported that Tc-99m DMSA shows a specificity of 100% and sensitivity of 80% for renal scarring.

The use of Tc-99m DMSA scanning can be helpful in the early diagnosis of acute pyelonephritis. About 50-85% of children show positive findings in the first week. Minimal parenchymal defects, when characterised by a slight area of hypoactivity, can resolve with antimicrobial therapy (39,40). However, defects lasting > 5 months are considered to be renal scarring (41) (LE: 2a).

Tc-99m DMSA scans are considered more sensitive than excretory urography and US in the detection of renal scars (42-45). It remains questionable whether radionuclide scans can substitute echography as a first-line diagnostic approach in children with a UTI (46,47).

7.7.3.3 Cystourethrography

7.7.3.3.1 Conventional voiding cystourethrography

Voiding cystourethrography (VCU) is the most widely used radiological exploration for the study of the lower urinary tract and especially of VUR. It is considered mandatory in the evaluation of UTIs in children < 1 year of age. Its main drawbacks are the risk of infection, the need for retrogrades filling of the bladder, and the possible deleterious effect of radiation on children (48). In recent years, tailored low-dose fluoroscopic VCU has been used for the evaluation of VUR in girls to minimise radiological exposure (49). VCU is mandatory in the assessment of febrile childhood UTI, even in the presence of normal US. Up to 23% of these patients may reveal VUR (50).

7.7.3.3.2 Radionuclide cystography (indirect)

This investigation is performed by prolonging the period of scanning after the injection of Tc-99m diethylene triamine pentaacetate (DTPA) or mercaptoacetyltriglycine (MAG-3) as part of dynamic renography. It represents an attractive alternative to conventional cystography, especially when following patients with reflux, because of its lower dose of radiation. Disadvantages are poor image resolution and difficulty in detecting lower urinary tract abnormalities (51,52).

7.7.3.3.3 Cystosonography

Contrast-material-enhanced voiding US has been introduced for the diagnoses of VUR without irradiation (47,52). Further studies are necessary to determine the role of this new imaging modality in UTI.

7.7.3.4 Additional imaging

Excretory urography remains a valuable tool in the evaluation of the urinary tract in children, but its use in UTIs is debatable unless preliminary imaging has demonstrated abnormalities that require further investigation. The major disadvantages in infants are the risks of side effects from exposure to contrast media and radiation (53). However, the role of excretory urography is declining with the increasing technical superiority of CT (54) and

MRI. However, the indications for their use is still limited in UTI.

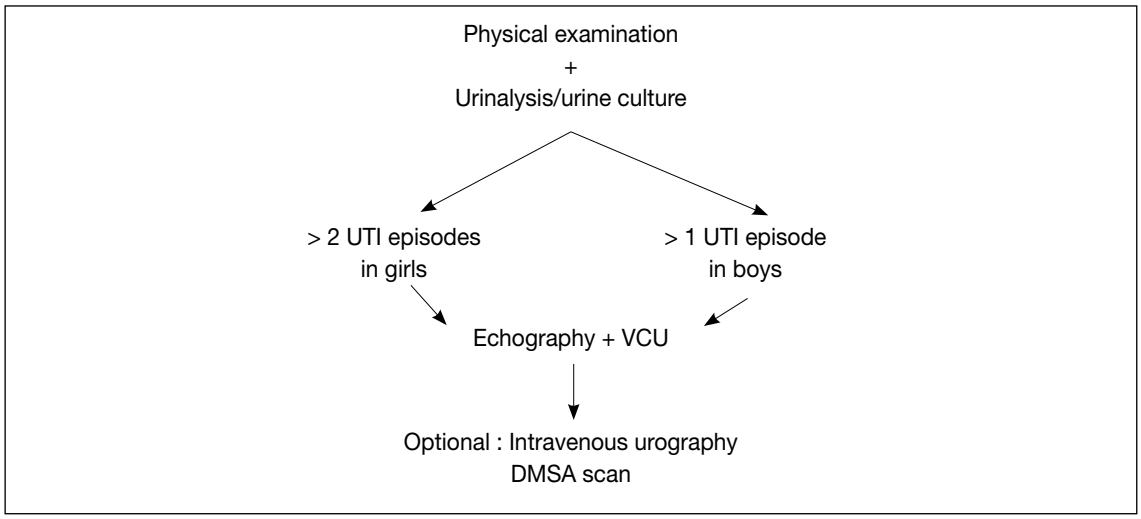
7.7.3.5 Urodynamic evaluation

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

7.8 Schedule of investigation

Screening of infants for asymptomatic bacteriuria is unlikely to prevent pyelonephritic scar formation, as these usually develop very early in infancy. Only a minority of children with a UTI have an underlying urological disorder, but when present, such a disorder can cause considerable morbidity. Thus, after a maximum of two UTI episodes in a girl and one in a boy, investigations should be undertaken (Figure 7.1), but not in the case of asymptomatic bacteriuria (51-58). The need for DTPA/MAG-3 scanning is determined by the US findings, particularly if there is suspicion of an obstructive lesion.

Figure 7.1: Schedule of investigation of a UTI in a child



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

7.9 Treatment

Treatment has four main goals:

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

7.9.1 ***Severe UTIs***

A severe UTI requires adequate parenteral fluid replacement and appropriate antimicrobial treatment, preferably with cephalosporins (third generation). If a Gram-positive UTI is suspected by Gram stain, it is useful to administer aminoglycosides in combination with ampicillin or amoxycillin/clavulanate (59) (LE: 2a). Antimicrobial treatment has to be initiated on an empirical basis, but should be adjusted according to culture results as soon as possible. In patients with an allergy to cephalosporins, aztreonam or gentamicin may be used. When aminoglycosides are necessary, serum levels should be monitored for dose adjustment.
Chloramphenicol, sulphonamides, tetracyclines, rifampicin, amphotericin B and quinolones should be avoided. The use of ceftriaxone must also be avoided due to its undesired side effect of jaundice.

A wide variety of antimicrobials can be used in older children, with the exception of tetracyclines (because of tooth staining). Fluorinated quinolones may produce cartilage toxicity (58), but if necessary, may be used as second-line therapy in the treatment of serious infections, because musculoskeletal adverse events are of moderate intensity and transient (60,61). For a safety period of 24-36 h, parenteral therapy should be administered. When the child becomes afebrile and is able to take fluids, he/she may be given an oral agent to complete the 10-14 days of treatment, which may be continued on an outpatient basis. This provides some advantages, such as less psychological impact on the child and more comfort for the whole family.
It is also less expensive, well tolerated and eventually prevents opportunistic infections (20). The preferred oral antimicrobials are: trimethoprim (TMP), co-trimoxazole (TMP plus sulphamethoxazole), an oral cephalosporin,

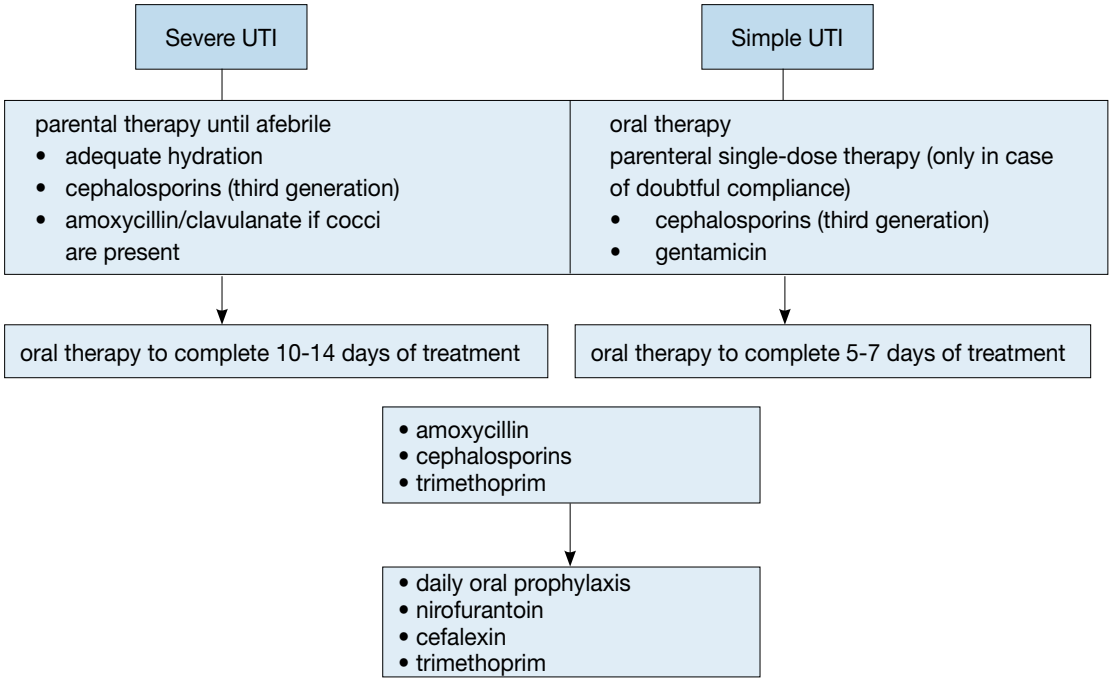
or amoxycillin/clavulanate. However, the indications for TMP are declining in areas with increasing resistance.

In children < 3 years of age, who have difficulty taking oral medications, parenteral treatment for 7-10 days seems advisable, with similar results to those with oral treatment (62).

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

An overview of the treatment of febrile UTIs in children is given in Figure 7.2 and the dosing of antimicrobial agents is outlined in Table 7.3 (63).

Figure 7.2: Treatment of febrile UTIs in children



7.9.2 ***Simple UTIs***

A simple UTI is considered to be a low-risk infection in children. Oral empirical treatment with TMP, an oral cephalosporin or amoxycillin/clavulanate is recommended, according to the local resistance pattern. The duration of treatment in uncomplicated UTIs treated orally should be 5-7 days (64,65) (LE: 1b). A single parenteral dose may be used in cases of doubtful compliance and with a normal urinary tract (66) (LE: 2a). If the response is poor or complications develop, the child must be admitted to hospital for parenteral treatment (67).

7.9.3 ***Prophylaxis***

If there is an increased risk of pyelonephritis, e.g. VUR, and recurrent UTI, low-dose antibiotic prophylaxis is recommended (68,69) (LE; 2a). It may also be used after an acute episode of UTI until the diagnostic work-up is completed. The most effective antimicrobial agents are: nitrofurantoin, TMP, cephalexin and cefaclor (68).

7.10 Acknowledgement

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Table 7.3: Dosing of antimicrobial agents in children aged 3 months to 12 years*

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

BW = body weight.
** Adapted from ref. 63.*

7.11 References

1. Jodal U. The natural history of bacteriuria in childhood. Infect Dis Clin North Am 1987 Dec;1(4):713-29. http://www.ncbi.nlm.nih.gov/pubmed/3333655
2. Jacobson SH, Eklöf O, Eriksson CG, et al. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. BMJ 1989 Sep;299(6701):703-6. http://www.ncbi.nlm.nih.gov/pubmed/2508881

3. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002 Jul;113 Suppl1A:5S-13S. http://www.ncbi.nlm.nih.gov/pubmed/12113866
4. Schulman SL. Voiding dysfunction in children. Urol Clin North Am 2004 Aug;31(3):481-90, ix. http://www.ncbi.nlm.nih.gov/pubmed/15313057
5. Shapiro ED. Infections of the urinary tract. Pediatr Infect Dis J 1992 Feb;11(2):165-8. http://www.ncbi.nlm.nih.gov/pubmed/1741197
6. Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Pediatrics 1999 Apr;103(4):e39. http://www.ncbi.nlm.nih.gov/pubmed/10103331
7. Abrahamsson K, Hansson S, Jodal U, et al. Staphylococcus saprophyticus urinary tract infections in children. Eur J Pediatr 1993 Jan;152(1):69-71. http://www.ncbi.nlm.nih.gov/pubmed/8444210
8. Ma JF, Shortliffe LM. Urinary tract infection in children: etiology and epidemiology. Urol Clin North Am 2004 Aug;31(3):517-26, ix-x. http://www.ncbi.nlm.nih.gov/pubmed/15313061
9. Craig JC, Knight JF, Sureshkuman P, et al. Effect of circumcision on incidence of urinary tract infection in preschool boys. J Pediatr 1996 Jan;128(1):23-7. http://www.ncbi.nlm.nih.gov/pubmed/8551417
10. To T, Agha M, Dick PT, et al. Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection. Lancet 1998 Dec;352(9143):1813-6. http://www.ncbi.nlm.nih.gov/pubmed/9851381
11. Fussell EN, Kaack MB, Cherry R, et al. Adherence of bacteria to human foreskins. J Urol 1988 Nov;140(5):997-1001. http://www.ncbi.nlm.nih.gov/pubmed/2902235
12. Wan J, Kaplinsky R, Greenfield S. Toilet habits of children evaluated for urinary tract infection. J Urol 1995 Aug;154(2 Pt 2):797-9. http://www.ncbi.nlm.nih.gov/pubmed/7609183
13. Yeung CK, Godley ML, Dhillon HK, et al. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. Br J Urol 1997 Aug;80(2):319-27. http://www.ncbi.nlm.nih.gov/pubmed/9284209
14. Lin DS, Huang SH, Lin CC, et al. Urinary tract infection in febrile infants younger than eight weeks of Age. Pediatrics 2000 Feb;105(2):E20. http://www.ncbi.nlm.nih.gov/pubmed/10654980
15. Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev 2005 Apr:18(2):417-22. http://www.ncbi.nlm.nih.gov/pubmed/15831830
16. Cavagnaro F. [Urinary tract infection in childhood.] Rev Chilena Infectol 2005 Jun:22(2):161-8. [Article in Spanish] http://www.ncbi.nlm.nih.gov/pubmed/15891797
17. Watson AR. Pediatric urinary tract infection. EAU Update Series 2, 2004 Sep, pp. 94-100. http://www.journals.elsevierhealth.com/periodicals/euus/article/PIIS1570912404000406/abstract
18. Koch VH, Zuccolotto SM. [Urinary tract infection: a search for evidence.] J Pediatr (Rio J) 2003 May;79 Suppl 1: S97-S106. [Article in Portuguese] http://www.ncbi.nlm.nih.gov/pubmed/14506522
19. Hellerstein, S. Urinary tract infection in children: pathophysiology, risk factors and management. Infect Med 2002;19:554-60. http://cat.inist.fr/?aModele=afficheN&cpsidt=14436165
20. Hoberman A, Wald ER. Urinary tract infections in young febrile children. Pediatr Infect Dis J 1997 Jan;16(1):11-7. http://www.ncbi.nlm.nih.gov/pubmed/9002094
21. Devillé WL, Yzermans JC, van Duijn NP, et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. BMC Urol 2004 Jun;4:4. http://www.ncbi.nlm.nih.gov/pubmed/15175113
22. Wettergren B, Jodal U. Spontaneous clearance of asymptomatic bacteriuria in infants. Acta Paediatr Scand 1990 Mar;79(3):300-4. http://www.ncbi.nlm.nih.gov/pubmed/2333743
23. Stamm WE. Measurement of pyuria and its relation to bacteriuria. Am J Med 1983 Jul;75(1B):53-8. http://www.ncbi.nlm.nih.gov/pubmed/6349345

24. Landau D, Turner ME, Brennan J, et al. The value of urinalysis in differentiating acute pyelonephritis from lower urinary tract infection in febrile infants. Pediatr Infect Dis J 1994 Sep;13(9):777-81. http://www.ncbi.nlm.nih.gov/pubmed/7808845
25. Hoberman A, Chao HP, Keller DM, et al. Prevalence of urinary tract infection in febrile infants. J Pediatr 1993 Jul;123(1):17-23. http://www.ncbi.nlm.nih.gov/pubmed/8320616
26. Piercey KR, Khoury AE, McLorie GA, et al. Diagnosis and management of urinary tract infections. Curr Opin Urol 1993 Feb;3:25-9. http://journals.lww.com/co-urology/Abstract/1993/02010/Diagnosis_and_management_of_pediatric_urinary.8.aspx
27. Jantausch BA, Rifai N, Getson P, et al. Urinary N-acetylbetaglucosaminidase and beta-2-microglobulin in the diagnosis of urinary tract infection in febrile infants. Pediatr Infect Dis J 1994 Apr;13(4):294-9. http://www.ncbi.nlm.nih.gov/pubmed/8036046
28. Benson M, Jodal U, Andreasson A, et al. Interleukin 6 response to urinary tract infection in childhood. Pediatr Infect Dis J 1994 Jul;13(7):612-6. http://www.ncbi.nlm.nih.gov/pubmed/7970949
29. Kass EJ, Fink-Bennett D, Cacciarelli AA, et al. The sensitivity of renal scintigraphy and sonography in detecting nonobstructive acute pyelonephritis. J Urol 1992 Aug;148(2 Pt 2):606-8. http://www.ncbi.nlm.nih.gov/pubmed/1640534
30. Pickworth FE, Carlin JB, Ditchfield MR, et al. Sonographic measurement of renal enlargement in children with acute pyelonephritis and time needed for resolution: implications for renal growth assessment. AJR Am J Roentgenol 1995 Aug;165(2):405-8. http://www.ncbi.nlm.nih.gov/pubmed/7618567
31. Kangarloo H, Gold RH, Fine RN, et al. Urinary tract infection in infants and children evaluated by ultrasound. Radiology 1985 Feb;154(2):367-73. http://www.ncbi.nlm.nih.gov/pubmed/3880909
32. Kass EJ. Imaging in acute pyelonephritis. Curr Opin Urol 1994 Jan;4:39-44.
33. Stutley JE, Gordon I. Vesico-ureteric reflux in the damaged non-scarred kidney. Pediatr Nephrol 1992 Jan;6(1):25-9. http://www.ncbi.nlm.nih.gov/pubmed/1311185
34. Britton KE. Renal radionuclide studies. In: Whitfield HN, Hendry WF, Kirby RS, Duckett JW, eds. Textbook of genitourinary surgery. Oxford: Blackwell Science, 1998; pp. 76-103.
35. Rosenberg AR, Rossleigh MA, Brydon MP, et al. Evaluation of acute urinary tract infection in children by dimercaptosuccinic acid scintigraphy: a prospective study. J Urol 1992 Nov;148(5 Pt 2):1746-9. http://www.ncbi.nlm.nih.gov/pubmed/1331546
36. Jakobsson B, Söderlundh S, Berg U. Diagnostic significance of 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy in urinary tract infection. Arch Dis Child 1992 Nov;67(11):1338-42. http://www.ncbi.nlm.nih.gov/pubmed/1335226
37. Rushton HG, Majd M, Jantausch B, et al. Renal scarring following reflux and nonreflux pyelonephritis in children: evaluation with 99mtechnetium-dimercaptosuccinic acid scintigraphy. J Urol 1992 May;147(5):1327-32. http://www.ncbi.nlm.nih.gov/pubmed/1314912
38. Ransley PG, Risdon RA. Renal papillary morphology in infants and young children. Urol Res 1975 Oct;3(3):111-3. http://www.ncbi.nlm.nih.gov/pubmed/1189138
39. Risdon RA. The small scarred kidney of childhood. A congenital or an acquired lesion. Pediatr Nephrol 1987 Oct;1(4):632-7. http://www.ncbi.nlm.nih.gov/pubmed/3153344
40. Risdon RA, Godley ML, Parkhouse HF, et al. Renal pathology and the 99mTc-DMSA image during the evolution of the early pyelonephritic scar: an experimental study. J Urol 1994 Mar;151(3):767-73. http://www.ncbi.nlm.nih.gov/pubmed/8309003
41. Jakobsson B, Svensson L. Transient pyelonephritic changes on 99mTechnetium dimercaptosuccinic acid scan for at least five months after infection. Acta Paediatr 1997 Aug;86(8):803-7. http://www.ncbi.nlm.nih.gov/pubmed/9307157
42. Rushton HG, Majd M, Chandra R, et al. Evaluation of 99mtechnetium-dimercapto-succinic acid renal scans in experimental acute pyelonephritis in piglets. J Urol 1988 Nov;140(5 Pt 2):1169-74. http://www.ncbi.nlm.nih.gov/pubmed/2846898
43. Bircan ZE, Buyan N, Hasanoglu E, et al. Radiologic evaluation of urinary tract infection. Int Urol Nephrol 1995;27(1):27-32. http://www.ncbi.nlm.nih.gov/pubmed/7615367

44. Elison BS, Taylor D, Van der Wall H, et al. Comparison of DMSA scintigraphy with intravenous urography for the detection of renal scarring and its correlation with vesicoureteric reflux. Br J Urol 1992 Mar;69(3):294-302.
http://www.ncbi.nlm.nih.gov/pubmed/1314684
45. MacKenzie JR, Fowler K, Hollman AS, et al. The value of ultrasound in the child with an acute urinary tract infection. Br J Urol 1994 Aug;74(2):240-4.
http://www.ncbi.nlm.nih.gov/pubmed/7921944
46. Mucci B, Maguire B. Does routine ultrasound have a role in the investigation of children with urinary tract infection? Clin Radiol 1994 May;49(5):324-5.
http://www.ncbi.nlm.nih.gov/pubmed/8013196
47. Westwood ME, Whiting PF, Cooper J, et al. Further investigation of confirmed urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr 2005 Mar;5(1):2.
http://www.ncbi.nlm.nih.gov/pubmed/15769296
48. Haycock GB. A practical approach to evaluating urinary tract infection in children. Pediatr Nephrol 1991 Jul;5(4):401-2.
http://www.ncbi.nlm.nih.gov/pubmed/1654977
49. Kleinman PK, Diamond BA, Karellas A, et al. Tailored low-dose fluoroscopic voiding cystourethrography for the reevaluation of vesicoureteral reflux in girls. AJR Am J Roentgenol 1994 May;162(5):1151-6.
http://www.ncbi.nlm.nih.gov/pubmed/8166001
50. Kass EJ, Kernen KM, Carey JM. Paediatric urinary tract infection and the necessity of complete urological imaging. BJU Int 2000 Jul;86(1):94-6.
http://www.ncbi.nlm.nih.gov/pubmed/10886091
51. De Sadeleer C, De Boe V, Keuppens F, et al. How good is technetium-99m mercaptoacetyltriglycine indirect cystography? Eur J Nucl Med 1994 Mar;21(3):223-7.
http://www.ncbi.nlm.nih.gov/pubmed/8200390
52. Piaggio G, Degl' Innocenti ML, Tomà P, et al. Cystosonography and voiding cystourethrography in the diagnosis of vesicoureteral reflux. Pediatr Nephrol 2003 Jan;18(1):18-22.
http://www.ncbi.nlm.nih.gov/pubmed/12488985
53. Vela Navarrete R. [Urinary tract infections in children.] In: Tratado de urología tomo I. Jiménez Cruz JF, Rioja LA, eds. Barcelona: Ed Prous, 1993; pp. 499-507. [Article in Spanish]
54. Huang JJ, Sung JM, Chen KW, et al. Acute bacterial nephritis: a clinicoradiologic correlation based on computer tomography. Am J Med 1992 Sep;93(3):289-98.
http://www.ncbi.nlm.nih.gov/pubmed/1524081
55. Majd M, Rushton HG, Jantausch B, et al. Relationship among vesicoureteral reflux, Pfimbriated Escherichia coli, and acute pyelonephritis in children with febrile urinary tract infection. J Pediatr 1991 Oct;119(4):578-85.
http://www.ncbi.nlm.nih.gov/pubmed/1681043
56. Melis K, Vandevivere J, Hoskens C, et al. Involvement of the renal parenchyma in acute urinary tract infection: the contribution of 99mTc dimercaptosuccinic acid scan. Eur J Pediatr 1992 Jul;151(7): 536-9.
http://www.ncbi.nlm.nih.gov/pubmed/1327798
57. Smellie JM, Rigden SP. Pitfalls in the investigation of children with urinary tract infection. Arch Dis Child 1995 Mar;72(3):251-8.
http://www.ncbi.nlm.nih.gov/pubmed/7741579
58. Smellie JM, Rigden SP, Prescod NP. Urinary tract infection: a comparison of four methods of investigation. Arch Dis Child 1995 Mar;72(3):247-50.
http://www.ncbi.nlm.nih.gov/pubmed/7741578
59. Broseta E, Jimenez-Cruz JF. [Urinary tract infection in children.] In: Broseta E, Jimenez-Cruz JF, eds. Infeccion urinaria. Madrid: Ed Aula Medica, 1999; pp. 185-194. [Article in Spanish]
60. Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J 2003 Mar;22(12):1128-32.
http://www.ncbi.nlm.nih.gov/pubmed/14688586
61. [No authors listed.] Fluoroquinoles in children: poorly defined risk of joint damage. Prescrire Int 2004 Oct;13(73):184-6.
http://www.ncbi.nlm.nih.gov/pubmed/15499700
62. Bloomfield P, Hodson EM, Craig JC. Antibiotics for acute pyelonephritis in children. Cohrane Database Syst Rev 2005 Jan;(1):CD003772.
http://www.ncbi.nlm.nih.gov/pubmed/15674914

63. Deutsche Gesellschaft für pädiatrische Infektiologie e.V. (DGPI) (ed). [Textbook for infections in children and adolescents.] 4th edn. Futuramed: Munich, 2003, pp. 148-157. [Article in German]
64. Michael M, Hodson EM, Craig JC, et al. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. Cochrane Database Syst Rev 2003;(1):CD003966. http://www.ncbi.nlm.nih.gov/pubmed/12535494
65. Tran D, Muchant DG, Aronoff SC. Short-course versus conventional length antimicrobial therapy for uncomplicated lower urinary tract infections in children: a meta-analysis of 1279 patients. J Pediatr 2001 Jul;139(1):93-9. http://www.ncbi.nlm.nih.gov/pubmed/11445800
66. Khan AJ. Efficacy of single-dose therapy of urinary tract infection in infants and children: a review. J Nalt Med Assoc 1994 Sep;86(9):690-6. http://www.ncbi.nlm.nih.gov/pubmed/7966433
67. Hellerstein S. Urinary tract infections. Old and new concepts. Pediatr Clin North Am 1995 Dec;42(6): 1433-57. http://www.ncbi.nlm.nih.gov/pubmed/8614594
68. Smellie JM, Gruneberg RN, Bantock HM, et al. Prophylactic co-trimoxazole and trimethoprim in the management of urinary tract infection in children. Pediatr Nephrol 1988 Jan;2(1):12-7. http://www.ncbi.nlm.nih.gov/pubmed/3152984
69. Arant BS Jr. Vesicoureteral reflux and evidence-based management. J Pediatr 2001 Nov;139(5):620-1. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/11713435

8. UTIs IN RENAL INSUFFICIENCY, TRANSPLANT RECIPIENTS, DIABETES MELLITUS AND IMMUNOSUPPRESSION

8.1 Summary and recommendations

*8.1.1 **Acute effects of UTI on the kidney***

In acute pyelonephritis, very dramatic changes can occur with focal reduction in perfusion on imaging and corresponding renal tubular dysfunction. However, if the adult's kidney is normal beforehand, chronic renal damage is unlikely. There is no evidence that prolonged or intensive antibiotic treatment of acute pyelonephritis shortens the episode or prevents complications.

In diabetes mellitus, overwhelming infection can predispose to pyogenic infection with intrarenal perinephric abscess formation, emphysematous pyelonephritis, and rarely, a specific form of infective interstitial nephropathy. Papillary necrosis is a common consequence of pyelonephritis in patients with diabetes. Women are more prone to asymptomatic bacteriuria than men with diabetes, but in both sexes, progression to clinical pyelonephritis is more likely than in normal individuals. The risk factors for developing asymptomatic bacteriuria differ between type 1 and type 2 diabetes.

It is arguable that diabetic patients are susceptible to rapid progression of parenchymal infection. However, the clearance of asymptomatic bacteriuria should not be attempted if the intention is to prevent complications, notably acute pyelonephritis (GR: A).

*8.1.2 **Chronic renal disease and UTI***

There are several factors of general potential importance that predispose to infection in uraemia, including the loss of several urinary defence mechanisms and a degree of immunosuppression. Typically, adult polycystic kidney disease (APCKD), gross VUR and end-stage obstructive uropathy harbour infective foci or promote ascending infection, but not invariably so. Clearly, severe UTI with accompanying bacteraemia can hasten progression of renal failure, but there is little evidence that vigorous treatment of lesser degrees of infection or prophylaxis will slow renal functional impairment once it is established (GR: C).

In patients with VUR and UTI in end-stage chronic renal failure, bilateral nephroureterectomy should only be undertaken as a last resort (GR: B).

8.1.2.1 Adult polycystic kidney disease

In patients with acute pyelonephritis and infected cysts (presenting as recurrent bacteraemia or local sepsis), treatment requires a long course of high-dose systemic fluoroquinolones, followed by prophylaxis. Bilateral

nephrectomy should be utilised as a last resort (GR: B).

8.1.2.2 Calculi and UTI

Management is similar to that for patients without renal impairment, i.e. to clear the stones if possible and to minimise antibiotic treatment if the calculus cannot be removed. Nephrectomy should be performed as a last resort, but even residual renal function may be of vital importance (GR: B).

8.1.2.3 Obstruction of the urinary tract and UTI

As in all other situations, the combination of obstruction and infection is dangerous and should be treated vigorously. Obstruction may be covert and require specific diagnostic tests, e.g. video-urodynamics, or upper urinary tract pressure flow studies.

*8.1.3 **UTI in renal transplantation and immunosuppression***

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

Immunosuppression is of secondary importance, although if this is extreme, it can promote persistent bacteriuria, which may become symptomatic. In the context of renal transplantation, UTI is very common, but immunosuppression is only one of many factors that are mainly classified as 'surgical'.

HIV infection is associated with acute and chronic renal disease, possibly through the mechanisms of thrombotic microangiopathy and immune-mediated glomerulonephritis. Steroids, angiotensin-converting enzyme (ACE) inhibitors and highly active retroviral therapy appear to reduce progression to end-stage renal disease.

*8.1.4 **Antibiotic treatment for UTI in renal insufficiency and after renal transplantation***

The principles of antibiotic treatment for UTI in the presence of renal impairment, during dialysis treatment and after renal transplantation are discussed in the text and summarised in Tables 8.1-8.4.

8.2 Background

Whenever UTI is present in patients with renal insufficiency, problems arise in both the treatment of infection and the management of renal disease. There are also important scientific issues to be considered concerning the cause, special susceptibilities, effects and complications of renal parenchymal infection, particularly in the immunosuppressed patient.

This part of the guidelines can be subdivided into four sections.

1. What are the acute effects of UTI on the kidney and do the lesions become chronic?
2. Does chronic renal disease progress more quickly as a result of infection, and do particular renal diseases predispose to UTI?
3. Are immunosuppressed patients prone to UTI, particularly in the context of renal transplantation? Is UTI a significant cause of graft failure?
4. Which problems arise in antibiotic therapy in patients with renal insufficiency and after renal transplantation?

8.3 Acute effects of UTI on the kidney

Some authors regard acute pyelonephritis as complicated because, in their view, it may cause renal scarring in a previously normal kidney (1,2) (LE: 2a). Pathologically, a similar process may occur in such fundamentally different situations as obstructive and reflux nephropathy, although the distribution and extent of the lesions may be different (3-5) (LE: 2a).

*8.3.1 **VUR and intrarenal reflux***

The effects of VUR and intrarenal reflux on the renal parenchyma, and the contribution of ascending infection are still unresolved. Renal scarring can certainly be acquired as a result of these three factors, although, in almost all cases, this usually occurs very early in life. In this narrow age range, developmental renal dysplasia must be a major consideration in the pathogenesis of chronic pyelonephritis.

Although acute infection is important in the early stages of this disease, the status of either recurrent acute UTI or asymptomatic bacteriuria specifically in the progression of scar formation is tenuous. Prophylactic antibiotics therefore offer little benefit in preserving renal tissue in reflux nephropathy in older children and adults, even if the reflux has not already been successfully treated (6) (GR: A). However, further discussion of reflux nephropathy is beyond the scope of these guidelines.

8.3.2 ***Obstructive neuropathy***

Obstruction occurring through a voiding disorder or supravesically causes renal tubular dysfunction and ultimately renal damage, mainly through the process of apoptosis. Infection enhances the process of parenchymal loss. In extreme cases, pyonephrosis, perinephric abscess and widespread systemic sepsis develop. Obstruction has to be cleared if infection is to be eradicated (7) (GR: A).

A detailed discussion of obstructive nephropathy is not appropriate here, but the kidney that is permanently damaged by any cause has less reserve to withstand the effects of reflux, obstruction and infection. In any circumstances, the combination of obstruction and infection is a surgical emergency and both must be relieved without delay. It is sometimes difficult to exclude an element of obstruction when discussing the pathogenesis of putative infective renal damage in the alleged normal kidney. Urinary calculi and pregnancy can cause urinary stasis and an intermittent increase in pressure in the upper urinary tract, which can cause subtle and persistent damage.

8.3.3 ***Renal effects of severe UTI***

Severe infection can lead to renal functional impairment through sepsis, endotoxaemia, hypotension and poor renal perfusion, as part of the process of multiorgan failure. The presence of renal calculi and diabetes mellitus further reduces host defences (8).

8.3.4 ***Acute effects of UTI on the normal kidney***

The acute effects of UTI on the normal kidney are complex. They are worth reviewing because they may provide a lead in deciding how chronic changes can occur and therefore a basis for the development of guidelines on the prevention of renal damage.

E. coli is the most common of the Gram-negative bacteria that are isolated in the majority of patients with acute pyelonephritis. The proportion of infections caused by *E. coli* is lower in adults than children (69% vs. 80%) (9) (LE: 2b).

Virulent microorganisms cause direct cellular injury, usually after colonising the renal pelvis. Damage can also occur indirectly from the effects of inflammatory mediators. Metastatic infection rarely causes renal infection, which presents as cortical abscesses, and usually only in susceptible individuals (see section 8.3.6.1 on Diabetes mellitus and section 8.7 on Immunosuppression) (10).

Bacterial infection in the urinary tract can induce fever and elevate acute phase reactants, such as C-reactive protein, and erythrocyte sedimentation rate (ESR). Bacterial infection also elicits immunoglobulin A and cytokine responses (11) (LE: 2b). In particular, serum levels of IL-6 and IL-8 are elevated (12,13) (LE: 2b). Tissue damage is reflected by urinary secretion of tubular proteins and enzymes, such as α2-macroglobulin, β2-microglobulin and N-acetyl-β-D-glucosaminidase. In functional terms, there may be a loss of concentrating power that can persist in the long term (14,15) (LE: 2b). The fact that there is a serological immune response and bacteria become coated with antibodies to various antigenic components of the microorganism is regarded as evidence of an immune response, and therefore, of exposure to microorganisms that are potentially damaging to the renal parenchyma (16) (LE: 2b).

There are many identifiable factors relating to virulence of the bacterial cell and to its ability to adhere to the mucosa as a preliminary to invasion (17). For example, type 1 pili or fimbriae combine with mannose receptors on the uromucoid, which is part of the protective mucopolysaccharide layer found on uroepithelial cells lining the urinary tract. Type 2 or P fimbriae bind to glycolipids of the blood group substances that are secreted by the host urothelium. In practical terms, *E. coli*, which is pathological to the kidney, appears to express P (or pyelonephritis-associated) or type 2 fimbriae, at least in children in whom 90% of individuals with acute pyelonephritis express these bacteria, compared with a much smaller proportion of those who have had cystitis or asymptomatic bacteriuria (18) (LE: 2b).

Bacterial adhesion may be of variable benefit to the bacterium, because its attachment may mean that it is easier for host defence mechanisms to localise and abolish it (19). The cellular and humoral inflammatory host response is also a crucial part of host defences. Various cytokines (e.g. IL-6 and IL-8) are responsible for inducing leukocyte migration, and may be intrinsically deficient in converting asymptomatic bacterial colonisation to clinical infection.

Paradoxically, reduced adhesiveness can facilitate silent penetration into the renal parenchyma. In a Swedish study, a group of 160 patients who had recently suffered acute UTI all developed reduced concentrating power, even though a significant proportion (40%) did not develop a febrile illness. In the majority of these patients, the infiltrating bacteria had reduced adhesive characteristics, perhaps facilitating their penetration into the renal parenchyma and promoting more permanent structural and functional damage (15) (LE: 2b).

8.3.5 ***Renal scarring***

The possible development of scarring, as a result of UTI in the absence of reflux, obstruction or calculi, is

controversial (20) (LE: 2a). It is agreed that dramatic reduction in renal perfusion and excretion can occur acutely and so-called 'lobar nephronia' has been demonstrated with the newer methods of imaging, such as CT or DMSA scanning, but not with standard intravenous urography (IVU).

A study has shown that 55% of patients with no pre-existing lesions developed acute parenchymal lesions during an episode of acute pyelonephritis (2) (LE: 2a). These lesions were found to have persisted after 3-6 months follow-up in 77% of patients (9) (LE: 3).

An earlier study by Alwall (21) involved 29 women who were followed for 20-30 years, with evidence of increasing renal damage and chronic pyelonephritis upon biopsy (LE: 3). That study used cruder diagnostic techniques, which might not have identified pre-existing disease, therefore, patients may have had renal damage initially. Over such a long period, it was impossible to exclude other causes of renal impairment and interstitial nephropathy, e.g. analgesic abuse. This important issue is clarified by a recent more critical study of DMSA scanning during the acute phase of acute pyelonephritis. In this study, 37 of 81 patients had one or more perfusion defects, of which, the majority resolved within 3 months. In lesions that persisted, further imaging invariably showed evidence of reflux or obstructive nephropathy that must have predated the acute infective episode (22) (LE: 2a).

In summary, small parenchymal scars demonstrated by modern imaging may develop as a result of acute non-obstructive pyelonephritis. However, such patients do not develop chronic renal failure and the scar is a very different lesion from the typical scar of reflux nephropathy. This is reflected in clinical experience. Thus, in acute pyelonephritis, IVU or DMSA scanning during an acute urinary infection can have alarming and dramatic results, but in practical terms the observed changes mostly resolve.

The poor correlation between the severity of the symptoms in an episode of acute pyelonephritis and the risk of permanent damage, which is very small, should discourage the clinician from prescribing excessive antibiotic treatment beyond that needed to suppress the acute inflammatory reaction (GR: A).

In future, the rare occurrence of renal damage apparently arising from acute or recurrent uncomplicated UTI may be prevented by targeting long-term treatment at selected patients. These patients will have been identified as having an intrinsic genetic defect in the host response of cytokine release to infection. Such a genetic defect would be even more important if a patient also had structural abnormalities that cause complicated UTI.

*8.3.6 **Specific conditions in which an acute UTI causes renal damage***

There are several specific conditions in which acute UTI can cause renal damage.

8.3.6.1 Diabetes mellitus

Asymptomatic bacteriuria is common in diabetic women. In a prospective study of non-pregnant women with diabetes mellitus, 26% had significant bacteriuria ($\geq 10^5$ cfu/mL) compared with 6% of controls. Women with type 1 diabetes are particularly at risk if they have had diabetes for a long time or complications have developed, particularly peripheral neuropathy and proteinuria. Risk factors in patients with type 2 diabetes were old age, proteinuria, a low body mass index and a past history of recurrent UTIs (23) (LE: 2a).

Diabetes mellitus increases the risk of acute pyelonephritis from infection by Enterobacteriaceae that originate in the lower urogenital tract. *Klebsiella* infection is particularly common (25% compared with 12% in non-diabetics).

Asymptomatic bacteriuria is common in women with diabetes (though not in men). If left untreated, it may lead to renal functional impairment (24). The mechanism is ill-understood and, as in uncomplicated acute pyelonephritis, a direct causal link is dubious. Other subtle factors may be present, such as underlying diabetic nephropathy (25) and autonomic neuropathy that causes voiding dysfunction. Impaired host resistance is thought to predispose to persistence of nephropathogenic organisms, but specific evidence is lacking for the development of renal complications. Glycosuria inhibits phagocytosis and perhaps cellular immunity, and encourages bacterial adherence. However, diabetic women with asymptomatic bacteriuria can have good glycaemic control, but still show reduced urinary cytokine and leukocyte concentrations (although polymorph function is normal). Poor glycaemic control has not been shown to increase the risk of bacteriuria (26).

It has always been recognised that diabetic patients are particularly susceptible to rapid progression of renal parenchymal infection and ensuing complications. Until recently, there was no consensus on the questions of pre-emptive screening, treatment and prophylaxis of asymptomatic bacteriuria. However, these issues have been addressed in a placebo-controlled, double-blind randomised trial (27) (LE: 1b), which has concluded that treatment does not reduce complications, and diabetes should not therefore be regarded as an indication for screening or treatment of asymptomatic bacteriuria. The findings from this trial have been subsequently recognised in the guidelines published by the Infectious Diseases Society of America (IDSA) on the diagnosis and treatment of asymptomatic bacteriuria in general (28).

Diabetic patients are also prone to an under-reported and probably unusual form of infective interstitial nephritis, which sometimes includes infection by gas-forming organisms, with a high mortality (emphysematous

pyelonephritis) (29). This is characterised histologically by acute pyogenic infiltration with micro-abscesses and the development of acute renal failure. The origin of the organisms may be haematogenous. Even in the absence of obstruction, acute parenchymal infection may progress insidiously to form an intrarenal abscess that ruptures, which leads to a perinephric collection and a psoas abscess. The presentation can occasionally be indolent.

Papillary necrosis is common in diabetics, particularly in association with acute pyelonephritis. It is certainly associated with permanent renal parenchymal scarring, although it is difficult to exclude obstruction by the sloughed papillae as the cause of the nephropathy. Antibiotic prophylaxis for the treatment of asymptomatic bacteriuria is probably required (GR: C).

8.3.6.2 Tuberculosis

Tuberculosis can cause acute and chronic renal damage through bilateral renal infiltration. Rarely, this can lead to end-stage renal failure. However, a more subtle form of interstitial granulomatous disease can occur, which is sufficient to cause renal failure in the absence of fibrosis, calcification or obstruction (30,31) (LE: 3).

Tuberculosis and leprosy can cause renal damage through the development of amyloid and a form of proliferative glomerulonephritis (32,33) (LE: 2b). For more details see the EAU guidelines on genitourinary tuberculosis (34).

8.4 Chronic renal disease and UTI

There are good reasons why all uraemic patients should be prone to UTI, and why UTI should increase the rate of deterioration of renal function. The antibacterial properties of normal urine, due to urea or low pH and high osmolality, may be lost (35). Uraemic patients are also mildly immunosuppressed and the formation of protective uroepithelial mucus may be inhibited (36-38) (LE: 2b).

However, apart from a few exceptions, there is little evidence for a causal relationship between pre-existing chronic renal disease and persistent UTI (7). The results of removing a scarred or hydronephrotic kidney in the hope of curing infection are often disappointing.

The few exceptions include the following.

*8.4.1 **Adult dominant polycystic kidney disease (ADPKD)***

Urinary tract infection is a prominent complication of ADPKD, with symptomatic UTI being the presenting feature in 23-42% of patients, who are usually female (39). It may be difficult to obtain a positive culture on standard laboratory media, but pyuria is common, particularly in the later stages of disease progression. Acute pyelonephritis is common and may originate from pyogenic infection in the cysts (40) (LE: 3).

The efficacy of antibiotic treatment may depend on whether cysts are derived from proximal (active secretion) or distal tubules (passive diffusion) and on the lipid solubility of the agent used. Cephalosporins, gentamicin and ampicillin, which are standard treatments of acute pyelonephritis and require active transport, are often ineffective (41) (LE: 2b). Fluoroquinolones are generally the most effective (GR: A).

After transplantation, overall graft and patient survival rates do not differ between ADPKD and control groups (42) (LE: 2a). However, despite close monitoring of patients, UTI and septicaemic episodes are still a significant cause of morbidity, such that bilateral nephrectomy may be the only option.

Polycystic disease is not to be confused with acquired renal cystic disease of the end-stage kidney, which has no predisposition to UTI.

The issue of whether urological complications, including UTI, affect the progression of renal failure in polycystic disease or in any other renal pathology is controversial. Severe symptomatic UTIs may indicate an adverse prognosis, particularly in men with ADPKD.

*8.4.2 **Renal calculi***

Nephrolithiasis, particularly from infective struvite stones, obstructive uropathy and gross reflux, clearly does promote infection, although not always. However, it is doubtful whether vigorous treatment of asymptomatic bacteriuria or even mild clinical UTI makes any difference to the progression of renal disease (43) (LE: 3).

It is disappointing that, as yet, few studies have provided long-term serial data that identify renal damage and its causal relationship with infection. In this respect, it is of some interest that a study of 100 patients who underwent reflux prevention surgery at least 20 years before has recently been published (44). It was concluded that even patients whose reflux prevention surgery had been successful were prone to recurrent UTI, hypertension and complications, which even occasionally included progressive renal scarring. Such consequences should at least inform the patient's decision in deciding between surgical and medical treatment of VUR.

8.5 UTI in renal transplantation

Urinary tract infection is common after renal transplantation. Bacteriuria is present in 35-80% of patients, although the risk has been reduced by improvements in donation surgery, which have lowered the dose of immunosuppressive therapy and prophylactic antibiotics (45).

8.5.1 ***Donor organ infection***

Early factors predisposing to UTI include infection in the transplanted kidney. Clearly, the organ donor should be screened for a variety of viral and bacterial infections. Detailed discussion of this process is beyond the limits of these guidelines. However, it must be acknowledged that the urinary tract of the cadaver donor is rarely investigated, even if the mid-stream urine (MSU) culture is positive. Antibiotics are given empirically, but usually the first suspicion of occurrence of a renal tract abnormality is raised during the organ donation operation. Under these circumstances, only the most obvious renal or ureteric abnormality will be detected. Very occasionally, organ donation will be abandoned at this late stage.

After the kidney is removed from its storage box, the effluent from the renal vein and surrounding fluid in the sterile plastic bags that contain the excised kidney should ideally be cultured because microorganisms are likely to have been introduced during the donation process. Bladder catheters and ureteric stents promote the loss of the glycosoaminoglycan layer from the uroepithelium, as well as providing a source of microorganisms within the mucous biofilm that covers the foreign body. Infection in the native kidney may worsen considerably as a result of maximum immunosuppression.

In renal transplant recipients, the following problems are most troublesome: papillary necrosis, particularly in diabetes mellitus (46), massive infective VUR, polycystic disease, and infective calculi. There is also concern about the increasing number of children with congenital uropathy, often associated with neuropathic bladder dysfunction and the sinister combination of intravesical obstruction, poor bladder compliance, residual urine, and VUR. A full urodynamic assessment, establishing a routine of intermittent self-catheterisation and any necessary bladder surgery must be completed well in advance of renal transplantation.

Urinary diversions and bladder augmentation and substitution have also been successfully completed in patients on dialysis treatment and after transplantation, although bacteriuria is common and may require antibiotic treatment (47).

In the first 3 months, UTI is more likely to be symptomatic with a high rate of relapse. Later on, there is a lower rate of pyelonephritis and bacteraemia, and a better response to antibiotics unless there are urological complications (e.g. fistula, or obstruction of the urinary tract). Infarction, either of the whole kidney or of a segment due to arterial damage, can promote UTI through bacterial colonisation of dead tissue. This often occurs by commensal or fastidious pathogens. The infection may be impossible to eradicate until the kidney, or at least the dead segment, is removed.

8.5.2 ***Graft failure***

There are several potential mechanisms by which severe UTI can cause graft failure. There was an early suggestion that reflux into the graft could lead to pyelonephritis and parenchymal scarring. However, these findings have not been confirmed and most surgeons do not make a special effort to perform an antireflux anastomosis.

Infection can theoretically induce graft failure by three other mechanisms, such as by the direct effect of cytokines, growth factors (e.g. tumour necrosis factor [TNF]) and free radicals as part of the inflammation cascade (45). UTIs can also reactivate cytomegalovirus infection, which can lead to acute transplant rejection. Sometimes it can be very difficult to distinguish rejection from infection (48) (LE: 2b).

For many years, the polyomavirus type BK has been listed as a possible candidate for causing transplant ureteric stenosis. Improved detection of so-called ‘decoy cells’ in urine and of virus DNA by polymerase chain reaction has confirmed the causal relationship between infection and obstruction, but also with interstitial nephropathy progressing to graft loss in possibly 5% of recipients. The virus is susceptible to treatment with the antiviral agent cidofovir (49) (LE: 2a).

8.5.3 ***Kidney and whole-organ pancreas transplantation***

Simultaneous kidney and whole-organ pancreas transplantation can present specific urological complications when the bladder is chosen for drainage of exocrine secretions. These may include recurrent UTI, chemical urethritis and bladder calculi of sufficient severity to warrant cystoenteric conversion. The risk of such complications is minimised if urodynamic abnormalities, e.g. obstruction, are identified and corrected well in advance of the transplant procedure (50) (LE: 3).

8.6 Antibiotic therapy in renal failure and transplant recipients

Much of the detailed information on antibiotics prescribed in renal failure are summarised in Tables 8.1-8.5 and Appendix 16.3. It is important to note that peritoneal dialysis and haemodialysis clear certain antibiotics, which

should either be avoided or given at much higher doses. Also, there are important interactions to consider between immunosuppressive agents and antibiotics.

Table 8.1: Use of antibiotics for UTI with renal impairment

Most antibiotics have a wide therapeutic index. No adjustment of dose is necessary until GFR < 20 mL/min, except antibiotics with nephrotoxic potential, e.g. aminoglycoside.
Drugs removed by dialysis should be administered after dialysis treatment.
Combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic.
Nitrofurantoin and tetracyclines are contraindicated, but not doxycycline.

GFR = glomerular filtration rate.

Table 8.2: Clearance of antibiotics at haemodialysis

Dialysed	**Slightly dialysed**	**Not dialysed**
Amoxycillin/ampicillin	Fluoroquinolones*	Amphotericin
Carbenicillin	Co-trimoxazole	Methicillin
Cephalosporins*	Erythromycin	Teicoplanin
Aminoglycosides*	Vancomycin	
Trimethoprim		
Metronidazole		
Aztreonam*		
Fluconazole*		

** Drugs cleared by peritoneal dialysis.*

Table 8.3: Treatment of tuberculosis in renal failure

Rifampicin and isoniazid (INH) not cleared by dialysis. Give pyridoxine.
Ethambutol not dialysed. Reduce dose if GFR < 30 mL/min.
Avoid rifampicin with cyclosporin.

GFR = glomerular filtration rate.

Table 8.4: Recommendations for prevention and treatment of UTI in renal transplanation

Treat infection in recipient before transplantation.
Culture donor tissue sample and perfusate.
Perioperative antibiotic prophylaxis.
Six months low-dose TMP-SMX (co-trimoxazole) (LE: 1b, GR: A).
Empirical treatment of overt infection (quinolone, TMP-SMX for 10-14 days).

TMP-SMX = trimethoprim-sulphamethoxazole.

Table 8.5: Drug interactions with cyclosporin and tacrolimus

Rifampicin
Erythromycin
Aminoglycosides
TMP-SMX
Amphotericin B

TMP-SMX = trimethoprim-sulphamethoxazole.

8.6.1 ***Treatment of UTI in renal transplant recipients***

The treatment of a symptomatic UTI is similar to treatment given to non-transplant patients. However, a short course of treatment has yet to be established, and in most cases a 10-14-day course of treatment is given.

The choice of antibiotic is dictated by the special need for penetration into the renal parenchyma rather than for merely a 'mucosal' antibiotic. Fluoroquinolones seem to be particularly effective.

There is good evidence for the beneficial effects of treating asymptomatic bacteriuria in the first six months after renal transplantation (51) (LE: 2a). Patients must be investigated for surgical complications.

In most units, the combination of trimethoprim and sulphamethoxazole (co-trimoxazole) is effective in preventing UTI (52) (LE: 1b). It will also prevent *Pneumocystis carinii* pneumonia (PCP) and infection with other rare fastidious organisms. Low-dose antibiotic prophylaxis with co-trimoxazole has been recommended for six months after transplantation. This will cover the high-risk period when infection is more likely to be symptomatic and associated with acute graft impairment. At a low dose, adverse interactions with cyclosporin do not occur, although the higher dose advocated by some units results in synergistic nephrotoxicity with trimethoprim.

A number of other drug interactions need to be considered, e.g. gentamicin, co-trimoxazole and amphotericin B promote cyclosporin and tacrolimus toxicity. Rifampicin and erythromycin also interact with calcineurin inhibitors by increasing cytochrome p450 synthetase and inhibiting hepatic cyclosporin A metabolism.

In any patients with relapsing or recurrent infection, an anatomical cause, such as a urological complication in the transplant kidney or recipient bladder dysfunction, must be considered and treated vigorously.

8.6.2 ***Fungal infections***

Candidal infections can occur in any immunosuppressed patient, but are more common in diabetic patients and those with chronic residual urine and in whom there is an indwelling catheter or stent. It is wise to treat all patients with antifungal agents (fluconazole, amphotericin B plus flucytosine) even when they are asymptomatic. Removal of the catheter or stents is usually necessary (GR: B).

8.6.3 ***Schistosomiasis***

Schistosomiasis is a familiar problem for patients treated for end-stage renal failure from locations where the disease is endemic. Renal transplantation is possible, even when live donors and recipients have active lesions, provided they are treated. Combined medication (praziquantil and oxaminoquine) is recommended for 1 month. In a trial that compared infected patients with those free of schistosomiasis, there was no difference between the incidence of acute and chronic rejection. However, UTI and urological complications occurred in the infected group and a higher cyclosporin dose was required. Despite this, however, it was concluded that active schistosomiasis did not preclude transplantation (53) (LE: 3). For further details on schistosomiasis in genitourinary tract infections see Bichler et al. (54).

8.7 Immunosuppression

It is well known that viral and fungal infections are common in immunosuppressed patients.

8.7.1 ***Human immunodeficiencey virus (HIV) infection***

HIV infection can lead to acute renal failure through non-specific severe systemic illness, and to chronic renal failure through a variety of nephropathies. These include HIV-induced thrombotic microangiopathy, immune-mediated glomerulonephritis and nephropathy due to virus-induced cellular damage, primarily to the glomerular epithelial cell. Combination therapy using corticosteroids, ACE inhibitors and highly active antiretroviral therapy seems to delay and prevent progression of nephropathy, although evidence from randomised trials is not available (55). HIV infection is therefore no longer a contraindication to renal replacement therapy.

The place of immunosuppression per se in the development of UTI remains unresolved (56). Patients with end-stage renal failure are generally not particularly susceptible to the usual Gram-negative urinary pathogens, although they may acquire unusual and granulomatous infections. Patients have evidence of reduced cellular and humoral immunity.

However, the situation is a little clearer in male patients with HIV and AIDS, in whom there is a close relationship between CD4 counts and the risk of bacteriuria, particularly in patients whose counts are < 200 cells/mL (57). About 40% of patients with bacteriuria are asymptomatic. In these patients, PCP prophylaxis of the type used in transplant patients may not reduce the rate of bacteriuria, perhaps due to the previous development of resistant organisms.

8.7.2 ***Viral and fungal infections***

Viral and fungal infections are relatively common in immunosuppressed patients.

8.8 References

1. Kincaid-Smith P, Fairley KF. Complicated urinary tract infection in adults. In: Cattell WR, ed. *Infections of the kidney and urinary tract*. Oxford: Oxford Medical Publications (Oxford University Press), 1996, pp. 186-205.
2. Meyrier A, Condamin MC, Fernet M, et al. Frequency of development of early cortical scarring in acute primary pyelonephritis. Kidney Int 1989 Feb;35(2):696-703. http://www.ncbi.nlm.nih.gov/pubmed/2651759
3. Matz LR, Hodson CJ, Craven JD. Experimental obstructive nephropathy in the pig. 3. Renal artery changes in experimental hydronephrosis, with special reference to renal artery stenosis due to fibromuscular hyperplasia. Br J Urol 1969 Dec;41 Suppl:36-41. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5359479
4. Hodson CJ, Maling TM, McManamon PJ, et al. The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). Br J Radiol 1975;Suppl 13:1-26. http://www.ncbi.nlm.nih.gov/pubmed/766885
5. Bishop MC. Obstructive uropathy. In: Mundy AR, ed. *Scientific basis of urology*. Edinburgh: Churchill Livingstone 1987, pp. 115-151.
6. Bailey RR. Vesico-ureteric reflux and reflux nephropathy. In: Cameron S et al., eds. *Oxford textbook of clinical nephrology*. Oxford: Oxford University Press,1992, pp. 1983-2002.
7. Bishop MC. Urosurgical management of urinary tract infection. J Antimicrob Chemother 1994 May;33 Suppl A:74-91. http://www.ncbi.nlm.nih.gov/pubmed/7928839
8. Roberts JA. Management of pyelonephritis and upper urinary tract infections. Urol Clin North Am 1999 Nov;26(4):753-63. http://www.ncbi.nlm.nih.gov/pubmed/10584616
9. Fraser IR, Birch D, Fairley KF, et al. A prospective study of cortical scarring in acute febrile pyelonephritis in adults: clinical and bacteriological characteristics. Clin Nephrol 1995 Mar;43(3): 159-64. http://www.ncbi.nlm.nih.gov/pubmed/7774071
10. George NJ. Urinary tract infection. In: Mundy AR, George NJ, Fitzpatrick JM, Neill DE, eds. *Scientific basis of urology*. 2nd edition. ISIS Medical Media, 1998, pp. 143-173.
11. Svanborg C, de Man P, Sandberg T. Renal involvement in urinary tract infection. Kidney Int 1991 Mar;39(3):541-9. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/2062037
12. Hedges S, Stenqvist K, Lidin-Janson G, et al. Comparison of urine and serum concentrations of interleukin-6 in women with acute pyelonephritis or asymptomatic bacteriuria. J Infect Dis 1992 Sep;166(3):653-6. http://www.ncbi.nlm.nih.gov/pubmed/1500753
13. Jacobson SH, Hylander B, Wretlind B, et al. Interleukin-6 and interleukin-8 in serum and urine in patients with acute pyelonephritis in relation to bacterial- virulence-associated traits and renal function. Nephron 1994;67(2):172-9. http://www.ncbi.nlm.nih.gov/pubmed/7915403
14. Ronald AR, Cutler RE, Turck M. Effect of bacteriuria on renal concentrating mechanisms. Ann Intern Med 1996 Apr;70(4):723-33. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5771530
15. de Man P, Cläeson I, Johnson IM, et al. Bacterial attachment as a predictor of renal abnormalities in boys with urinary tract infection. J Pediatr 1989 Dec;115(6):915-22. http://www.ncbi.nlm.nih.gov/pubmed/2685219
16. Percival A, Birumfitt W, Delouvois J. Serum antibody levels as an indication of clinically inapparent pyelonephritis. Lancet 1964 Nov;2:1027-33. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/14206013
17. Wullt B, Bergsten G, Fischer H. Application of laboratory research in UTI. European Urology EAU Update Series 2, 2004, pp. 116-124.
18. Kallenius G, Mollby R, Svenson SB, et al. Occurrence of Pfimbriated Escherichia coli in urinary tract infections. Lancet 1981 Dec;2(8260-8261):1369-72. http://www.ncbi.nlm.nih.gov/pubmed/6171697
19. Mulvey MA, Schilling JD, Martinez JJ, et al. Bad bugs and beleaguered bladders: interplay between uropathogenic Escherichia coli and innate host defenses. Proc Natl Acad Sci USA 2000 Aug;97(16):8829-35. http://www.ncbi.nlm.nih.gov/pubmed/10922042

20. Gordon I, Barkovics M, Pindoria S, et al. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and metaanalysis. J Am Soc Nephrol 2003 Mar;14(3):739-44.
http://www.ncbi.nlm.nih.gov/pubmed/12595511
21. Alwall N. On controversial and open questions about the course and complications of non-obstructive urinary tract infection in adult women. Follow-up for up to 80 months of 707 participants in a population study and evaluation of a clinical series of 36 selected women with a history of urinary tract infection for up to 40 years. Acta Med Scand 1978;203(5):369-77. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/665302
22. Bailey RR, Lynn KL, Robson RA, et al. DMSA renal scans in adults with acute pyelonephritis. Clin Nephrol 1996 Aug;46(2):99-104.
http://www.ncbi.nlm.nih.gov/pubmed/8869786
23. Geerlings SE, Stolk RP, Camps MJ, et al. Asymptomatic bacteriuria may be considered a complication in women with diabetes. Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht Study Group. Diabetes Care 2000 Jun;23(6):744-9.
http://www.ncbi.nlm.nih.gov/pubmed/10840989
24. Ooi BS, Chen BT, Yu M. Prevalence and site of bacteriuria in diabetes mellitus. Postgrad Med J 1974 Aug;50(586):497-9.
http://www.ncbi.nlm.nih.gov/pubmed/4464512
25. Korzeniowski OM. Urinary tract infection in the impaired host. Med Clin North Am 1991 Mar;75(2): 391-404.
http://www.ncbi.nlm.nih.gov/pubmed/1996041
26. Mackie AD, Drury PL. Urinary tract infection in diabetes mellitus. In: Cattell WR, ed. *Infections of the kidney and urinary tract*. Oxford: Oxford, Medical Publications (Oxford University Press), 1996, pp. 218-233.
27. Harding GK, Zhanel GG, Nicolle LE, et al; Manitoba Diabetes Urinary Tract Infection Study Group. Antimicrobial treatment of diabetic women with asymptomatic bacteriuria. N Eng J Med 2002 Nov;347(20):1576-83.
http://www.ncbi.nlm.nih.gov/pubmed/12432044
28. Nicolle LE, Bradley S, Colgan R, et al; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005 Mar;40(5):643-54.
http://www.ncbi.nlm.nih.gov/pubmed/15714408
29. Cattell WR. Urinary tract infection and acute renal failure. In: Raine AE, ed. *Advanced renal medicine*. Oxford: Oxford University Press, 1992, pp. 302-313.
30. Mallinson WJ, Fuller RW, Levison DA, et al. Diffuse interstitial renal tuberculosis - an unusual cause of renal failure. Q J Med 1981 Mar;50(198):137-48.
http://www.ncbi.nlm.nih.gov/pubmed/7302115
31. Morgan SH, Eastwood JB, Baker LR. Tuberculous interstitial nephritis - the tip of an iceberg? Tubercle 1990 Mar;71(1):5-6. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/2371760
32. McAdam KP, Anders RF, Smith SR, et al. Association of amyloidosis with erythema nodosum leprosum reactions and recurrent neutrophil leucocytosis in leprosy. Lancet 1975 Sep;2(7935):572-3.
http://www.ncbi.nlm.nih.gov/pubmed/51405
33. Ng WL, Scollard DM, Hua A. Glomerulonephritis in leprosy. Am J Clin Pathol 1981 Sep;76(3):321-9.
http://www.ncbi.nlm.nih.gov/pubmed/6456662
34. Çek M, Lenk S, Naber KG, et al; Members of the Urinary Tract Infection (UTI) Working Group of the European Association of Urology (EAU) Guidelines Office. EAU guidelines for the management of genitourinary tuberculosis. Eur Urol 2005 Sep;48(3):353-62.
http://www.ncbi.nlm.nih.gov/pubmed/15982799
35. Neal DE Jr. Host defense mechanisms in urinary tract infections. Urol Clin North Am 1999 Nov;26(4):677-86, vii.
http://www.ncbi.nlm.nih.gov/pubmed/10584610
36. Khan I H, Catto GR. Long-term complications of dialysis: infection. Kidney Int Suppl 1993 Jun;41:S143-S148.
http://www.ncbi.nlm.nih.gov/pubmed/8320909
37. Kessler M, Hoen B, Mayeux D, et al. Bacteremia in patients on chronic hemodialysis. A multicenter prospective survey. Nephron 1993;64(1):95-100.
http://www.ncbi.nlm.nih.gov/pubmed/8502343

38. Saitoh H, Nakamura K, Hida M, et al. Urinary tract infection in oliguric patients with chronic renal failure. J Urol 1985 Jun;133(6):990-3.
http://www.ncbi.nlm.nih.gov/pubmed/3999225
39. Elzinga LW, Bennett WM. Miscellaneous renal and systemic complications of autosomal dominant polycystic kidney disease including infection. In: Watson ML and Torres VE, eds. Polycystic kidney disease. Oxford: Oxford Clinical Nephrology series. Oxford: Oxford University Press, 1996, pp. 483-499.
40. Sklar AH, Caruana RJ, Lammers JE, et al. Renal infections in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1987 Aug;10(2):81-8.
http://www.ncbi.nlm.nih.gov/pubmed/3300296
41. Schwab SJ, Bander SJ, Klahr S. Renal infection in autosomal dominant polycystic kidney disease. Am J Med 1987 Apr;82(4):714-8.
http://www.ncbi.nlm.nih.gov/pubmed/3565428
42. Stiasny B, Ziebell D, Graf S, et al. Clinical aspects of renal transplantation in polycystic kidney disease. Clin Nephrol 2002 Jul;58(1):16-24.
http://www.ncbi.nlm.nih.gov/pubmed/12141402
43. Gower PE. A prospective study of patients with radiological pyelonephritis, papillary necrosis and obstructive atrophy. Q J Med 1976 Apr;45(187):315-49.
http://www.ncbi.nlm.nih.gov/pubmed/940921
44. Mor Y, Leibovitch I, Zalts R, et al. Analysis of the long term outcome of surgically corrected vesicoureteric reflux. BJU Int 2003 Jul;92(1):97-100.
http://www.ncbi.nlm.nih.gov/pubmed/12823390
45. Tolkoff-Rubin NE, Rubin RH. Urinary tract infection in the renal transplant recipient. In: Bergan T, ed. Urinary tract infections. Basel: Karger 1997, pp. 27-33.
46. Tolkoff-Rubin NE, Rubin RH. The infectious disease problems of the diabetic renal transplant recipient. Infect Dis Clin North Am 1995 Mar;9(1):117-30.
http://www.ncbi.nlm.nih.gov/pubmed/7769213
47. Müller T, Arbeiter K, Aufricht C. Renal function in meningomyelocele: risk factors, chronic renal failure, renal replacement therapy and transplantation. Curr Opin Urol 2002 Nov;12(6):479-84.
http://www.ncbi.nlm.nih.gov/pubmed/12409876
48. Steinhoff J, Einecke G, Niederstadt C, et al. Renal graft rejection or urinary tract infection? The value of myeloperoxidase, C-reactive protein, and alpha2-macroglobulin in the urine. Transplantation 1997 Aug;64(3):443-7.
http://www.ncbi.nlm.nih.gov/pubmed/9275111
49. Keller LS, Peh CA, Nolan J, et al. BK transplant nephropathy successfully treated with cidofovir. Nephrol Dial Transplant 2003 May;18(5):1013-4.
http://www.ncbi.nlm.nih.gov/pubmed/12686681
50. Blanchet P, Droupy S, Eschwege P, et al. Urodynamic testing predicts long term urological complications following simultaneous pancreas-kidney transplantation. Clin Transplant 2003 Feb;17(1):26-31.
http://www.ncbi.nlm.nih.gov/pubmed/12588318
51. Snydman DR. Posttransplant microbiological surveillance. Clin Infect Dis 2001 Jul;33 Suppl 1: S22-S25.
http://www.ncbi.nlm.nih.gov/pubmed/11389518
52. Fox BC, Sollinger HW, Belzer FO, et al. A prospective, randomised double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: clinical efficacy, absorption of trimethoprim-sulphamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. Am J Med 1990 Sep;89(3):255-74.
http://www.ncbi.nlm.nih.gov/pubmed/2118307
53. Mahmoud KM, Sobh MA, El-Agroudy AE, et al. Impact of schistosomiasis on patient and graft outcome after renal transplantation: 10 years' follow-up. Nephrol Dial Transplant 2001 Nov;16(11):2214-21.
http://www.ncbi.nlm.nih.gov/pubmed/11682670
54. Bichler KH, Savatovsky I; the Members of the Urinary Tract Infection (UTI) Working Group of the Guidelines Office of the European Association of Urology (EAU). EAU Guidelines for the management of urogenital schistosomiasis. Eur Urol 2006 Jun;49(6):998-1003.
http://www.ncbi.nlm.nih.gov/pubmed/16519990

55. Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases: lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations. Ann Intern Med 2003 Aug;139(3):214-26. http://www.ncbi.nlm.nih.gov/pubmed/12899589
56. Tolkoff-Rubin NE, Rubin RH. Urinary tract infection in the immunocompromised host. Lessons from kidney transplantation and the AIDS epidemic. Infect Dis Clin North Am 1997 Sep;11(3):707-17. http://www.ncbi.nlm.nih.gov/pubmed/9378931
57. Van Dooyeweert DA, Schneider MM, Borleffs JC, et al. Bacteriuria in male patients infected with human immunodeficiency virus type 1. In: Bergan T, ed. *Urinary tract infections*. Basel: Karger, 1997, pp. 37-45.

8.8.1 ***Further reading***

Antibiotic prescribing in renal failure: evidence base of guidelines. Information has been derived from the following standard reference sources:

1. BMA and RPSGB. British national formulary. Summary of product characteristics from electronic medicines compendium for individual drugs. Datapharm Communications Ltd. Available from http://emc.medicines.org.uk
2. Ashley C, Currie A. The renal drug handbook. 2nd edn. Oxford: Radcliffe Medical Press, 2004.

9. URETHRITIS

9.1 Epidemiology

From a therapeutic and clinical point of view, gonorrhoeal urethritis has to be differentiated from non-specific urethritis. In Central Europe, non-specific urethritis is much more frequent than gonorrhoeal urethritis. There is a correlation between promiscuity and low socioeconomic status and the frequency of infections due to *Neisseria gonorrhoeae* and *C. trachomatis*. Infection is spread by sexual contact.

9.2 Pathogens

Pathogens include *N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium* and *Trichomonas vaginalis*. The frequency of the different species varies between patient populations (1-5). *Mycoplasma hominis* probably does not cause urethritis, and *Ureaplasma urealyticum* is an infrequent cause. In most cases, clinical evidence of *Mycoplasma* or *Ureaplasma* is caused by asymptomatic colonisation of the urogenital tract.

9.3 Route of infection and pathogenesis

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women. Recent evidence has suggested that *Myc. genitalium* can also cause cervicitis and pelvic inflammatory disease in women (6) (LE: 3).

9.4 Clinical course

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

9.5 Diagnosis

A Gram stain of a urethral discharge or a urethral smear that shows more than five leukocytes per high power field (× 1,000) and eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis (7) (LE: 3, GR: B). The Gram stain is the preferred rapid diagnostic test for evaluating urethritis. It is highly sensitive and specific for documenting urethritis and the presence or absence of gonococcal infection. A positive leukocyte esterase test or > 10 leucocytes per high power field (× 400) in the first voiding urine specimen is diagnostic. In all patients with urethritis, and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. If an amplification system is used for identifying the pathogens, the first voiding urine specimen can be taken instead of a urethral smear. *Trichomonas* sp. can usually be identified microscopically.

9.6 Therapy

*9.6.1 **Treatment of gonorrhoeal urethritis***

The following guidelines for therapy comply with the recommendations of the US Centers for Disease Control and Prevention (8-10). The following antimicrobials can be recommended for the treatment of gonorrhoea:

As first-choice treatment

- ceftriaxone, 1 g intramuscularly (with local anaesthetic) as a single dose;
- azithromycin, 1 g orally as a single dose.

Alternative regimens

- ciprofloxacin, 500 mg orally as single dose;
- ofloxacin, 400 mg orally as single dose;
- levofloxacin, 250 mg orally as single dose.

Note that fluoroquinolones are contraindicated in adolescents (< 18 years) and pregnant women.
As a result of the continuous spread of fluoroquinolone-resistant *N. gonorrhoeae*, this class of antibiotics is no longer recommended for the treatment of gonorrhoea in the United States (11). In Europe, knowledge of local susceptibility patterns is mandatory for the correct treatment of gonorrhoeal urethritis.

Because gonorrhoeae is frequently accompanied by chlamydial infection, an active antichlamydial therapy should be added.

*9.6.2 **Treatment of non-gonorrhoeal urethritis***

The following treatment has been successfully applied to non-gonorrhoeal urethritis:

As first choice of treatment:	**LE**	**GR**
azithromycin, 1 g orally as single dose	1b	A
doxycycline, 100 mg orally twice daily for 7 days	1b	A
As second choice of treatment:		
erythromycin base, 500 mg orally four times daily for 14 days	1b	A
erythromycin ethylsuccinate, 800 mg orally four times daily for 7 days		
ofloxacin, 300 mg orally twice daily for 7 days	1b	A
levofloxacin, 500 mg orally once daily for 7 days		

Doxycycline and azithromycin are considered to be equally effective in the treatment of chlamydial infections, however, infections with *Myc. genitalium* may respond better to azithromycin (12). Erythromycin is less effective and causes more side effects. In pregnant women, fluoroquinolones and doxycycline are contraindicated, therefore, besides erythromycin and azithromycin, a regimen with amoxicillin 500 mg three times daily for 7 days is also recommended.

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

9.7 Follow-up and prevention

Patients should return for evaluation if symptoms persist or recur after completion of therapy. Patients should be instructed to abstain from sexual intercourse for 7 days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV.

9.8 References

1. Borchardt KA, al-Haraci S, Maida N. Prevalence of Trichomonas vaginalis in a male sexually transmitted disease clinic population by interview, wet mount microscopy, and the InPouch TV test. Genitourin Med 1995 Dec;71(6):405-6.
   http://www.ncbi.nlm.nih.gov/pubmed/8566985
2. Busolo F, Camposampiero D, Bordignon G, et al. Detection of Mycoplasma genitalium and Chlamydia trachomatis DNAs in male patients with urethritis using the polymerase chain reaction. New Microbiol 1997 Oct;20(4):325-32.
   http://www.ncbi.nlm.nih.gov/pubmed/9385602

3. Evans BA, Bond RA, MacRae KD. Racial origin, sexual behaviour, and genital infection among heterosexual men attending a genitourinary medicine clinic in London (1993-4). Sex Transm Infect 1998 Feb;74(1):40-4.
http://www.ncbi.nlm.nih.gov/pubmed/9634302
4. Evans BA, Kell PD, Bond RA, et al. Racial origin, sexual lifestyle, and genital infection among women attending a genitourinary medicine clinic in London (1992). Sex Transm Infect 1998 Feb;74(1):45-9.
http://www.ncbi.nlm.nih.gov/pubmed/9634303
5. Krieger JN. Trichomoniasis in men: old issues and new data. Sex Transm Dis 1995 Mar-Apr;22(2): 83-96.
http://www.ncbi.nlm.nih.gov/pubmed/7624817
6. Haggerty CL. Evidence for a role of Mycoplasma genitalium in pelvic inflammatory disease. Curr Opin Infect Dis. 2008 Feb;21(1):65-9.
http://www.ncbi.nlm.nih.gov/pubmed/18192788
7. Swartz SL, Kraus SJ, Herrmann KL, et al. Diagnosis and etiology of nongonococcal urethritis, J Infect Dis 1978 Oct;138(4):445-54.
http://www.ncbi.nlm.nih.gov/pubmed/213495
8. Workowski KA, Berman SM. CDC sexually transmitted diseases treatment guidelines. Clin Infect Dis 2002 Oct 15;35(Suppl 2):S135-7.
http://www.ncbi.nlm.nih.gov/pubmed/12353199
9. Burstein GR, Workowski KA. Sexually transmitted diseases treatment guidelines. Curr Opin Pediatr 2003 Aug;15(4):391-7.
http://www.ncbi.nlm.nih.gov/pubmed/12891051
10. Scharbo-Dehaan M, Anderson DG. The CDC 2002 guidelines for the treatment of sexually transmitted diseases: implications for women's health care. J Midwifery Womens Health 2003 Mar-Apr;48(2): 96-104.
http://www.ncbi.nlm.nih.gov/pubmed/12686941
11. Centers for Disease Control and Prevention (CDC) 2010 STD Treatment Guidelines.
www.cdc.gov/std/treatment/2010/default.htm
12. Falk L, Fredlund H, Jensen JS. Tetracycline treatment does not eradicate Mycoplasma genitalium. Sex Transmit Infect 2003 Aug;79:318-9.
http://www.ncbi.nlm.nih.gov/pubmed/12902584

10. BACTERIAL PROSTATITIS

10.1 Summary and recommendations

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

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

In chronic bacterial prostatitis, and if infection is strongly suspected in CPPS, preferably a fluoroquinolone should be given for a least 4 weeks. In case of fluoroquinolones resistance or adverse reactions, trimethoprim can be given orally for a period of 4-12 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics only continued if pre-treatment cultures are positive and/or the patient has reported positive effects from the treatment. A total treatment period of 4-6 weeks is recommended (LE: 3, GR: B).

Patients with CPPS are treated empirically with numerous medical and physical modalities. The management of pain and other related symptoms are covered in the EAU Guidelines on Chronic Pelvic Pain (1).

10.2 Introduction and definition

Traditionally, the term prostatitis has included both acute and chronic bacterial prostatitis, in which an infective

origin is accepted, and the term prostatitis syndrome or, more recently, CPPS, in which no infective agent can be found and whose origin is multifactorial and in most cases obscure.

Prostatitis and CPPS are diagnosed by symptoms and evidence of inflammation and infection localised to the prostate (2). A causative pathogen, however, is detected by routine methods in only 5-10% of cases (3), and for whom antimicrobial therapy therefore has a rational basis. The remainder of patients are treated empirically with numerous medical and physical modalities. However, recent improvement in classification and application of modern methods, including molecular biology, should allow proper systematisation of treatment (4-6).

This chapter reviews documented or suspected bacterial infections of the prostate.

10.3 Diagnosis

10.3.1 ***History and symptoms***

According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, the latter being defined by symptoms that persist for at least 3 months (4-6). The predominant symptoms are pain at various locations and LUTS (Tables 10.2 and 10.3) (7-9). Chronic bacterial prostatitis is the most frequent cause of recurrent UTI in men (10).

Table 10.1: Classification of prostatitis and CPPS according to NIDDK/NIH (4-6)

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

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

Table 10.2: Localisation of pain in patients with prostatitis like symptoms*

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

**Adapted from Zermann et al. (6).*

Table 10.3: LUTS in patients with prostatitis like symptoms*

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

**Adapted from Alexander et al. (9).*

10.3.1.1 Symptom questionnaires

Symptoms appear to have a strong basis for use as a classification parameter in bacterial prostatitis as well as in CPPS (11). Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms (11,12). They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH (USA) (13).

Although the CPSI has been validated, to date, its benefit in clinical studies is still uncertain. The questionnaire contains four questions regarding pain or discomfort, two regarding urination, and three related to quality of life (see Appendix 16.5).

10.3.2 ***Clinical findings***

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

in the clinical evaluation is to exclude prostatic abscess.
In case of lasting symptoms ("chronic prostatitis" symptoms) CPPS as well as other urogenital and ano-rectal disorders must be taken into consideration.

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

*10.3.3 **Urine cultures and expressed prostatic secretion***

The most important investigations in the evaluation of the patient with acute prostatitis is mid-stream urine culture. In chronic bacterial prostatitis, quantitative bacteriological localisation cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey (2) are important investigations (see Appendix 16.6).

The Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in acute bacterial prostatitis (Table 10.4) (14). In chronic bacterial prostatitis, the spectrum of strains is wider. The significance of intracellular bacteria, such as *C. trachomatis*, is uncertain (15). In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis, Candida* sp. and rare pathogens, such as *Coccidioides immitis, Blastomyces dermatitidis*, and *Histoplasma capsulatum* (16). In case of suspected prostate tuberculosis, the urine should be investigated for Mycobacterium spp by PCR technique.

Table 10.4: Most common pathogens in prostatitis

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

**Adapted from Weidner et al. (3) and Schneider et al. (14).*

*10.3.4 **Prostate biopsy***

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

*10.3.5 **Other tests***

Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles but is unreliable and cannot be used as a diagnostic tool in prostatitis (17).

*10.3.6 **Additional investigations***

10.3.6.1 Ejaculate analysis

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

10.3.6.2 Prostate Specific Antigen (PSA)

Prostate specific antigen is often increased in acute bacterial prostatitis and other urogenital infections. If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalise after antimicrobial treatment for 4 weeks in about 50% of patients (18). A delay of at least 3 months should be allowed before

it can be assumed that a stable level of PSA has been reached. Measurement of free and total PSA adds no practical diagnostic information in prostatitis (19).

10.4 Treatment

10.4.1 ***Antibiotics***

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

Acute bacterial prostatitis is a serious infection with fever, intense local pain, and general symptoms. Parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone, should be administered. For initial therapy, any of these antibiotics may be combined with an aminoglycoside. After defervescence and normalisation of infection parameters, oral therapy can be substituted and continued for a total of 2-4 weeks (20).

The recommended antibiotics in chronic bacterial prostatitis, together with their advantages and disadvantages, are listed in Table 10.5 (21). Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties (21) (LE: 2b, GR: B), their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including *P. aeruginosa*. In addition, levofloxacin is active against Gram-positive and atypical pathogens, such as C. trachomatis and genital mycoplasmas (LE: 2b, GR: B).

The duration of antibiotic treatment is based on experience and expert opinion and is supported by many clinical studies (22). In chronic bacterial prostatitis antibiotics should be given for 4-6 weeks after initial diagnosis. Relatively high doses are needed and oral therapy is preferred (21,22) (LE: 3, GR: B). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given (21,23) (LE: 2b, GR: B).

Table 10.5: Antibiotics in chronic bacterial prostatitis*

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

**Adapted from Bjerklund Johansen et al. (21).*

10.4.2 ***Intraprostatic injection of antibiotics***

This treatment has not been evaluated in controlled trials and should not be considered (24,25).

10.4.3 ***Drainage and surgery***

Approximately 10 per cent of men with acute prostatitis will experience urinary retention (26) which can be managed by suprapubic, intermittent or indwelling catheterisation. Suprapubic cystostomy placement is generally recommended. The use of catheterisation without evidence of retention may increase the risk of progression to chronic prostatitis (27). Alpha-blocker treatment has also been recommended, but clinical evidence of benefit is poor.

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible (28). The size may matter. In one study conservative treatment was successful if the abscess cavities were smaller than 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage (29). Surgery should be avoided in the treatment of bacterial prostatitis.

10.5 References

1. Engeler D, Baranowski, AP, Dinis Oliveira P, et al. Members of the EAU Guidelines Office. Guidelines on Chronic Pelvic Pain. In: EAU Guidelines, edition presented at the 27th EAU Annual Congress, Paris, 2012. ISBN 978-90-79754-83-0.
2. Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 1968 Mar;5(5):492-518. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/4870505
3. Weidner W, Schiefer HG, Krauss H, et al. Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. Infection 1991;19 Suppl 3:S119-25. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/2055646
4. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA 1999 Jul;282(3):236-7. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/10422990
5. Workshop Committee of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). Chronic prostatitis workshop. Bethesda, Maryland, 1995, Dec 7-8.
6. Schaeffer AJ. Prostatitis: US perspective. Int J Antimicrob Agents 1999 May;11(3-4):205-11. http://www.ncbi.nlm.nih.gov/pubmed/10394972
7. Zermann DH, Ishigooka M, Doggweiler R, et al. Neurourological insights into the etiology of genitourinary pain in men. J Urol 1999 Mar;161(3):903-8. http://www.ncbi.nlm.nih.gov/pubmed/10022711
8. Alexander RB, Ponniah S, Hasday J, et al. Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. Urology 1998 Nov;52(5):744-9. http://www.ncbi.nlm.nih.gov/pubmed/9801092
9. Alexander RB, Trissel D. Chronic prostatitis: results of an Internet survey. Urology 1996 Oct;48(4): 568-74. http://www.ncbi.nlm.nih.gov/pubmed/8886062
10. Krieger JN. Recurrent lower urinary tract infections in men. J New Rem Clin 1998;47:4-15.
11. Krieger JN, Egan KJ, Ross SO, et al. Chronic pelvic pains represent the most prominent urogenital symptoms of 'chronic prostatitis'. Urology 1996 Nov;48(5):715-21. http://www.ncbi.nlm.nih.gov/pubmed/8911515
12. Nickel JC. Effective office management of chronic prostatitis. Urol Clin North Am 1998 Nov;25(4): 677-84. http://www.ncbi.nlm.nih.gov/pubmed/10026774
13. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institute of Health chronic prostatitis symptom index: development and validation of new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999 Aug;162(2):369-75. http://www.ncbi.nlm.nih.gov/pubmed/10411041
14. Schneider H, Ludwig M, Hossain HM, 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 Oct;35(5):258-62. http://www.ncbi.nlm.nih.gov/pubmed/14535851
15. Badalyan RR, Fanarjyan SV, Aghajanyan IG. Chlamydial and ureaplasmal infections in patients with nonbacterial chronic prostatitis. Andrologia 2003 Oct;35(5):263-5. http://www.ncbi.nlm.nih.gov/pubmed/14535852

16. Naber KG, Weidner W. Prostatitits, epididymitis and orchitis. In: Armstrong D, Cohen J, eds. Infectious diseases. London: Mosby, 1999; Chapter 58.
17. Doble A, Carter SS. Ultrasonographic findings in prostatitis. Urol Clin North Am 1989 Nov;16(4): 763-72.
http://www.ncbi.nlm.nih.gov/pubmed/2683305
18. Bozeman CB, Carver BS, Eastham JA, et al. Treatment of chronic prostatitis lowers serum prostate specific antigen. J Urol 2002 Apr;167(4):1723-6.
http://www.ncbi.nlm.nih.gov/pubmed/11912396
19. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery - what we have learned and where we are going. J Urol 1999 Aug;162(2):293-306.
http://www.ncbi.nlm.nih.gov/pubmed/10411025
20. Schaeffer AJ, Weidner W, Barbalias GA, et al. Summary consensus statement: diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol 2003 Aug;43(Suppl 2):1-4.
21. Bjerklund Johansen TE, Grüneberg RN, Guibert J, et al. The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. Eur Urol 1998 Dec;34(6):457-66.
http://www.ncbi.nlm.nih.gov/pubmed/9831786
22. Naber KG. Antimicrobial treatment of bacterial prostatitis. Eur Urol 2003;43(Suppl 2):23-6.
http://www.sciencedirect.com/science/article/pii/S1569905602001963
23. Ohkawa M, Yamaguchi K, Tokunaga S, et al. Antimicrobial treatment for chronic prostatitis as a means of defining the role of Ureaplasma urealyticum. Urol Int 1993;51(3):129-32.
http://www.ncbi.nlm.nih.gov/pubmed/8249222
24. Mayersak JS. 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 Oct-Dec;83(4):347-9.
http://www.ncbi.nlm.nih.gov/pubmed/10096759
25. Jiménez-Cruz JF, Tormo FB, Gómez JG. Treatment of chronic prostatitis: intraprostatic antibiotic injections under echography control. J Urol 1988 May;139(5):967-70.
http://www.ncbi.nlm.nih.gov/pubmed/3283385
26. Hua LX, Zhang JX, Wu HF, et al. [The diagnosis and treatment of acute prostatitis: report of 35 cases]. Zhonghua Nan Ke Xue 2005 Dec;11(12):897-9. [Article in Chinese]
http://www.ncbi.nlm.nih.gov/pubmed/16398358
27. Yoon BI, Kim S, Han DS, et al. Acute bacterial prostatitis: how to prevent and manage chronic infection? J Infect Chemother. 2012 Aug;18(4):444-50.
http://www.ncbi.nlm.nih.gov/pubmed/22215226
28. Ludwig M, Schroeder-Printzen I, Schiefer HG, et al. Diagnosis and therapeutic management of 18 patients with prostatic abscess. Urology. 1999 Feb;53(2):340-5.
http://www.ncbi.nlm.nih.gov/pubmed/9933051
29. Chou YH, Tiu CM, Liu JY, et al. Prostatic abscess: transrectal color Doppler ultrasonic diagnosis and minimally invasive therapeutic management. Ultrasound Med Biol. 2004 Jun;30(6):719-24.
http://www.ncbi.nlm.nih.gov/pubmed/15219951

11. EPIDIDYMITIS AND ORCHITIS

11.1 Summary and recommendations

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

Epididymitis is almost always unilateral and relatively acute in onset. In young males it is associated with sexual activity and infection of the consort (LE: 3). The majority of cases in sexually active males aged < 35 years are due to sexually transmitted organisms, whereas in elderly patients, it is usually due to common urinary pathogens (LE: 3). Epididymitis causes pain and swelling, which begins in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information. The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria (LE: 3). A urethral swab and MSU should be obtained for microbiological

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

11.2 Definition and classification

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

Orchitis and epididymitis are classified as acute or chronic processes according to the onset and clinical course. Chronic disease with induration develops in 15% of acute epididymitis cases. In the case of testicular involvement, chronic inflammation may result in testicular atrophy and the destruction of spermatogenesis (1,2).

11.3 Incidence and prevalence

There are no new data available concerning the incidence and prevalence of epididymitis. According to older data, acute epididymitis has been a major cause for admission to hospitals of military personnel (2) (LE: 3). Acute epididymitis in young men is associated with sexual activity and infection of the consort (3) (LE: 3).

The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. The incidence depends upon the vaccination status of the population (4). Primary chronic orchitis is a granulomatous disease, and a rare condition with uncertain aetiology that has been reported in about 100 cases in the literature (5).

11.4 Morbidity

Complications in epididymo-orchitis include abscess formation, testicular infarction, testicular atrophy, development of chronic epididymal induration and infertility (2).

Epididymitis caused by sexually transmitted organisms occurs mainly in sexually active males aged < 35 years (2,6) (LE: 3). The majority of cases of epididymitis are due to common urinary pathogens, which are also the most common cause of bacteriuria (2,6) (LE: 3). Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection.

11.5 Pathogenesis and pathology

Typically, in epididymitis due to common bacteria and sexually transmitted organisms, the infection is spread from the urethra or bladder. In non-specific granulomatous orchitis, autoimmune phenomena are assumed to trigger chronic inflammation (5,7). Paediatric orchitis and mumps orchitis are of haematogenous origin (7).

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

11.6 Diagnosis

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

The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria. The presence of intracellular Gram-negative diplococci on the smear correlates with infection with *N. gonorrhoeae*. The presence of only WBC on a urethral smear indicates the presence of non-gonorrhoeal urethritis. *C. trachomatis* is isolated in approximately two-thirds of these patients (2,6) (LE: 3).

Ejaculate analysis according to WHO criteria including leukocyte analysis indicates persistent inflammatory activity. In many cases, transient decreased sperm counts and forward motility can be found. Azoospermia due to complete obstruction of both epididymides is a rare complication (8). If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis. In about

20% of mumps orchitis cases, the disease occurs bilaterally in post-pubertal men with a risk of testicular atrophy and azoospermia (3) (LE: 3).

11.6.1 ***Differential diagnosis***

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

11.7 Treatment

Only a few studies have measured the penetration of antimicrobial agents into the epididymis and testes in humans. Of these, the fluoroquinolones have shown favourable properties (9) (LE: 2a).

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

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

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

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

11.8 References

1. Naber KG, Weidner W. Prostatitis, epididymitis, orchitis. In: Armstrong D, Cohen J, eds. Infectious diseases. London: Mosby, Harcourt Publishers Ltd, 1999, pp. 1-58.
2. Berger RE. Epididymitis. In: *Sexually transmitted diseases*. Holmes KK, Mardh P-A, Sparling PF, Wiesner PJ (eds). New York: McGraw-Hill, 1984; pp. 650-662.
3. Robinson AJ, Grant JB, Spencer RC, et al. Acute epididymitis: why patient and consort must be investigated. Br J Urol 1990 Dec;66(6):642-5. http://www.ncbi.nlm.nih.gov/pubmed/2265337
4. Rüther U, Stilz S, Röhl E, Nunnensiek C, et al. Successful interferon-alpha 2, a therapy for a patient with acute mumps orchitis. Eur Urol 1995;27(2):174-6. http://www.ncbi.nlm.nih.gov/pubmed/7744163
5. Aitchison M, Mufti GR, Farrell J, et al. Granulomatous orchitis. Review of 15 cases. Br J Urol 1990 Sep;66(3):312-4. http://www.ncbi.nlm.nih.gov/pubmed/2207549
6. Weidner W, Schiefer HG, Garbe C. Acute nongonococcal epididymitis. Aetiological and therapeutic aspects. Drugs 1987;34 Suppl 1:111-7. http://www.ncbi.nlm.nih.gov/pubmed/3481311
7. Nistal M, Paniagua R. Testicular and Epididymal Pathology. Stuttgart: Thieme, 1984.
8. Weidner W, Garbe C, Weissbach L, et al. [Initial therapy of acute unilateral epididymitis using ofloxacin. II. Andrological findings]. Urologe A 1990 Sep;29(5):277-80. [Article in German] http://www.ncbi.nlm.nih.gov/pubmed/2120839
9. Ludwig M, Jantos CA, Wolf S, et al. Tissue penetration of sparfloxacin in a rat model of experimental Escherichia coli epididymitis. Infection 1997 May-Jun;25(3):178-84. http://www.ncbi.nlm.nih.gov/pubmed/9181388

12. FOURNIER'S GANGRENE

12.1 Summary of recommendations

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

12.2 Background

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

12.3 Clinical presentation

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

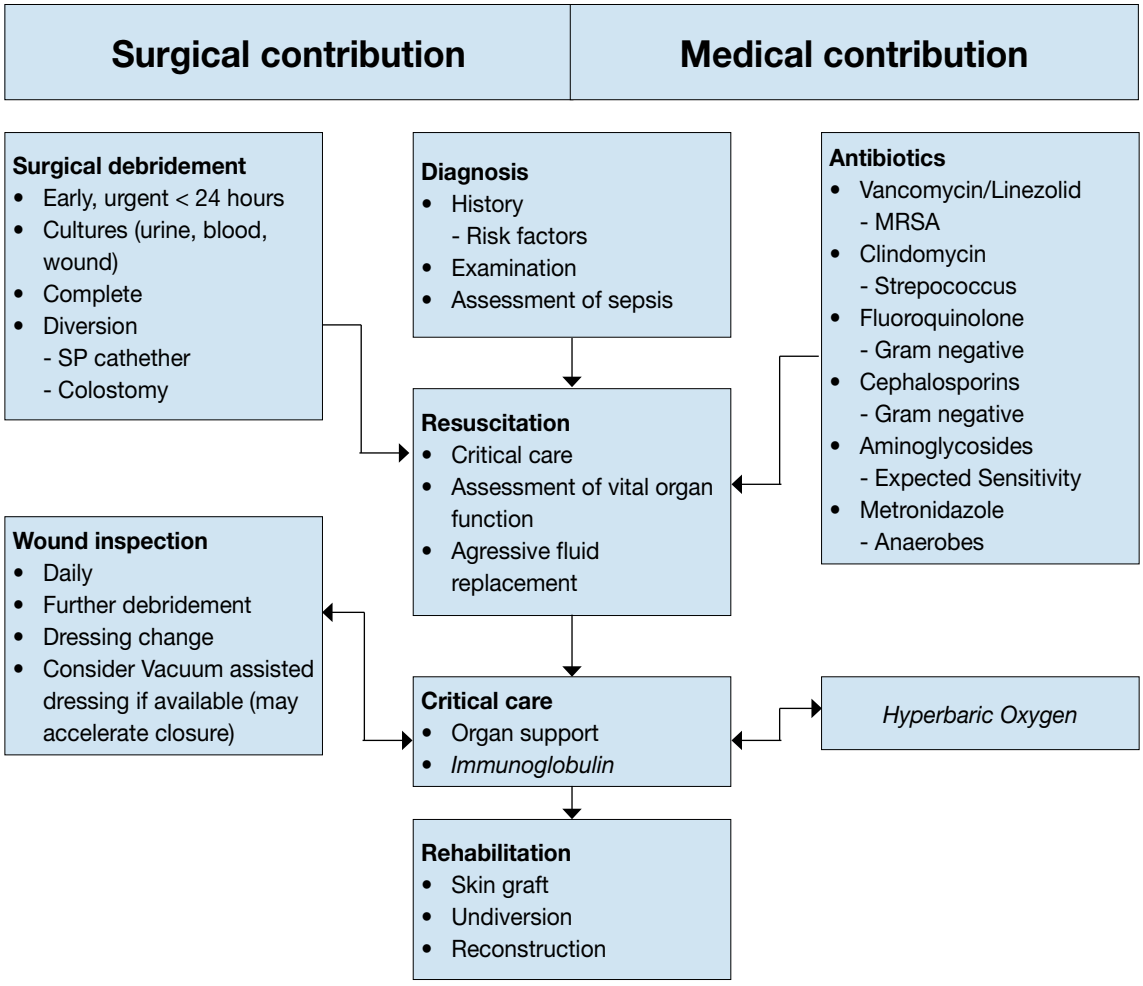
12.4 Microbiology

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

12.5 Management

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

Figure 12.1 Care pathway



12.6 Further reading

1. Erol B, Tuncel A, Hanci V, et al. Fournier's gangrene: overview of prognostic factors and definition of new prognostic parameter. Urology 2010 May;75(5):1193-8. http://www.ncbi.nlm.nih.gov/pubmed/20451745
2. Roghmann F, von Bodman C, Löppenberg B, 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 Intern 2012 Nov;110(9):1359-65. http://www.ncbi.nlm.nih.gov/pubmed/22494217
3. Ozturk E, Sonmez Y, Yilmazlar T. What are the indications for a stoma in Fournier's gangrene? Colorectal Dis 2011 Sep;13(9):1044-7. http://www.ncbi.nlm.nih.gov/pubmed/20579084
4. Sarani B, Strong M, Pascual J, et al. Necrotizing fasciitis: Current concepts and review of the literature. J Am Coll Surg 2009 Feb;208:279-88. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/19228540

13. SEXUALLY TRANSMITTED INFECTIONS

The classical bacteria that cause venereal diseases, e.g. gonorrhoea, syphilis, chancroid and inguinal granuloma, only account for a small proportion of all known sexually transmitted deceases (STDs) today. Other bacteria and viruses as well as yeasts, protozoa and epizoa must also be regarded as causative organisms of STD. Taken together, all STDs are caused by > 30 relevant pathogens. However, not all pathogens that can be sexually transmitted manifest genital diseases, and not all genital infections are exclusively sexually transmitted. At present, the reader is refered to the 2010 CDC STD Treatment Guidelines (1).

The human immunodeficiency virus (HIV) causes a disease of the immune system leading to a

vast panorama of complications and complex medical conditions also called acquired immunodeficiency synbdrome (AIDS). The urogenital tract is rarely involved. The topic is beyond the scope of these guidelines.

13.1 Reference

1. Centers for Disease Control and Prevention (CDC) 2010 STD Treatment Guidelines. www.cdc.gov/std/treatment/2010/default.htm

14. SPECIFIC INFECTIONS

Urogenital tuberculosis and bilharziasis are two infections that may affect the urogenital tract. Although not endemic in Europe, cases of urogenital tuberculosis are occasionally diagnosed in all communities. In a world of globalisation, travellers are regularly confronted with situations in which they may be infected. Guidelines on the diagnosis and management of these two infections have been published elsewhere. Following the abstract printed here, there is a direct link to these published guidelines, which can be consulted for free.

14.1 Urogenital tuberculosis

Nearly one third of the world's population is estimated to be infected with *M. tuberculosis*. Moreover, tuberculosis is the most common opportunistic infection in AIDS patients. Urogenital tuberculosis is not very common but it is considered a severe form of extra-pulmonary tuberculosis. The diagnosis of urogenital tuberculosis is made based on culture studies by isolation of the causative organism; however, biopsy material on conventional solid media may occasionally be required. Drugs are the first-line therapy in urogenital tuberculosis. Treatment regimens of six months are effective in most patients. Although chemotherapy is the mainstay of treatment, surgery in the form of ablation or reconstruction may be unavoidable. Both radical and reconstructive surgery should be carried out in the first two months of intensive chemotherapy. The management should be done by, or in direct cooperation with, a specialist in the field of tuberculosis (1-3).

14.1.1 ***References***

1. Mete Çek M, Lenk S, Naber KG, et al; the Members of the Urinary Tract Infection (UTI). EAU Guidelines for the Management of Genitourinary Tuberculosis. Eur Urol 2005 Sep;48(3):353-62. http://www.ncbi.nlm.nih.gov/pubmed/15982799
2. Lenk S and Yasuda M. Urinary tuberculosis. In Naber KG, Schaeffer AJ, Heynes CF, Matsumoto T et al (edts). Urogenital Infections (chapter 15.2). European Association of Urology - International Consultations on Urological Diseases. 2010. ISBN: 970-90-79754-41-0.
3. Kulchavenya E and Kim C-S. Male genital tuberculosis. In Naber KG, Schaeffer AJ, Heynes CF, Matsumoto T et al (edts). Urogenital Infections (chapter 15.3). European Association of Urology - International Consultations on Urological Diseases. 2010. ISBN: 970-90-79754-41-0.

14.2 Urogenital schistosomiasis

More than 200 million people worldwide are affected by bilharziasis, which is caused by Schistosoma heamatobium. For travellers, precautions are most important. For the population in endemic areas, an integrated approach including health education is necessary. Effective pharmacological treatment is available (1,2).

14.2.1 ***References***

1. Bichler KH, Savatovsky I; the Members of the Urinary Tract Infection (UTI) Working Group of the Guidelines Office of the European Association of Urology (EAU): EAU guidelines for the management of urogenital schistosomiasis. Eur Urol 2006 Jun;49(6):998-1003. http://www.ncbi.nlm.nih.gov/pubmed/16519990
2. Khalaf IM and Shikeir A. Genitourinary Schistosomiasis. In Naber KG, Schaeffer AJ, Heynes CF, Matsumoto T et al (edts). Urogenital Infections (chapter 15.8). European Association of Urology - International Consultations on Urological Diseases. 2010. ISBN: 970-90-79754-41-0.

15. PERIOPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

15.1 Summary and recommendations

The aim of antimicrobial prophylaxis in urological surgery is to decrease the load of microorganisms in the surgical field at the time of surgery in order to prevent infective complications resulting from diagnostic and therapeutic procedures. However, evidence for the best choice of antibiotics and prophylactic regimens is limited (Table 15.1).

Before surgery, it is essential to categorise the patients in relation to (1):

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

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

For open and laparoscopic surgery, the same rules as in abdominal and gynaecological surgery can be applied. No antibiotic prophylaxis is recommended for clean operations, whereas a single or 1-day dose is recommended in clean-contaminated. The approach in contaminated operations varies with the type of procedure, the level of surgical site contamination and level of difficulty. Opening of the urinary tract is considered as clean-contaminated surgery.

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

Many antibiotics are suitable for perioperative antibacterial prophylaxis, e.g. co-trimoxazole, second-generation cephalosporins, fluoroquinolones, aminopenicillins plus a beta-lactam inhibitor, and aminoglycosides. Broader-spectrum antibiotics including fluoroquinolones should be used cautiously and reserved for treatment. This applies also to the use of vancomycin.

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

Table 15.1: Level of evidence and grade of recommendation for standard urological procedures (for practical management of antibiotic prophylaxis, refer to Tables 15.4a,b and Table 15.5)

Procedure	LE	GR	Remarks
Diagnostic procedures			
Cystoscopy	1b	A	Low frequency of infections Confounding findings
Urodynamic study	1a	A	Low frequency of infections Confounding findings
Transrectal core biopsy of prostate	1b	A	High risk of infection Assess carefully risk factors including risk of carrying resistant bacterial strains (i.e. fluoroquinolones resistance)
Diagnostic ureteroscopy	4	C	No available studies
Therapeutic procedures			
TURB	2b	C	Poor data. No concern given to burden of tumour, i.e. size, multiplicity, necrosis
TURP	1a	A	Good documentation (2 meta-analysis)
SWL (standard, no risk factors such as the presence of a stent or nephrostomy tube)	1a	A	Low frequency of infections Confounding findings

Ureteroscopy for stone management	2b	B	Literature does not distinguish between severity of stone management
Percutaneous stone management	1b	A	High risk of infection
Open and laparoscopic surgery			
Clean operations (no opening of urinary tract)			
Nephrectomy	3	C	SSI poorly documented Catheter-related UTI poorly documented
Scrotal surgery	3	C	Review studies contradictory
Prosthetic implants	3	B	Limited documentation Regimen not well defined
Clean-contaminated (opening of urinary tract)			
Nephroureterectomy	3	B	Limited documentation
Ureteropelvic junction repair	4	C	Limited documentation
Total (radical) prostatectomy	2a	B	Limited documentation
Partial bladder resection	3	C	No specific RCT studies
Clean-contaminated/contaminated (opening of bowel, urine deviation)			
Cystectomy with urine deviation	2a	B	Limited documentation

SWL = extracorporeal shockwave lithotripsy; TURB = transurethral resection of the bladder; SSI = surgical site infection; TURP = transurethral resection of the prostate; RCT= randomised controlled trials.

15.2 Introduction

Antibiotic prophylaxis in urology has been controversial for many years. Most studies in the past have been poorly designed and lacked statistical power. There has been inconsistency concerning definitions and assessment of risk factors. Urological practice has changed particularly in the last decade and older studies are no longer relevant. Several surveys among urologists in Europe have revealed wide differences in regimens and choice of antibiotics for prophylaxis. Clearly, there is a need for evidence-based guidelines (2-6).

The present section aims to clarify the current state of knowledge and to propose practical recommendations based on clinical studies, expert opinion and professional consensus. The section also considers the recommendations of societies, such as the Paul Ehrlich Society for Chemotherapy, the corresponding working groups of the German Society of Urology (7), French Association of Urology (8), the Swedish Council on Health Technology Assessment and an international consensus working group (1).

One systematic review of antibiotic prophylaxis in urological surgery has been published (9). The results of the review strengthen the underlying documentation for the present recommendations.

A recent pan-European survey was carried out by the EAU Section for Infection in Urology (ESIU) in a large number of European countries, including > 200 urological services or units. The survey found that ≥ 10% of patients had a healthcare-associated UTI (10). Moreover, a review showed large discrepancies in the use of antibiotic prophylaxis in all types of procedures and between countries, and low compliance to the guidelines (11). The surveys illustrate the need for a stringent antibiotic policy throughout Europe, and that recommendations for antibiotic prophylaxis should be included in the general antibiotic policy of each hospital.

The microbial development of resistance presents a challenge to the urological community for both treatment and prophylaxis. It is essential that the urologist is aware of the microbial pattern and resistance profile in his/her community and can assess the risk of each individual patient of harbouring resistant strains (see Section 1.2).

15.3 Goals of perioperative antibacterial prophylaxis

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

There is a dilemma regarding the definition of infections. The US CDC have presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications (12). These definitions have also been used in the recent pan-European study on nosocomial UTI (10). Revision of definitions and recommendations are on-going in some countries (13). Table 15.2 illustrates the different types of infectious complications encountered in urological surgery.

Table 15.2: Main types of healthcare-associated infections encountered in urological practice

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

Surgical site infections are seen after open surgery and to some extent after laparoscopic surgery. Febrile and complicated UTIs are mainly complications of endoscopic surgery and the use of indwelling catheters and stents. They can also occur following open surgery of the urinary tract. Sepsis can be seen with all types of procedures.

The endpoints of perioperative prophylaxis in urology are debatable. It is generally agreed that its main aim is to prevent symptomatic, febrile urogenital infections such as acute pyelonephritis, prostatitis, epididymitis and urosepsis, as well as serious wound infections directly related to surgery (Table 15.2). This might be extended to asymptomatic bacteriuria and even minor wound infections, which could easily be treated on an outpatient basis. In some circumstances, even minor wound infections can have serious consequences, as in implant surgery. However, asymptomatic bacteriuria after TURP or other endourological procedures can disappear spontaneously and is usually of no clinical significance. Another question is whether perioperative prophylaxis should also be concerned with the prevention of non-urological infections, e.g. endocarditis and postoperative pneumonia. Perioperative antibacterial prophylaxis in urology must go beyond the traditional aim of prophylaxis in surgery, which is the prevention of wound infections.

15.4 Risk factors

Risk factors (Table 15.3 and 2.1) are underestimated in most trials. However, they are important in the preoperative assessment of the patient. They are related to:

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

The traditional classification of surgical procedures according to Cruse and Foord (14) into clean, clean-contaminated, contaminated, and infected/dirty operations applies to open surgery but not to endourological interventions. It is still debated whether opening of the urinary tract (i.e. bladder surgery, radical prostatectomy, or surgery of the renal pelvis and ureter) should be classified as clean or clean-contaminated surgery in cases of negative urine culture. The same applies to endoscopic and transurethral surgery. However, members of the EAU Expert Group consider these procedures as clean-contaminated because urine culture is not always a predictor of bacterial presence, and the lower genitourinary tract is colonised by microflora, even in the presence of sterile urine (6,15,16).

Table 15.3: Generally accepted risk factors for infectious complications

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

The pan-European study on nosocomial UTI (10) has identified the three most important risk factors for infectious complications as:

- an indwelling catheter;
- previous urogenital infection;
- long preoperative hospital stay.

The risk of infection varies with the type of intervention. The wide spectrum of interventions further complicates the provision of clear-cut recommendations. Furthermore, the bacterial load, the duration and difficulty of the operation, the surgeon's skill, and perioperative bleeding may also influence the risk of infection (6). For elective urological surgery, general and urinary tract specific risk factors must be controlled (i.e. bacteriuria, obstruction).

15.5 Principles of antibiotic prophylaxis

Antibiotic prophylaxis aims at protecting the patient but not at the expense of promoting resistance. However, there is good evidence that intelligent use of prophylaxis can lower the overall consumption of antibiotics (16,17). It is essential to individualise the choice of antibiotic prophylaxis according to each patient's cumulative risk factors (18). Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection (19-21).

Unfortunately, the benefit of antibiotic prophylaxis for most modern urological procedures has not yet been established by well-designed interventional studies.

*15.5.1 **Timing***

There is a given time-frame during which antibiotic prophylaxis should be administered. Although the following guidelines are based on research into skin wounds and clean-contaminated and contaminated bowel surgery, there is good reason to believe that the same findings apply to urological surgery. The optimal time for antibiotic prophylaxis is 1-2 h before instrumentation. Some studies on bowel surgery indicate similar results up to 3 h after the start of an intervention (22-24).

For practical purposes, oral antibiotic prophylaxis should be given approximately 1 h before the intervention. Intravenous antibiotic prophylaxis should be given at the induction of anaesthesia. These timings allow antibiotic prophylaxis to reach a peak concentration at the time of highest risk during the procedure, and an effective concentration shortly afterwards (25). It is worth noting that a bloodstream infection can develop in less than an hour (22).

*15.5.2 **Route of administration***

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

*15.5.3 **Duration of the regimen***

For most procedures, duration of antibiotic prophylaxis has not yet been adequately addressed and rarely can a defined regimen be recommended. In principle, the duration of perioperative prophylaxis should be minimised; ideally to a single preoperative antibiotic dose. Perioperative prophylaxis should be prolonged only where there are significant risk factors (see Section 15.4).

*15.5.4 **Choice of antibiotics***

No clear-cut recommendations can be given, as there are considerable variations in Europe regarding

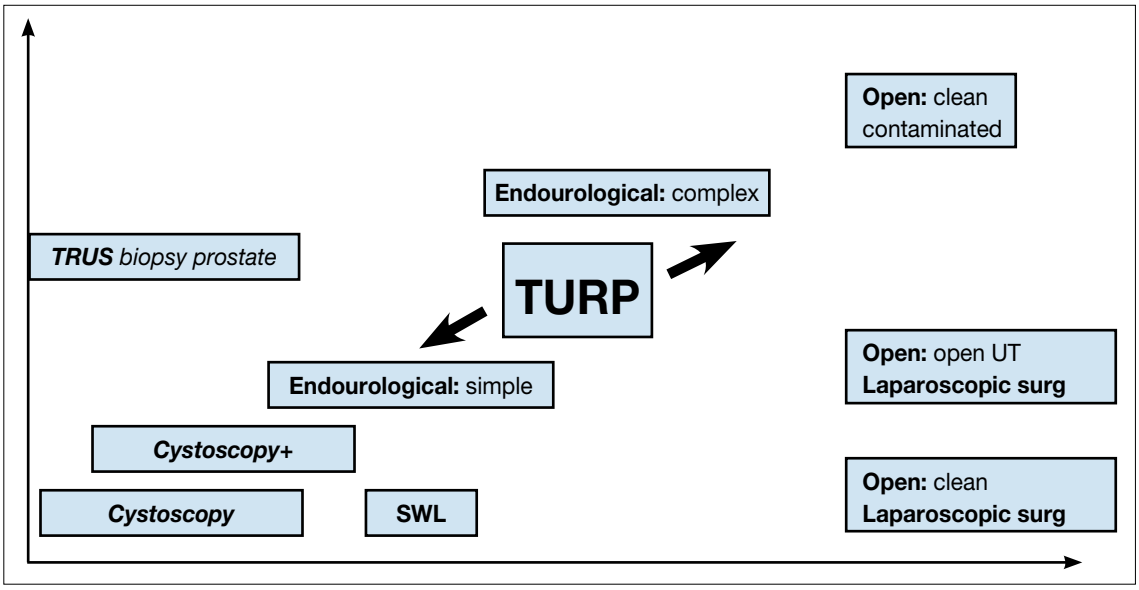
both bacterial spectra and susceptibility to different antibiotics. Antimicrobial resistance is usually higher in Mediterranean compared with Northern European countries; resistance is correlated with an up to four-fold difference in sales of antibiotics (26). Thus, knowledge of the local pathogen profile, susceptibility and virulence is mandatory in establishing local antibiotic guidelines. It is also essential to define the predominant pathogens for each type of procedure. When choosing an antimicrobial agent, it is necessary to consider the procedure-specific risk factors, contamination load, target organ, and the role of local inflammation.

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

15.6 Prophylactic regimens in defined procedures

All procedures are not alike. There is a large variation in invasiveness and risk for identical interventions. The empirical relationship between the level of invasiveness and risk for infective complications is illustrated in Figure 15.1. Moreover, a tentative classification of the urological procedures in relation to the surgical field contamination level is given in Table 15.5.a and 15.5.b.

Figure 15.1: Level of invasiveness and risk of infection in urological procedures (empirical scheme) (5)



The EAU/ESIU working group has suggested a distribution of the different common diagnostic and therapeutic urological procedures in relation to the categories of surgical site contamination after adaptation to the urological context (14,27). The recommendations for antibiotic prophylaxis in standard urological surgery are summarised in Table 15.4a and 15.4b (28,29).

*15.6.1 **Diagnostic procedures***

15.6.1.1 Transrectal prostate biopsy

Antimicrobial prophylaxis in core biopsy of the prostate is generally recommended (LE: 1b, GR: A). However, the choice of regimens remains debatable. Most regimens used are effective, and recent studies have suggested that 1-day and even single doses are sufficient in low-risk patients (30-45) (LE: 1b, GR: A). The increase in fluoroquinolone resistance in the faecal flora has raised the question of appropriateness of the current recommendations (46,47). No clear-cut alternative is evidence-based. In a recent review, it was recommended that men at risk for harbouring fluoroquinolone resistant strains should receive an alternate targeted regiment based on rectal swab finding (48). Also several forms of bowel preparation are under investigation, although none has yet been shown to significantly reduce infection rates (48). Each urologist must weigh the need for a prostate biopsy in relation to the risk, assess the individual risks factors including the risk of harbouring a resistant bacteria (i.e. ESBL) and consider the need for a rectal swab before the instrumentation.

15.6.1.2 Cystoscopy

The frequency of infectious complications after cystoscopy, urodynamic studies and diagnostic simple ureteroscopy is low. The use of antibiotic prophylaxis is still debated and the results are controversial. In a

recent one-centre series of 2,010 cystocopic control for bladder cancer, only 1.9% developed a febrile UTI. It was 1.1% for patients without bacteriuria and 4.5% in colonised patients (49). In one other recent placebo controlled randomised clinical trial, there was no difference in UTI between the antibiotic and the placebo groups in patients with sterile urine (50). In view of the very large number of cystoscopic examinations, the low infectious risk and the potential adverse effect on bacterial sensitivity, antibiotic prophylaxis is not recommended in standard cases. However, bacteriuria, indwelling catheters, and a history of urogenital infection are risk factors that must be considered (51-65) (LE: 1b, GR: A).

*15.6.2 **Endourological treatment procedures (urinary tract entered)***

There is little evidence for any benefit of antibiotic prophylaxis in TURB. However, antibiotic prophylaxis should be considered in patients with large tumours with a prolonged resection time, large necrotic tumours, and with risk factors (52,66,67) (LE: 2b, GR: C).

Transurethral resection of the prostate is the best-studied urological intervention. A meta-analysis of 32 prospective, randomised and controlled studies, including > 4,000 patients, showed a benefit of antibiotic prophylaxis with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively (16,68,69) (LE: 1a, GR: A). A recent systematic review confirms this view (70). There is a difference between smaller resections in healthy patients and large resections in at-risk patients (Figure 15.1).

There have been few studies that have defined the risk of infection following ureteroscopy and percutaneous stone removal, and no clear-cut evidence exists (68). It is reasonable, however, to distinguish low-risk procedures, such as simple diagnostic and distal stone treatment, from higher-risk procedures, such as treatment of proximal impacted stones and intrarenal interventions (Figure 15.1) (5). Other risk factors (i.e. size, length, bleeding, and surgeon's experience) also need to be considered in the choice of regimen (72-79) (LE: 2b, GR: B). In a review of a large database of patients undergoing percutaneous nephrolithotomy, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of postoperative fever and other complications (80). Single dose administration was found sufficient (81).

Shockwave lithotripsy is one of the most commonly performed procedures in urology. No standard prophylaxis is recommended. However, prophylaxis is recommended in cases of internal stent and treatment, due to the increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, or infectious stones) (82-91) (LE: 1a-1b, GR: A).

Most antibiotic groups have been evaluated, such as fluoroquinolones, BLIs, including cephalosporins, and co-trimoxazole, but comparative studies are limited.

*15.6.3 **Laparoscopic surgery***

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

*15.6.4 **Open or laparoscopic urological operations without opening of the urinary tract (clean procedures)***

No standard antibiotic prophylaxis is recommended in clean operations (92-99) (LE: 3, GR: C).

*15.6.5 **Open or laparoscopic urological operations with open urinary tract (clean-contaminated procedures)***

In cases of opening the urinary tract, a single perioperative parenteral dose of antibiotics is recommended (LE: 3, GR: C). This is valuable for standard procedures such as total (radical) prostatectomy (97-100). In open enucleation of prostatic adenoma, the risk of postoperative infection is particularly high (101) (LE: 2b, GR: B).

*15.6.6 **Open urological operations with bowel segment (clean-contaminated or contaminated procedures)***

Antibiotic prophylaxis is recommended, as for clean-contaminated operations in general surgery. Single or 1-day dosage is recommended, although prolonged operation and other morbidity risk factors might support the use of a prolonged regimen, which should be < 72 h. The choice of antibiotic should focus on aerobic and anaerobic pathogens. Evidence is based on colorectal surgery (LE: 1a, GR: A), but experience is limited as for specific urological interventions (102-105) (LE: 2a, GR: B).

*15.6.7 **Postoperative drainage of the urinary tract***

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

*15.6.8 **Implantation of prosthetic devices***

When infectious complications occur in implant surgery, they are usually problematic and often result in removal of the prosthetic device. Diabetes mellitus is considered a specific risk factor for infection. Skin-related staphylococci are responsible for most infections. The antibiotics used must be chosen to target these strains (106-109) (LE: 2a, GR: B).

Table 15.4a: Surgical Wound classes modified from (13) and adapted to urological surgery. Tentative classification of urological procedures in relation to the different levels of surgical field contamination. The risk of wound infection or SSI expressed in per cent (within brackets in left column) is that of classical wound infections without antibiotic prophylaxis and not bacteriuria or clinical UTI in urological surgery (Modified from Urogenital infections, EAU/ICUD, 2010, p 674-75). In this table some examples of open and laparoscopic procedures are given and the ABP basic principle.

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

Table 15.4b: Tentative classification of the different diagnostic and therapeutic endoscopic urological procedures in relation to the level of surgical field contamination. Bacteriuria is a key factor to separate between clean-contaminated and contaminated surgical environment (modified from Urogenital infections EAU/ICUD, 2010, p 674-75).

Level of surgical field contamination	Bacter-iuria	Diagnostic procedures	TURB and TURP	URS PCNL	SWL	Antibiotic prophylaxis
Clean (I)	No	Cystoscopy Urodynamic study	Small TURB/ fulguration (similar cystoscopy)	Diagnostic URS (simple, no history of UTI)	Standard kidney of ureter No obstruction, no history of UT	No
Clean-contaminated (UT) (IIA)	No	Trans-perineal prostate biopsy	TURB large tumour (no history of UTI) TURP (no history UTI or other identified RF) Controlled BU	Diagnostic URS Uncomplicated stone (no obstruction, no stent, not "impacted") History of UTI	Standard kidney or ureter Moderate obstruction and/or history of UTI	Single dose prior to (oral) or at surgery (i.v.)
Contaminated (UT=IIIA)	Yes	Trans-perineal prostate biopsy (history of UTI) Trans-rectal prostate biopsy	TURB necrosis/ bacteriuria TURP in men with indwelling catheter or bacteriuria	Complicated stone (Moderate obstruction, "impacted")	Complex stone Obstruction Nephrostomy or JJ-stent present	Control of bacteriuria prior to surgery Single dose at surgery. Consider prolonged regimen
Infected/Dirty (IV)	Yes	Prostate biopsy in men with catheter or UTI	Clinical UTI Drainage as required Emergency TURB, TURP			Antibiotic treatment

Table 15.5: Recommendations for perioperative antibiotic prophylaxis in urology

Procedure	Pathogens (expected)	Prophylaxis	Antibiotics	Remarks
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes?	All patients Targeted alternative[2]	Fluoroquinolones TMP ± SMX Metronidazole?[1] Targeted alternative[2]	Single dose effective in low-risk patients. Consider prolonged course in high-risk patients
Cystoscopy Urodynamic examination	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd Generation	Consider in high-risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd generation	Consider in high-risk patients
Endourological surgery and SWL				
SWL	Enterobacteriaceae Enterococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI[a]	

SWL with stent or nephrostomy tube	Enterobacteriaceae Enterococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI[a]	Risk patients
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones	Consider in risk patients
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI Fluoroquinolones	Short course Length to be determined Intravenous suggested at operation
TURP	Enterobacteriaceae Enterococci	All patients	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Low-risk patients and small-size prostate probably do not require prophylaxis
TUR of bladder tumour	Enterobacteriaceae Enterococci	No	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Consider in high-risk patients and large tumours
Open or laparoscopic urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens	No		Consider in high-risk patients Short postoperative catheter requires no treatment
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	TMP ± SMX Cephalosporin 2nd or 3rd generation Aminopenicillin/BLI	Single perioperative course
Clean-contaminated/ contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	Cephalosporin 2nd or 3rd generation Metronidazole	As for colonic surgery
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients	Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)	

[1]No evidence for metronidazole in core biopsy of the prostate; [2]Increasing fluoroquinolone resistance has to be assessed.

[a] = gram-negative bacteria excluding Pseudomonas aeruginosa.

15.7 References

1. Naber KG (chair), Schaeffer AJ, Hynes CF, et al (Eds) (2010). EAU/International Consultation on Urological Infections. The Netherlands, European Association of Urology.
2. Hedelin H, Bergman B, Frimodt-Møller C, et al. [Antibiotic prophlaxis in diagnostic and therapeutic urological interventions.] Nord Med 1995;110(1):9-11,25. [Article in Swedish] http://www.ncbi.nlm.nih.gov/pubmed/7831109
3. Wilson NI, Lewis HJ. Survey of antibiotic prophylaxis in British urological practice. Br J Urol 1985 Aug;57(4):478-82. http://www.ncbi.nlm.nih.gov/pubmed/4040787

4. Taylor HM, Bingham JB. Antibiotic prophylaxis for transrectal prostate biopsy. J Antimicrob Chemother 1997Feb;39(2):115-7. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/9069529
5. Grabe M. Perioperative antibiotic prophylaxis in urology. Curr Opin Urol 2001 Jan;11(1):81-5.
http://www.ncbi.nlm.nih.gov/pubmed/11148751
6. Grabe M. Controversies in antibiotic prophylaxis in urology. Int J Antimicrob Agents 2004 Mar;23 Suppl 1:S17-S23.
http://www.ncbi.nlm.nih.gov/pubmed/15037324
7. Naber KG, Hofstetter AG, Brühl P, et al. Guidelines for perioperative prophylaxis in interventions of the urinary and the male genital tract. Int J Antimicrob Agents 2001 Apr;17(4):321-6.
http://www.ncbi.nlm.nih.gov/pubmed/11295416
8. Societé Francaise d'Anesthésie et de Réanimation (SFAR). [Recommendations for antibacterial prophylaxis in surgery. Actualisation 1999]. Pyrexie 1999;3:21-30. [Article in French]
9. Bootsma AM, Laguna Pes MP, Geerlings SE, et al. Antibiotic prophylaxis in urologic procedures: a systematic review. Eur Urol, 2008 Dec. 54(6): 1270-86.
http://www.ncbi.nlm.nih.gov/pubmed/18423974
10. Bjerklund Johansen TE, Cek M, Naber K, et al. PEAP study investigators; European Society of Infections in Urology. Prevalence of hospital-acquired urinary tract infections in urology departments. Eur Urol 2007 Apr;51(4):1100-11;discussion 1112.
http://www.ncbi.nlm.nih.gov/pubmed/17049419
11. Cek M, Tandogdu Z, Tenke P, Wagenlehner F et al. Antibiotic Prophylaxis in Urology Departments, 2005-2010. Eur Urol 2013;63:386-94.
http://www.ncbi.nlm.nih.gov/pubmed/23031676
12. Horan TC, Gaynes RP. Surveillance of nosocomial infections. In: Mayhall CG (ed). *Hospital epidemiology and infection control*. 3rd edn. Philadelphia: Lippincott, Williams & Wilkins, 2004: pp. 1659-1702.
13. Association Française d'Urologie et Société de Pathologie Infectieuse de Langue Française. [Nosocomial urinary tract infections in adults.] [Article in French]
www.urofrance.org
14. Cruse PJ, Foord R. The epidemiology of wound infection. A 10-year prospective of 62,939 wounds. Surg Clin North Am 1980 Feb;60(1):27-40. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/7361226
15. Love TA. Antibiotic prophylaxis and urologic surgery. Urology 1985 Nov; 26(5 Suppl):2-5.
http://www.ncbi.nlm.nih.gov/pubmed/3904137
16. Wagenlehner FM, Wagenlehner C, Schinzel S, et al; Working Group 'Urological Infections' of German Society of Urology. Prospective, randomized, multicentric, open, comparative study on the efficacy of a prophylactic single dose of 500 mg levofloxacin versus 1920 mg trimethoprim/sulfamethoxazole versus a control group in patients undergoing TUR of the prostate. Eur Urol 2005;47(4):549-56.
http://www.ncbi.nlm.nih.gov/pubmed/15774257
17. Grabe M, Forsgren A, Björk T, Hellsten S. Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. Eur J Clin Microbiol 1987;6(1): 11-7.
http://www.ncbi.nlm.nih.gov/pubmed/3569248
18. Grabe M, Shortliffe L, Lobel B, et al. Risk factors. In: Naber KG, Pechère JC, Kumazawa J et al., eds. Nosocomial and health care associated infections in urology. Health Publications Ltd, 2001, pp. 35-57.
19. Adam D, Daschner F. [Prevention of infection in surgery: hygienic measurements and antibiotic prophylaxis.] Stuttgart: Wissenschaftliche Verlagsgesellschaft, 1993. [Article in German]
20. Blumenberg EA, Abrutyn E. Methods for reduction of UTI. Curr Opin Urol 1997;7:47-51.
21. Mignard JP for the Comité de Formation Continue, Association Francaise d'Urologie. [Sterilisation and disinfection of instruments.] Progrès en Urologie 2004;14 (Suppl 1):1049-92. [Article in French]
22. Burke JF. The effective period of preventive antibiotic action in experimental incision and dermal lesion. Surgery 1961 Jul;50:161-8.
http://www.ncbi.nlm.nih.gov/pubmed/16722001
23. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992 Jan;326(5):281-6.
http://www.ncbi.nlm.nih.gov/pubmed/1728731
24. Bates T, Siller G, Crathern BC, et al. Timing of prophylactic antibiotics in abdominal surgery: trial of a pre-operative versus an intra-operative first dose. Br J Surg 1989 Jan;76(1):52-6.
http://www.ncbi.nlm.nih.gov/pubmed/2645013

25. Bergamini TM, Polk HC Jr. The importance of tissue antibiotic activity in the prevention of operative wound infection. J Antimicrob Chemother 1989 Mar;23(3):301-13. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/2659564
26. Kahlmeter G. Prevalence and antimicrobial susceptibility of pathogens in uncomplicated cystitis in Europe. The ECO.SENS study. Int J Antimicrob Chemother 2003 Oct;22 Suppl 2:49-52. http://www.ncbi.nlm.nih.gov/pubmed/14527771
27. Grabe M, Botto H, Cek M, Tenke P et al. Preoperative assessment of the patient and risk factors for infectious complications and tentative classification of surgical field contamination of urological procedures. World J Urol 2012;30:39-50. http://www.ncbi.nlm.nih.gov/pubmed/21779836
28. Wagenlehner FM, Grabe M, Naber KG, et al. Antibiotikaprophylaxe in der Urologie. Urologe 2011;50:1469-78. [Article in German] http://www.ncbi.nlm.nih.gov/pubmed/21997660
29. Grabe M. Antibiotic prophylaxis in urological surgery: a European viewpoint. Int J Antimicrob Agents 2011 Dec;38:Suppl:58-63. http://www.ncbi.nlm.nih.gov/pubmed/21996404
30. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int 2000 Apr;85(6):682-5. http://www.ncbi.nlm.nih.gov/pubmed/10759665
31. Webb NR, Woo HH. Antibiotic prophylaxis for prostate biopsy. BJU Int 2002 May;89(8):824-8. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/11972504
32. Sabbagh R, McCormack M, Péloquin F, et al. A prospective randomized trial of 1-day versus 3-day antibiotic prophylaxis for transrectal ultrasound guided prostate biopsy. Can J Urol 2004 Apr;11(2):2216-9. http://www.ncbi.nlm.nih.gov/pubmed/15182413
33. Lindstedt S, Lindström U, Ljunggren E, et al. Single dose antibiotic prophylaxis in core prostate biopsy: Impact of Timing and identification of risk factors. Eur Urol 2006 Oct;50(4):832-7. http://www.ncbi.nlm.nih.gov/pubmed/16750292
34. Enlund AL,Varenhorst E. Morbidity of ultrasound-guided transrectal core biopsy of the prostate without prophylactic antibiotic therapy. A prospective study in 415 cases. Br J Urol 1997 May;79(5):777-80. http://www.ncbi.nlm.nih.gov/pubmed/9158518
35. Larsson P, Norming U, Tornblom M, et al. Antibiotic prophylaxis for prostate biopsy: benefits and costs. Prostate Cancer Prostatic Dis 1999 Mar;2(2): 88-90. http://www.ncbi.nlm.nih.gov/pubmed/12496844
36. Puig J, Darnell A, Bermudez P, et al. Transrectal ultrasound-guided prostate biopsy: is antibiotic prophylaxis necessary? Eur Radiol 2006 Apr;16(4):939-43. http://www.ncbi.nlm.nih.gov/pubmed/16391904
37. Kapoor DA, Klimberg IW, Malek GH, et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology 1998 Oct;52(4):552-8. http://www.ncbi.nlm.nih.gov/pubmed/9763070
38. Isen K, Kupeli B, Sinik Z, 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(4):491-5. http://www.ncbi.nlm.nih.gov/pubmed/10668944
39. Crawford ED, Haynes AL, Jr., et al. Prevention of urinary tract infection and sepsis following transrectal prostatic biopsy. J Urol 1982 Mar;127(3):449-51. http://www.ncbi.nlm.nih.gov/pubmed/6895918
40. Melekos MD. Efficacy of prophylactic antimicrobial regimens in preventing infectious complications after transrectal biopsy of the prostate. Int Urol Nephrol 1990;22(3):257-62. http://www.ncbi.nlm.nih.gov/pubmed/2210982
41. Yamamoto S, Ishitoya S, Segawa T, et al. Antibiotic prophylaxis for transrectal prostate biopsy: a prospective randomized study of tosufloxacin versus levofloxacin. Int J Urol 2008 Jul;15(7):604-6. http://www.ncbi.nlm.nih.gov/pubmed/18462354
42. Schaeffer AJ, Montorsi F, Scattoni V, et al. Comparison of a 3-day with a 1-day regimen of an extended-release formulation of ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate. BJU Int 2007 Jul;100(1):51-7. http://www.ncbi.nlm.nih.gov/pubmed/17552953

43. Briffaux R, Merlet B, Normand G, et al, [Short or long schemes of antibiotic prophylaxis for prostate biopsy. A multicentre prospective randomised study]. Prog Urol 2009 Jan;19(1):39-46. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/19135641
44. Shandera KC, Thibault GP, Deshon GE, Jr. Efficacy of one dose fluoroquinolone before prostate biopsy. Urology 1998 Oct;52(4):641-3.
http://www.ncbi.nlm.nih.gov/pubmed/9763085
45. Griffith BC, Morey AF, Ali-Khan MM, et al. Single dose levofloxacin prophylaxis for prostate biopsy in patients at low risk. J Urol 2002 Sep;168(3):1021-3.
http://www.ncbi.nlm.nih.gov/pubmed/12187213
46. Wagenlehner FM, van Ostrum E, Tenke P, et al. Infective complications after Prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, A prospective Multinational Multicentre Prostate Biopsy Study. Eur Urol 2013;63:521-7.
http://www.ncbi.nlm.nih.gov/pubmed/22704727
47. Taylor AK, Zembower TR, Nadler RB, et al. Targeted antimicrobial prophylaxis using rectal swab cultures in men undergoping transrectal ultrasound guided prostate biopsy is associated with reduced incidence of postoperative infectious complications and cost of care. J Urol 2012;187:1275-9.
http://www.ncbi.nlm.nih.gov/pubmed/22341272
48. Wagenlehner FM, Pilatz A, Waliszewski P, et al. Reducing infection rates after prostate biopsy. Nat Rev Urol 2014 Feb;11(2):80-6.
http://www.ncbi.nlm.nih.gov/pubmed/24418806
49. Herr HW. Should Antibiotic be given prior to outpatient cystoscopy? A plea to urologists to practice Antibiotic Stewarship. Eur Urol 2014 Apr;65(4):839-42.
http://www.ncbi.nlm.nih.gov/pubmed/24012206
50. Garcia-Perdomo HA, Lopez H, Carbonell J, Castillo D et al. Efficacy of antibiotic prophylaxis in patients undergoing cystocopy: a randomised clinical trial. World J Urol 2013 Dec;31(6):1433-9.
http://www.ncbi.nlm.nih.gov/pubmed/23412704
51. Kraklau DM, Wolf JS Jr. Review of antibiotic prophylaxis recommendations for office based urologic procedures. Tech Urol 1999 Sep;5(3):123-8.
http://www.ncbi.nlm.nih.gov/pubmed/10527253
52. Wilson L, Ryan J, Thelning C, et al. Is antibiotic prophylaxis required for flexible cystoscopy? A truncated randomized double-blind controlled trial. J Endourol 2005 Oct;19(8):1006-8.
http://www.ncbi.nlm.nih.gov/pubmed/16253070
53. Latthe PM, Foon R, Toozs-Hobson P. Prophylactic antibiotics in urodynamics: a systematic review of effectiveness and safety. Neurourol Urodyn 2008;27(3):167-73.
http://www.ncbi.nlm.nih.gov/pubmed/17849482
54. Clark KR, Higgs MJ. Urinary infection following out-patient flexible cystoscopy. Br J Urol1990 Nov; 66(5):503-5.
http://www.ncbi.nlm.nih.gov/pubmed/2249120
55. Almallah YZ, Rennie CD, Stone J, et al. Urinary tract infection and patient satisfaction after flexible cystoscopy and urodynamic evaluation. Urology 2000 Jul;56(1):37-9.
http://www.ncbi.nlm.nih.gov/pubmed/10869618
56. Burke DM, Shackley DC, O'Reilly PH.The community-based morbidity of flexible cystoscopy. BJU Int 2002 Mar;89(4):347-9.
http://www.ncbi.nlm.nih.gov/pubmed/11872022
57. Johnson MI, Merrilees D, Robson WA, et al. Oral ciprofloxacin or trimethoprim reduces bacteriuria after flexible cystoscopy. BJU Int 2007 Oct;100(4):826-9.
http://www.ncbi.nlm.nih.gov/pubmed/17822463
58. Jimenez Cruz JF, Sanz Chinesta S, Otero G, et al. [Antimicrobial prophylaxis in urethrocystoscopy. Comparative study]. Actas Urol Esp 1993 Mar;17(3):172-5.
http://www.ncbi.nlm.nih.gov/pubmed/8506770
59. MacDermott JP, Ewing RE, Somerville JF, et al. Cephradine prophylaxis in transurethral procedures for carcinoma of the bladder. Br J Urol 1988 Aug;62(2):136-9.
http://www.ncbi.nlm.nih.gov/pubmed/3044484
60. Rane A, Cahill D, Saleemi A, et al. The issue of prophylactic antibiotics prior to flexible cystoscopy. Eur Urol 2001 Feb;39(2):212-4.
http://www.ncbi.nlm.nih.gov/pubmed/11223682
61. Manson AL. Is antibiotic administration indicated after outpatient cystoscopy. J Urol 1988 Aug;140(2):316-7.
http://www.ncbi.nlm.nih.gov/pubmed/3398127

62. Karmouni T, Bensalah K, Alva A, et al. [Role of antibiotic prophylaxis in ambulatory cystoscopy]. Prog Urol 2001 Dec;11(6):1239-41. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/11859658
63. Tsugawa M, Monden K, Nasu Y, et al. Prospective randomized comparative study of antibiotic prophylaxis in urethrocystoscopy and urethrocystography. Int J Urol 1998 Sep;5(5):441-3.
http://www.ncbi.nlm.nih.gov/pubmed/9781431
64. Cundiff GW, McLennan MT, Bent AE. Randomized trial of antibiotic prophylaxis for combined urodynamics and cystourethroscopy. Obstet Gynecol 1999;93(5 Pt 1):749-52.
http://www.ncbi.nlm.nih.gov/pubmed/10912979
65. Logadottir Y, Dahlstrand C, Fall M, et al. Invasive urodynamic studies are well tolerated by the patients and associated with a low risk of urinary tract infection. Scand J Urol Nephrol 2001 Dec;35(6):459-62.
http://www.ncbi.nlm.nih.gov/pubmed/11848424
66. Upton JD, Das S. Prophylactic antibiotics in transurethral resection of bladder tumors: are they necessary? Urology 1986 May;27(5):421-3.
http://www.ncbi.nlm.nih.gov/pubmed/3518183
67. Delavierre D, Huiban B, Fournier G, et al. [The value of antibiotic prophylaxis in transurethral resection of bladder tumors. Apropos of 61 cases]. Prog Urol 1993 Aug-Sep;3(4):577-82. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/8401618
68. Grabe M. Antimicrobial agents in transurethral prostatic resection. J Urol 1987 Aug;138(2):245-52. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/3298693
69. Berry A, Barratt A. Prophylactic antibiotic use in transurethral prostatic resection: a meta-analysis. J Urol 2002 Feb;167(2 Pt 1):571-7.
http://www.ncbi.nlm.nih.gov/pubmed/11792921
70. Alsaywid BS and Smith GH. Antibiotic prophylaxis for transurethral urological surgeries: Systematic review. Urol Ann 2013 Apr;5(2):61-74.
http://www.ncbi.nlm.nih.gov/pubmed/23798859
71. Dasgupta R, Grabe M. Preoperative antibiotics before endourologic surgery: current recommendations. J Endourol 2009 Oct;23:1567-70
http://www.ncbi.nlm.nih.gov/pubmed/19785548
72. Fourcade RO. Antibiotic prophylaxis with cefotaxime in endoscopic extraction of upper urinary tract stones: a randomized study. The Cefotaxime Cooperative Group. J Antimicrob Chemother 1990 Sep;26 Suppl A:77-83.
http://www.ncbi.nlm.nih.gov/pubmed/2228847
73. Knopf HJ, Graff HJ, Schulze H. Perioperative antibiotic prophylaxis in ureteroscopic stone removal. Eur Urol, 2003.;44(1):115-8.
http://www.ncbi.nlm.nih.gov/pubmed/12814685
74. Hendrikx AJ, Strijbos WE, de Knijff DW, et al. Treatment for extended-mid and distal ureteral stones: SWL or ureteroscopy? Results of a multicenter study. J Endourol 1999;13(10):727-33.
http://www.ncbi.nlm.nih.gov/pubmed/10646679
75. Rao PN, Dube DA, Weightman NC, et al. Prediction of septicaemia following endourological manipulation for stones in the upper urinary tract. J Urol 1991;146:955-60.
http://www.ncbi.nlm.nih.gov/pubmed/1895450
76. Charton M, Vallancien G, Veillon B, et al. Urinary tract infection in percutaneous surgery for renal calculi. J Urol 1986 Jan;135(1):15-7.
http://www.ncbi.nlm.nih.gov/pubmed/3510316
77. Osman M, Wendt-Nordahl G, Heger K, et al. Percutaneous nephrolithotomy with ultrasonographyguided renal access: experience from over 300 cases. BJU Int 2005 Oct;96(6):875-8.
http://www.ncbi.nlm.nih.gov/pubmed/16153221
78. Dogan HS, Sahin A, Cetinkaya Y, et al. Antibiotic prophylaxis in percutaneous nephrolithotomy: prospective study in 81 patients. J Endourol 2002 Nov;16(9):649-53.
http://www.ncbi.nlm.nih.gov/pubmed/12490017
79. Mariappan P, Smith G, Bariol SV, et al. Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. J Urol 2005 May;173(5):1610-4.
http://www.ncbi.nlm.nih.gov/pubmed/15821509
80. Gravas S, Montanari E, Geavlete P, et al. Postoperative Infection Rates in Low Risk Patients Undergoing Percutaneous Nephrolitotomy with and without Antibiotic Prophylaxis: A Matched Case Control Study. J Urol 2012 Sep;188:843-7.
http://www.ncbi.nlm.nih.gov/pubmed/22819398

81. Seyrek M, Binbay M, Yuruk E, et al. Perioperative Prophylaxis for Percutaneous Nephrolitotomy: Randomized Study Concerning the Drug and Dosage. J Endourol 2012 Nov; 26(11):1431-6.
http://www.ncbi.nlm.nih.gov/pubmed/22612061
82. Charton M, Vallancien G, Veillon B, et al. Use of antibiotics in the conjunction with extracorporeal lithotripsy. Eur Urol 1990;17(2):134-8.
http://www.ncbi.nlm.nih.gov/pubmed/2178940
83. Deliveliotis C, Giftopoulos A, Koutsokalis G, et al. The necessity of prophylactic antibiotics during extracorporeal shock wave lithotripsy. Int Urol Nephrol 1997;29(5):517-21.
http://www.ncbi.nlm.nih.gov/pubmed/9413755
84. Dincel C, Ozdiler E, Ozenci H, et al. Incidence of urinary tract infection in patients without bacteriuria undergoing SWL: comparison of stone types. J Endourol 1998 Feb;12(1):1-3.
http://www.ncbi.nlm.nih.gov/pubmed/9531141
85. Claes H, Vandeursen R, Baert L. Amoxycillin/clavulanate prophylaxis for extracorporeal shock wave lithotripsy - a comparative study. J Antimicrob Chemother, 1989 Nov;24 Suppl B:217-20.
http://www.ncbi.nlm.nih.gov/pubmed/2691484
86. Gattegno B, Sicard F, Alcaidinho D, et al. [Extracorporeal lithotripsy and prophylactic antibiotic therapy]. Ann Urol (Paris) 1988;22(2):101-2.
http://www.ncbi.nlm.nih.gov/pubmed/3382159
87. Pettersson B, Tiselius HG. Are prophylactic antibiotics necessary during extracorporeal shockwave lithotripsy? Br J Urol 1989 May;63(5):449-52.
http://www.ncbi.nlm.nih.gov/pubmed/2659132
88. Knipper A, Bohle A, Pensel J, et al. [Antibiotic prophylaxis with enoxacin in extracorporeal shockwave lithotripsy]. Infection 1989;17 Suppl 1:S37-8. [Article in German]
http://www.ncbi.nlm.nih.gov/pubmed/2807562
89. Bierkens AF, Hendrikx AJ, Ezz el Din KE, et al. The value of antibiotic prophylaxis during extracorporeal shock wave lithotripsy in the prevention of urinary tract infections in patients with urine proven sterile prior to treatment. Eur Urol 1997;31(1):30-5.
http://www.ncbi.nlm.nih.gov/pubmed/9032531
90. Pearle MS, Roehrborn CG. Antimicrobial prophylaxis prior to shock wave lithotripsy in patients with sterile urine before treatment: a meta-analysis and cost-effectivness analysis. Urology 1997 May;49(5):679-86.
http://www.ncbi.nlm.nih.gov/pubmed/9145970
91. Lu Y, Tianyoung F, Ping H, Liangren L et al. Antibiotic Prophylaxis for Shock Wave Lithotripsy in Patients with Sterile Urine Before Treatment May be Unnecesssary: A Systematic Review and Meta-Analysis. J Urol 2012;188:441-8.
http://www.ncbi.nlm.nih.gov/pubmed/22704118
92. Steiner T, Traue C, Schubert J. [Perioperative antibiotic prophylaxis in transperitoneal tumor nephrectomy: does it lower the rate of clinically significant postoperative infections?]. Urologe A 2003 Jan;42(1):34-7. [Article in German]
http://www.ncbi.nlm.nih.gov/pubmed/12574881
93. Montgomery JS, Johnston WK, 3rd, Wolf JS, Jr. Wound complications after hand assisted laparoscopic surgery. J Urol 2005 Dec;174(6):2226-30.
http://www.ncbi.nlm.nih.gov/pubmed/16280775
94. Pessaux P, Atallah D, Lermite E, et al. Risk factors for prediction of surgical site infections in “clean surgery”. Am J Infect Control 2005 Jun;33(5):292-8.
http://www.ncbi.nlm.nih.gov/pubmed/15947746
95. Kiddoo DA, Wollin TA, Mador DR. A population based assessment of complications following outpatient hydrocelectomy and spermatocelectomy. J Urol 2004 Feb;171(2 Pt 1):746-8.
http://www.ncbi.nlm.nih.gov/pubmed/14713801
96. Swartz MA, Morgan TM, Krieger JN. Complications of scrotal surgery for benign conditions. Urology 2007 Apr;69(4):616-9.
http://www.ncbi.nlm.nih.gov/pubmed/17445635
97. Stranne J, Aus G, Hansson C, et al. Single-dose orally administered quinolone appears to be sufficient antibiotic prophylaxis for radical retropubic prostatectomy. Scand J Urol Nephrol 2004;38(2):143-7.
http://www.ncbi.nlm.nih.gov/pubmed/15204401
98. Terai A, Ichioka K, Kohei N, et al. Antibiotic prophylaxis in radical prostatectomy: 1-day versus 4-day treatments. Int J Urol 2006 Dec;13(12):1488-93.
http://www.ncbi.nlm.nih.gov/pubmed/17118023

99. Takeyama K, Takahashi S, Maeda T, et al. Comparison of 1-day, 2-day, and 3-day administration of antimicrobial prophylaxis in radical prostatectomy. J Infect Chemother 2007 Oct;13(5):320-3. http://www.ncbi.nlm.nih.gov/pubmed/17982721
100. Sakura M, Kawakami S, Yoshida S, et al. Prospective comparative study of single dose versus 3-day administration of antimicrobial prophylaxis in minimum incision endoscopic radical prostatectomy. Int J Urol 2008 Apr;15(4):328-31. http://www.ncbi.nlm.nih.gov/pubmed/18380822
101. Richter S, Lang R, Zur F, et al. Infected urine as a risk factor for postprostatectomy wound infection. Infect Control Hosp Epidemiol 1991 Mar;12(3):147-9. http://www.ncbi.nlm.nih.gov/pubmed/2022859
102. Takeyama K, Matsukawa M, Kunishima Y, et al. Incidence of and risk factors for surgical site infection in patients with radical cystectomy with urinary diversion. J Infect Chemother 2005 Aug;11(4):177-81. http://www.ncbi.nlm.nih.gov/pubmed/16133708
103. Hara N, Kitamura Y, Saito T, et al. Perioperative antibiotics in radical cystectomy with ileal conduit urinary diversion: efficacy and risk of antimicrobial prophylaxis on the operation day alone. Int J Urol 2008 Jun;15(6):511-5. http://www.ncbi.nlm.nih.gov/pubmed/18422576
104. Studer UE, Danuser H, Merz VW, et al. Experience in 100 patients with an ileal low pressure bladder substitute combined with an afferent tubular isoperistaltic segment. J Urol 1995 Jul;154(1):49-56. http://www.ncbi.nlm.nih.gov/pubmed/7776455
105. Mangram AJ, Horan TC, Pearson ML, et al. Guidelines for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1999 Apr;27(2):97-132. http://www.ncbi.nlm.nih.gov/pubmed/10196487
106. Kabalin JN, Kessler R. Infectious complications of penile prosthesis surgery. J Urol 1988 May;139(5):953-5. http://www.ncbi.nlm.nih.gov/pubmed/3361672
107. Radomski SB, Herschorn S. Risk factors associated with penile prosthesis infection. J Urol 1992 Feb;147(2):383-5. http://www.ncbi.nlm.nih.gov/pubmed/1732599
108. Mould JW, Carson CC. Infectious complications of penile prostheses. Infections in Urology 1989;139:50-2.
109. Carson CC. Diagnosis. treatment and prevention of penile prosthesis infection. Int J Impot Res 2003 Oct;15 Suppl 5:S139-46. http://www.ncbi.nlm.nih.gov/pubmed/14551594

16. APPENDICES

16.1 Criteria for the diagnosis of UTI, as modified according to IDSA/European Society of Clinical Microbiology and Infectious Diseases guidelines (1-3)

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

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

16.1.1 ***References***

1. Rubin RH, Shapiro ED, Andriole VT, 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 Nov;15 Suppl 1:S216-27. http://www.ncbi.nlm.nih.gov/pubmed/1477233
2. Rubin RH, Shapiro ED, Andriole VT, et al, with modifications by a European Working Party (Norrby SR). General guidelines for the evaluation of new anti-infective drugs for the treatment of UTI. Taufkirchen, Germany: The European Society of Clinical Microbiology and Infectious Diseases, 1993; pp. 294-310.
3. Naber KG. Experience with the new guidelines on evaluation of new anti-infective drugs for the treatment of urinary tract infections. Int J Antimicrob Agents 1999 May;11(3-4):189-96;discussion 213-6. http://www.ncbi.nlm.nih.gov/pubmed/10394969

16.2 Recommendations for antimicrobial therapy in urology

Diagnosis	Most frequent pathogen/species	Initial, empirical antimicrobial therapy	Therapy duration
Cystitis acute, uncomplicated	• *E. coli* • *Klebsiella* • *Proteus* • Staphylococci	• TMP-SMX[1] • Nitrofurantoin • Fosfomycin trometamol • Pivmecillinam Alternative: • Fluoroquinolone[2,3]	3 days (5-)7 days 1 day (3-)5 days (1-)3 days
Pyelonephritis acute, uncomplicated	• *E. coli* • *Proteus* • *Klebsiella* • Other enterobacteria • Staphylococci	• Fluoroquinolone[2] • Cephalosporin (group 3a) Alternatives: • Aminopenicillin/BLI • Aminoglycoside	7-10 days
UTI with complicating factors	• *E. coli* • Enterococci • *Pseudomonas* • Staphylococci	• Fluoroquinolone[2] • Aminopenicillin/BLI • Cephalosporin (group 2) • Cephalosporin (group 3a) • Aminoglycoside In case of failure of initial therapy within 1-3 days or in clinically cases: Anti-*Pseudomonas* active: • Fluoroquinolone, if not used initially • Acylaminopenicillin/BLI • Cephalosporin (group 3b) • Carbapenem • ± Aminoglycoside In case of Candida: • Fluconazole • Amphotericin B	3-5 days after defervescence or control/elimination of complicating factor
Nosocomial UTI	• *Klebsiella* • *Proteus*		
Pyelonephritis severe acute, complicated	• *Enterobacter* • Other enterobacteria • *(Candida)*		
Prostatitis acute, chronic	• *E. coli* • Other enterobacteria • *Pseudomonas* • Enterococci Chronic: • Staphylococci • *Chlamydia* • *Ureaplasma* • *E. coli* • Other enterobacteria After urological interventions - multi-resistant pathogens: • *Pseudomonas* • *Proteus* • *Serratia* • *Enterobacter*	• Fluoroquinolone[2] Alternative in acute bacterial prostatitis: • Cephalosporin (group 3a/b) In case of *Chlamydia* or *Ureaplasma*: • Doxycycline • Macrolide • Cephalosporin (group 3a/b) • Fluoroquinolone[2] • Anti-*Pseudomonas* active acylaminopenicillin/BLI • Carbapenem • ± Aminoglycoside	Acute: 2-4 weeks Chronic: 4-6 weeks or longer 3-5 days after defervescence or control/elimination of complicating factor
Epididymitis Ureaplasma: Acute			
Urosepsis			

[1]*Only in areas with resistance rate < 20% (for* E. coli*).*
[2]*Fluoroquinolone with mainly renal excretion (see text).*
[3]*Avoid Fluoroquinolones in uncomplicated cystitis whenever possible.*

16.3 Recommendations for antimicrobial prescription in renal failure

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

Doxycycline	normal	normal	normal	All other tetracyclines contraindicated in renal impairment
Erythromycin IV + po	normal	normal	normal Max. 1.5 g/day (500 mg qds)	
*Ethambutol	normal	24-36 h	48 h	Give post-HD
	Monitor levels if GFR < 30mL/min (contact Mirco)			
Flucloxacillin IV + po	normal	normal	normal Max. 4 g/day	
Fluconazole	normal	normal	50%	Give post-HD No adjustments in single-dose therapy required
*Flucytosine	50 mg/kg 12 h	50 mg/kg 24 h	50 mg/kg stat then dose according to levels	Give post-HD Levels should be monitored predialysis.
Fusidic acid	normal	normal	normal	
1) Gentamicin ONCE DAILY	**GFR 10-40 mL/min** 3 mg/kg stat (max. 300 mg) Check pre-dose levels 18-24 h after first dose Redose only when level < 1 mg/L		**GFR < 10 mL/min** 2 mg/kg (max. 200 mg) redose according to levels	BOTH METHODS Give post-HD Monitor blood levels:
2) Gentamicin CONVENTIONAL	80 mg 12 h	80 mg 48 h	80 mg 24 h HD: 1-2 mg/kg Post-HD: redose according to levels	Once daily: pre only Conventional: pre and 1 h post level required.
Imipenem	500 mg 8-12 h	250-500 mg bid	Risk of convulsions - use Meropenem: *see below*	Give post-HD
Isoniazid	normal	normal	200-300 mg 24 h	Give post-HD
Itraconazole	normal	normal	normal	
Levoflaxacin	500 mg stat then 250 mg bid**	500 mg stat then 125 mg bid**	500 mg stat then 125 mg od	**Applies if full dose is 500 mg bid If full dose is 500 mg od, five reduced doses daily
Linezolid	normal	normal	normal	Give post-HD
Meropenem	12 h	50% 12 h	50% 24 h	Give post-HD
Metronidazole	normal	normal	12 h (normal)	Give post-HD
Nitrofurantoin	Do **NOT** use in renal impairment			
Penicillin V	normal	normal	normal	Give post-HD
Piperacillin/ Tazobactam (Tazocin)	4.5 g 8 h	4.5 g 12 h	4.5 g 12 h	Give post-HD
Pyrazinamide	normal	normal	normal	
Rifampicin	normal	normal	50-100%	

*Teicoplanin	100% 48 h	100% 72 h	100% 72 h	Dose reduction after day 3 of therapy
Tetracycline	See **Doxycycline**			
Trimethoprim	normal	Normal for 3/7 then 50% 18 h	50% 24 h	Give post-HD
Vancomycin	1 g od Check pre-dose level before 3rd dose	1 g 48 h Check pre-dose level before 2nd dose	1 g stat (or 15 mg/kg, up to max. 2 g). Recheck level after 4-5 days ONLY give subsequent dose when level < 12mg/L	Monitor pre-dose levels and adjust dose as required
Vorinconazole	normal	normal	normal	Give post HD

bid = twice daily; HD = haemodialysis; od = once daily; po = by mouth; qid = four times daily; SBE = subacute bacterial endocarditis; tds = total dissolved solids; qds = Quantum Dots.

16.4 CPSI

from: Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun MA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. The National Institute of Health chronic prostatitis symptom index: development and validation of new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999:162;369-375.

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	☐ 1	☐ 0
b. Testicles	☐ 1	☐ 0
c. Tip of penis (not related to urination)	☐ 1	☐ 0
d. Below your waist, in your pubic or bladder area	☐ 1	☐ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	☐ 1	☐ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	☐ 1	☐ 0

3. How often have you had pain or discomfort in any of these areas over the last week?

☐ 0 Never
☐ 1 Rarely
☐ 2 Sometimes
☐ 3 Often
☐ 4 Usually
☐ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating over the last week?
☐ 0 Not at all
☐ 1 Less than 1 time in 5
☐ 2 Less than half the time
☐ 3 About half the time
☐ 4 More than half the time
☐ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

☐ 0 Not at all
☐ 1 Less than 1 time in 5
☐ 2 Less than half the time
☐ 3 About half the time
☐ 4 More than half the time
☐ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do over the last week?

☐ 0 None
☐ 1 Only a little
☐ 2 Some
☐ 3 A lot

8. How much did you think about your symptoms, over the last week?

☐ 0 None
☐ 1 Only a little
☐ 2 Some
☐ 3 A lot

Quality of life

9. If you were to spend the rest of your life with your symptoms, just the way they have been during the last week, how would you feel about that?

☐ 0 Delighted
☐ 1 Pleased
☐ 2 Mostly satisfied
☐ 3 Mixed (about equally satisfied and dissatisfied)
☐ 4 Mostly dissatisfied
☐ 5 Unhappy
☐ 6 Terrible

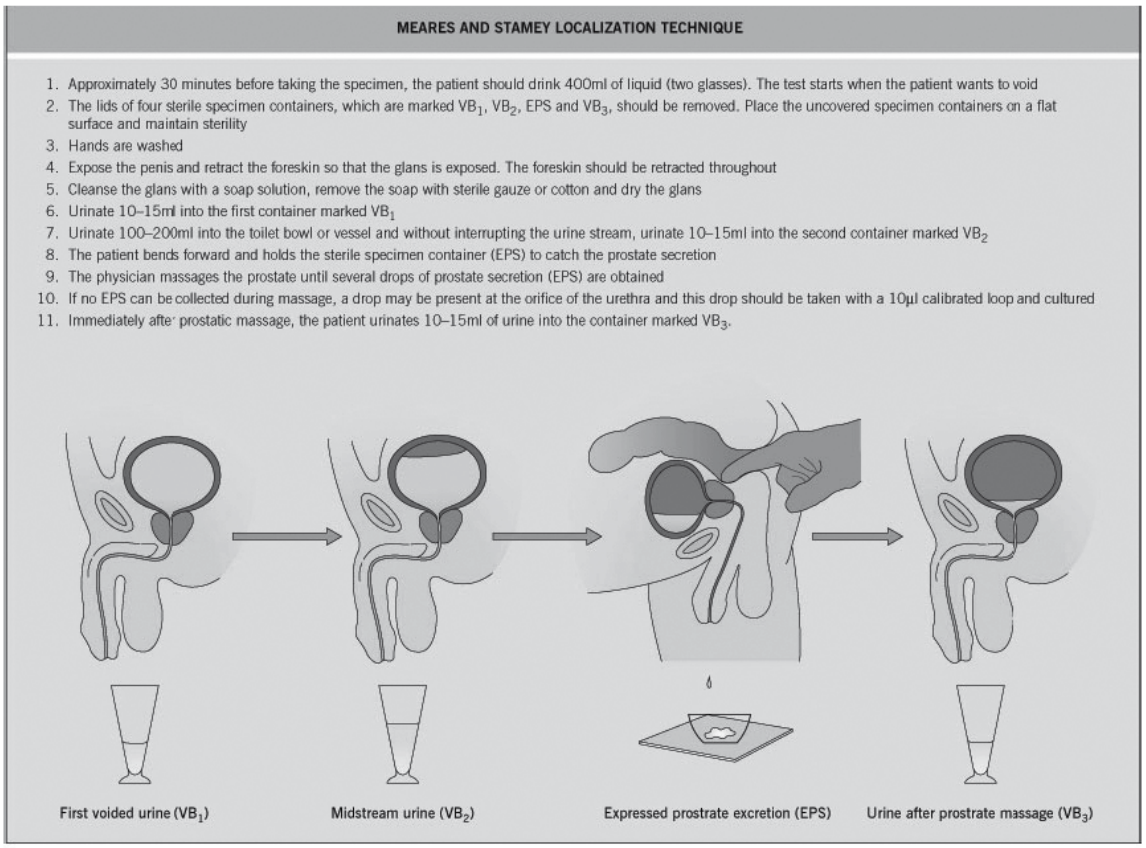
Scoring the NIH-CPSI Prostatitis Symptom Index Domain

Pain:
Total of items 1a,1b,1c,1d,2a,2b,3 and 4 = _____

Urinary Symptoms:
Total of items 5 and 6 = _____

Quality of Life Impact:
Total of items 7,8, and 9 = _____

16.5 Meares & Stamey localisation technique*



* Naber KG, Weidner W. Prostatitis, epididymitis, orchitis. In: Armstrong D, Cohen J, eds. Infectious Diseases. London: Mosby, Harcourt Publishers Ltd, 1999, pp. 1-58.

16.6 Antibacterial agents

Groups	Agents
Trimethoprim-sulphonamide combinations	Trimethoprim, co-trimoxazole, co-tetroxoprime (trimethoprim plus sulfametrol)
Fluoroquinolones[1,2]	
Group 1	Norfloxacin, pefloxacin
Group 2	Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin
Group 3	Levofloxacin
Group 4	Gatifloxacin, moxifloxacin
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
Tetracyclines	Doxycycline, minocycline, tetracycline
Fosfomycin	Fosfomycin sodium, fosfomycin trometamol3
Nitrofuran[4]	Nitrofurantoin
Penicillins	
Benzylpenicillin	Penicillin G
Phenoxypenicillins	Penicillin V, propicillin, azidocillin
Isoxazolylpenicillins	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin
Aminobenzylpenicillins[5]	Ampicillin, amoxycillin, bacampicillin
Aminopenicillins/BLI[6]	Ampicillin/sulbactam, amoxycillin/clavulanic acid[7]
Acylaminopenicillins	Mezlocillin, piperacillin

±BLI[6]	Piperacillin/tazobactam, sulbactam[6]
Cephalosporins[1]	
Group 1 (oral)	Cefalexin, cefadroxil, cefaclor
Group 2 (oral)	Loracarbef, cefuroxime axetile
Group 3 (oral)	Cefpodoxime proxetile, cefetamet pivoxil, ceftibuten, cefixime
Group 1 (parenteral)	Cefazolin
Group 2 (parenteral)	Cefamandole, cefuroxime, cefotiam
Group 3a (parenteral)	Cefodizime, cefotaxime, ceftriaxone
Group 3b (parenteral)	Cefoperazone, ceftazidime
Group 4 (parenteral)	Cefepime, cefpirome
Group 5 (parenteral)	Cefoxitin
Monobactams	Aztreonam
Carbapenems	Imipenem, meropenem, ertapenem
Aminoglycosides	Gentamicin, netilmicin, tobramycin, amikacin
Glycopeptides	Vancomycin, teicoplanin
Oxazolidones	Linezolid

[1]Classification according to the Paul Ehrlich Society for Chemotherapy (1-3).
[2]Only in adults, except pregnant and lactating women.
[3]Only in acute, uncomplicated cystitis as a single dose.
[4]Contraindicated in renal failure and in newborns.
[5]In cases of resistance, the pathogen is most likely to be a β-lactamase producer.
[6]BLIs can only be used in combination with β-lactam antibiotics.
[7]In solution, storage instability.

16.6.1 ***Penicillins***

Penicillin G and the oral penicillins, penicillin V, propicillin and azidocillin, have a high intrinsic activity against streptococci and pneumococci. However, the resistance rate of pneumococci may vary considerably between countries. In Germany, penicillin resistance in pneumococci is still < 1%. Because of their narrow spectrum of activity, these penicillins do not have any role in the treatment of urogenital infections.

16.6.1.1 Aminopenicillins

Aminopenicillins, e.g. ampicillin and amoxycillin, have a broader spectrum of activity. Apart from streptococci and pneumococci, they cover enterococci, *Haemophilus influenzae*, *Haemophilus parainfluenzae, Listeria sp*., *E. coli*, *Pr. mirabilis*, and *Salmonella* and *Shigella* sp. However, resistance may occur.

Aminopenicillins are sensitive to β-lactamases. They are therefore not sufficiently active against certain species, such as staphylococci, *Moraxella catarrhalis*, *Bacteroides fragilis* and many enterobacteria. This gap in the spectrum of activity can be closed by the use of a BLI (clavulanic acid, or sulbactam). Amoxycillin/clavulanic acid and ampicillin/sulbactam are available on the market as fixed combinations. Indications for aminopenicillins and their combinations with a BLI are mild respiratory tract infections, UTIs, as well as infections of the skin and soft tissues.

16.6.1.2 Acylaminopenicillins

The acylaminopenicillins include apalcillin, azlocillin, mezlocillin and piperacillin. They are characterised by their high activity against enterococci, enterobacteria and *Pseudomonas* (weaker activity of mezlocillin). Acylaminopenicillins are hydrolyzed by β-lactamases and are therefore active only against β-lactamase-producing strains of staphylococci, *B. fragilis*, and if used in combination with a BLI, some of the enterobacteria. The acylaminopenicillin/BLI combination provides a broad spectrum of activity and may be used for a large number of indications, including complicated UTIs and urosepsis. A selection of free combinations with sulbactam is available, or there is the fixed combination of tazobactam and piperacillin, which has the advantages of being easy to use and a well-documented database drawn from qualified clinical studies.

16.6.1.3 Isoxazolylpenicillins

Isoxazolylpenicillins are available as parenteral drugs with oxacillin and flucloxacillin, and have a narrow spectrum of activity. Their indications are limited to infections caused by *S. aureus*. Due to their suboptimal

pharmacokinetic parameters, isoxazolylpenicillins are preferably used in milder infections of the skin and soft tissues, and of the ear, nose and throat area. They play no role in the treatment of UTIs, but may be used for staphylococcal abscesses in the genital area.

16.6.2 ***Parenteral cephalosporins***

According to the Paul Ehrlich Society for Chemotherapy (1), the parenteral cephalosporins have been classified into five groups, according to their spectrum of activity (Table 16.7.2).

16.6.2.1 Group 1 cephalosporins

Group 1 cephalosporins (cefazolin and cefazedone) are very active against streptococci and staphylococci (including penicillin-G-resistant strains). They have only weak activity against Gram-negative microorganisms. Like all cephalosporins, cefazolin is not active against enterococci and MRSA and methicillin-resistant coagulase-negative staphylococci (MRSE).

16.6.2.2 Group 2 cephalosporins

Compared with Group 1 cephalosporins, Group 2 cephalosporins, e.g. cefuroxime, cefotiame and cefamandole, exhibit markedly improved activity against Gram-negative pathogens and maintain high activity against staphylococci.

16.6.2.3 Group 3a cephalosporins

Group 3a cephalosporins have high activity against Gram-negative bacteria and less activity against staphylococci. They differ mainly in their pharmacokinetic characteristics.

16.6.2.4 Group 3b cephalosporins

Group 3b cephalosporins, e.g. ceftazidime and cefoperazone, have added high anti-pseudomonal activity. However, the activity of cefoperazone against P. aeruginosa is markedly inferior to that of the other substances in this group.

16.6.2.5 Group 4 cephalosporins

Group 4 cephalosporins, e.g. cefepime and cefpirome, have a comparable activity against Gram-negative bacteria, but are more stable against extended-spectrum β-lactamases, and a better activity against Gram-positive bacteria.

16.6.2.6 Group 5 cephalosporins

The Group 5 cephalosporins are characterised by their anti-anaerobic activity. These cephalosporins have superior activity against Gram-negative bacteria compared with Group 1 and 2 cephalosporins, but most of them are weaker than Group 3 drugs. At present, cefoxitin is the only drug of that group available on the market in some countries.

Table 16.6.2: Classification of parenteral cephalosporins (2)

Group	Generic names	Features of the group
Group 1 (1st generation)	Cefazolin Cefazedone	• Active against Gram-positive and partly against Gram-negative bacteria • Stable against staphylococcal penicillinases • Unstable against β-lactamases of Gram-negative bacteria
Group 2 (2nd generation)	Cefuroxime Cefotiame Cefamandole	• Activity against Gram-positive bacteria good, but weaker than Group 1 • Activity against Gram-negative bacteria superior to that of Group 1 • Stable against staphylococcal penicillinases • Limited stability against β-lactamases of Gram-negative bacteria
Group 3a (3rd generation)	Cefotaxime Ceftriaxone Ceftizoxime Cefmenoxime Cefodizime	• Activity against Gram-negative bacteria clearly superior to that of Groups 1 and 2 • Stable against numerous β-lactamases of Gram-negative bacteria • Microbiologically less active against staphylococci
Group 3b (3rd generation)	Ceftazidime	• Spectrum of antibacterial activity similar to that of Group 3a
	Cefoperazone	• Additional activity against P. aeruginosa
Group 4	Cefepime Cefpirome	• Spectrum of antibacterial activity similar to that of Group 3a
Group 5	Cefoxitin	• Additional activity against P. aeruginosa • Higher stability against beta-lactamases than group 3b • With anti-anaerobic activity • Superior activity against Gram-negative bacteria than Group 1 and 2 • Weaker than Group 3

*16.6.3 **Oral cephalosporins***

Oral cephalosporins are classified into three groups, based on their spectrum of activity, according to the recommendations of the Paul Ehrlich Society for Chemotherapy (1) (Table 16.7.3).

Table 16.7.3: Classification of oral cephalosporins (1)

Oral cephalosporins	Drug names
Group 1	Cefalexin Cefadroxil Cefaclor
Group 2	Cefprozil Loracarbef Cefuroxime axetile
Group 3	Cefpodoxime proxetile Cefetamet pivoxile Ceftibuten Cefixime

16.6.3.1 Group 1 oral cephalosporins

Group 1 oral cephalosporins include cefalexin, cefadroxil and cefaclor. They are mainly active against Gram-positive cocci with limited activity against *H. influenzae* (cefaclor). Their main indications are skin and soft tissue infections and, with limitations, respiratory tract infections. Their activity against enterobacteria is limited, therefore, they can only be recommended for the treatment or prophylaxis of uncomplicated UTIs in children or

pregnant women, for whom the use of other antibiotics is limited.

16.6.3.2 Group 2 oral cephalosporins

The activity of cefprozil against *S. aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *H. influenzae* and *Mor. catarrhalis* is somewhat higher than that of cefaclor. However, cefprozil is less active than cefaclor against *E. coli*, *Klebsiella pneumoniae* and *Pr. mirabilis*.

Loracarbef is structurally close to cefaclor. In contrast to cefaclor, it is stable in solution, has better pharmacokinetics and a broader antibacterial spectrum. However, its activity against staphylococci is lower than that of cefaclor. The main indications are respiratory tract, skin and soft-tissue infections and uncomplicated UTIs.

Cefuroxime axetile has a higher β-lactamase stability and thus a broader spectrum than others in this group. It can be used mainly for bacterial infections of the upper (including otitis media) and lower respiratory tract, for skin and soft-tissue infections, and UTIs.

16.6.3.3 Group 3 oral cephalosporins

Group 3 oral cephalosporins have a higher activity and a broader spectrum against enterobacteria than group 2 cephalosporins. In contrast, their activity against Gram-positive bacteria is lower. Against staphylococci, the activity of cefpodoxime proxetil is intermediate, whereas cefetamet pivoxil, ceftibuten and cefixime are inactive.

The main indications for the oral cephalosporins of group 3 are complicated infections of the respiratory tract (provided that staphylococci can be excluded) and infections due to enterobacteria, e.g. UTIs or infections in immunocompromised patients. Group 3 oral cephalosporins are also suitable for oral switch therapy, i.e. when initial parenteral therapy (using a parenteral group 3a cephalosporin) needs to be continued orally. In addition, cefixime is licensed also for treatment of gonorrhoea.

*16.6.4 **Monobactams***

Among the monobactams, only aztreonam is available. It is active only against Gram-negative aerobes. In this respect, its spectrum and activity are similar to those of the parenteral group 3b cephalosporins.

*16.6.5 **Carbapenems***

Carbapenems are broad-spectrum antibiotics with good activity against Gram-positive and Gram-negative bacteria, including anaerobes. They are preferably used in the treatment of mixed infections and in the initial therapy of life-threatening diseases, including urosepsis. Imipenem/cilastatin, meropenem and doripenem are also active against P. aeruginosa. However, ertapenem is not active against P. aeruginosa. Ertapenem has a longer half-life than imipenem/cilastatin and meropenem, and is therefore, suitable for once-daily dosing.

*16.6.6 **Fluoroquinolones***

Non-fluorinated quinolones are no longer recommended because of their poor antibacterial activity. According to the Paul Ehrlich Society for Chemotherapy, the fluoroquinolones are classified into four groups, based on their spectrum of activity, their pharmacokinetics and indications (Table 16.7.4).

Table 16.6.4: Classification of fluoroquinolones, as modified according to the Paul Ehrlich Society for Chemotherapy (3)

Generic name	**Trade name*/features of the group**
Group 1	**Indications essentially limited to UTIs in some countries, e.g. Germany**
	Norfloxacin
	Pefloxacin**
Group 2	**Broad indications for systemic use**
	Enoxacin
	Fleroxacin***
	Lomefloxacin
	Ofloxacin
	Ciprofloxacin

Group 3	Improved activity against Gram-positive and atypical pathogens
	Levofloxacin
Group 4	Improved activity against Gram-positive and atypical pathogens and anaerobes
	Gatifloxacin
	Moxifloxacin

** Listed according to increasing in vitro activity (minimum inhibitory concentration) against indicative pathogens.*
*** In France and other countries, pefloxacin is also available for systemic use.*
**** Investigated in acute exacerbations of chronic bronchitis, UTIs, gonorrhoea and gastrointestinal infections.*

16.6.6.1 Group 1 fluoroquinolones

The indications for group 1 fluoroquinolones are limited to UTIs in some countries, e.g. Germany. In France and some other countries, pefloxacin is also used for systemic oral and parenteral use. Norfloxacin is not available as parenteral antibiotic.

16.6.6.2 Group 2 fluoroquinolones

Group 2 fluoroquinolones includes fluoroquinolones for systemic use with a broad spectrum of indications. These include infections of the urinary tract, respiratory tract, skin and soft tissues, bones and joints, as well as systemic infections and even sepsis. Group 2 fluoroquinolones exhibit good activity against enterobacteria and *H. influenzae*, with less activity against staphylococci, pneumococci, enterococci and atypical pathogens, e.g. *Chlamydia, Legionella* and *Mycoplasma* sp. Their activity against *P. aeruginosa* varies, with ciprofloxacin being most active in vitro. In addition, ciprofloxacin, ofloxacin and fleroxacin are also available for parenteral use.

16.6.6.3 Group 3 fluoroquinolones

The main difference in the spectra of activity of group 3 fluoroquinolones (levofloxacin) and group 4 fluoroquinolones (gatifloxacin and moxifloxacin) is that the former have a higher intrinsic activity against Gram-positive pathogens, such as staphylococci, streptococci, pneumococci and enterococci.

However, group 3 and group 4 fluoroquinolones have comparable activity against Gram-negative pathogens. In addition, they have improved activity against the so-called atypical pathogens, such as *Chlamydia, Mycoplasma* and *Legionella* sp. In addition, group 4 fluoroquinolones have improved anti-anaerobic activity.

The only group 3 fluoroquinolone available for parenteral use is levofloxacin; the left enantiomer of the ofloxacin racemate. The main indications for levofloxacin are respiratory tract infections, and, due to its high renal elimination rate, UTIs, as well as skin and soft-tissue infections.

Among group 4 fluoroquinolones, gatifloxacin (not on the market in Europe), moxifloxacin and trovafloxacin have been licensed. However, in June 1999, trovafloxacin was taken off the market because of severe side effects. Thus, to date, no parenteral fluoroquinolone of this group has been made available.

Apart from respiratory tract infections, these broad-spectrum fluoroquinolones are appropriate for treatment of skin, soft-tissue and intra-abdominal infections, and oral treatment of gynaecological infections. However, final judgement of their position in the treatment of these diseases is not yet possible. Gatifloxacin has the highest renal excretion (about 84%) after oral administration. It is therefore also the most suitable for the treatment of uncomplicated and complicated UTI. Urinary excretion of moxifloxacin after oral administration is only in the range of about 20%.

16.6.7 ***Co-trimoxazole***

The treatment of UTIs is the main indication for trimethoprim alone or in combination with a sulphonamide, e.g. sulphamethoxazole. Trimethoprim with or without sulphamethoxazole can also be used for the prophylaxis of recurrent cystitis. The resistance rate against *E. coli* can vary between countries. It is therefore not recommended for empirical therapy of acute uncomplicated cystitis or pyelonephritis, when the resistance rate in the area is > 10-20% (4). In complicated UTIs, co-trimoxazole should only be used in accordance with sensitivity testing. Trimethoprim, especially in combination with sulphamethoxazole, can lead to severe although rare adverse events, such as Lyell syndrome, Stevens-Johnson syndrome and pancytopenia.

16.6.8 ***Fosfomycin***

Fosfomycin is active against Gram-negative and Gram-positive bacteria. The sodium salt is only for parenteral use. Fosfomycin trometamol is licensed for single-dose (3 g) treatment of uncomplicated cystitis in women.

16.6.9 ***Nitrofurantoin***

The antibacterial activity of nitrofurantoin is limited to the urinary tract because of its low serum concentrations. It is active against *E. coli*, *Citrobacter* and most strains of *Klebsiella* and *Enterobacter*, whereas *Providencia* and *Serratia* are mostly resistant. *Proteus, P. aeruginosa* and *Acinetobacter* are almost always resistant. It is active against Gram-positive cocci, e.g. enterococci and staphylococci.

It is suitable only for the treatment or prophylaxis of uncomplicated UTIs. Short-term therapy for this indication has not been proven in sufficiently large studies. Little development of resistance has been observed over many years. Treatment can lead to severe, though rare adverse events, such as chronic desquamative interstitial pneumonia with fibrosis.

16.6.10 ***Macrolides***

Erythromycin is the only macrolide that is available for both oral and parenteral use. The newer macrolides, roxithromycin, clarithromycin and azithromycin, are better tolerated than erythromycin, but can only be administered orally. The macrolides have good activity against streptococci, pneumococci, *Bordetella pertussis*, and *Chlamydia, Mycoplasma* and *Legionella* sp. The macrolides are not active against Gram-negative rods, therefore, their use in the treatment of UTIs is limited to special indications, such as non-gonococcal urethritis due to *C. trachomatis*.

16.6.11 ***Tetracyclines***

The resistance against doxycycline and tetracycline of pneumococci, streptococci, *H. influenzae* and *E. coli* shows marked regional differences. Tetracyclines are therefore only suitable for initial empirical therapy if the local resistance situation is sufficiently well known and justifies their use. As a result of their high activity against the so-called atypical pathogens (*Legionella, Chlamydia* and *Mycoplasma* sp.), they may be used as alternative antibiotics in infections caused by these microorganisms, e.g. in non-gonococcal urethritis due to *C. trachomatis*.

16.6.12 ***Aminoglycosides***

Aminoglycosides are for parenteral use only. These drugs have a narrow therapeutic window. Their effective levels of activity are close to toxic borderline concentrations, making a strict therapeutic indication mandatory. With few exceptions (e.g. treatment of UTIs), aminoglycosides should only be used in combination with another appropriate antibiotic. Ideal partners are β-lactam antibiotics, because this combination has a marked synergistic effect against certain bacterial species. Streptomycin is one of the older aminoglycosides and is used only for the treatment of tuberculosis.

Newer aminoglycosides include netilmicin, gentamicin, tobramycin and amikacin. They have good activity against enterobacteria and *Pseudomonas* (especially tobramycin). Their activity against streptococci, anaerobes and *H. influenzae* is not satisfactory. Resistance data for tobramycin, gentamicin and netilmicin are almost identical, whereas the resistance situation is more favourable for amikacin against many enterobacteria.

16.6.13 ***Glycopeptides***

The glycopeptides vancomycin and teicoplanin are active against Gram-positive pathogens, i.e. staphylococci (including oxacillin-resistant strains), streptococci, enterococci, *Clostridium difficile*, diphtheria bacteria and Gram-positive aerobes. They are inactive against Gram-negative pathogens. Their use is indicated:

- In infections caused by the above-mentioned pathogens in case of allergy against all other suitable antibiotics.
- In infections caused by ampicillin-resistant enterococci or oxacillin-resistant staphylococci, or multi-resistant corynebacteria.
- As an alternative, in oral form, to metronidazole for the treatment of pseudomembranous colitis. Due to the risk of selection of glycopeptide-resistant enterococci and staphylococci, the use of glycopeptides should be highly restricted. Similar to the aminoglycosides, glycopeptides have a narrow therapeutic window.

16.6.14 ***Oxazolidinones***

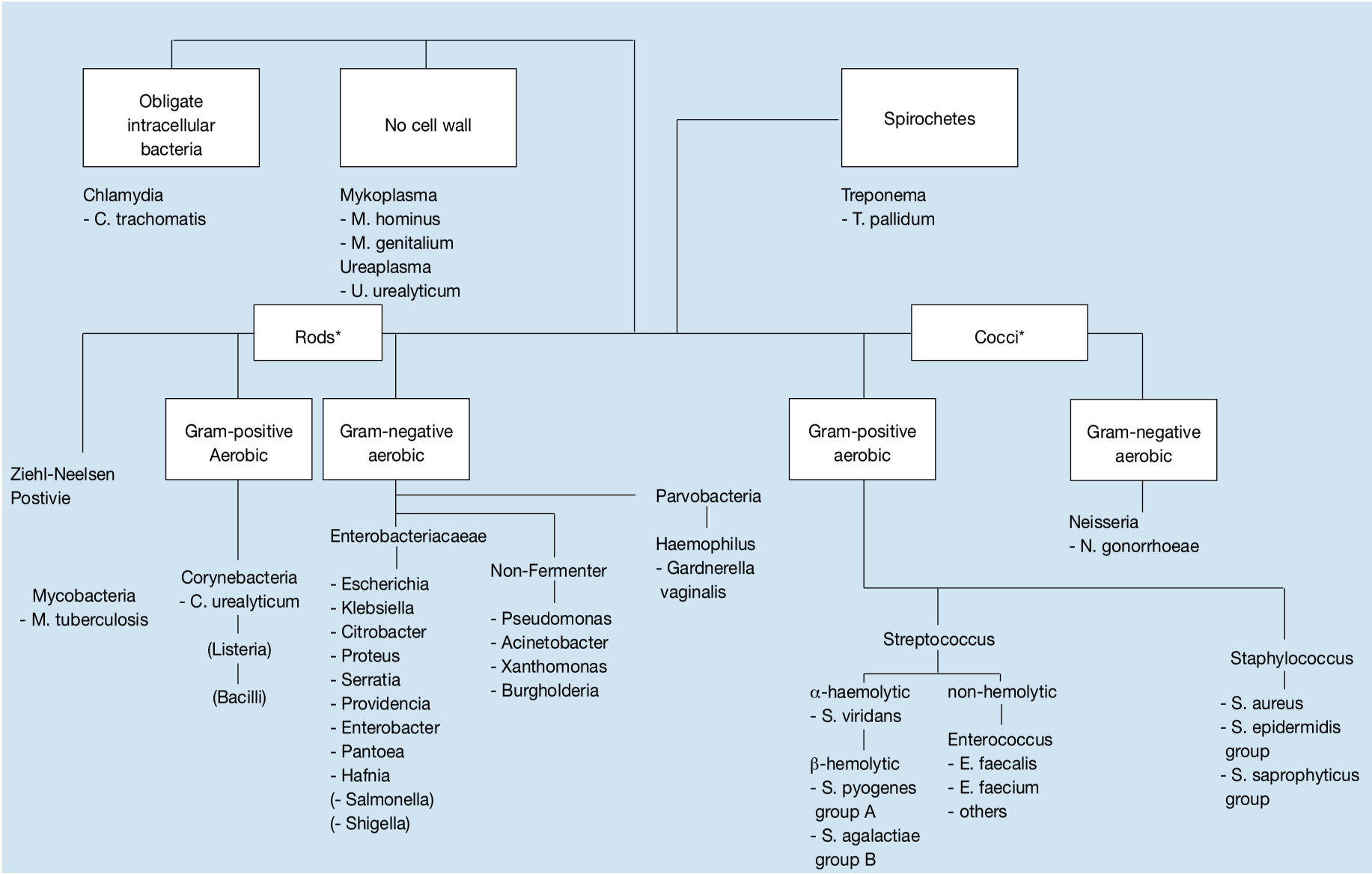
The only substance of this group is linezolid, which can be administered parenterally and orally. It has good activity against Gram-positive cocci, such as staphylococci, including methicillin (oxacillin)-resistant strains, enterococci, including vancomycin-resistant strains, and streptococci.

16.6.15 ***References***

1. Scholz H, Naber KG, and an expert group of the Paul Ehrlich Society for Chemotherapy. [Classification of oral cephalosporins.] Chemotherapie Journal 1999;8:227-9. [Article in German]

2. Vogel F, Bodmann K-F and the expert group of the Paul Ehrlich Society for Chemotherapy. [Recommendations for empiric parenteral initial therapy of bacterial infections in adults.] Chemotherapie Journal 2004;13:46-105. [Article in German]
3. Naber KG, Adam D, and an expert group of the Paul Ehrlich Society for Chemotherapy. [Classification of fluoroquinolones.] Chemotherapie Journal 1998;7:66-8. [Article in German]
4. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999 Oct;29(4):745-58. http://www.ncbi.nlm.nih.gov/pubmed/10589881

16.7 Relevant bacteria for urological infections



**Anaerobic bacteria not considered.*

17. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

ABU	asymptomatic bacteriuria
ACE	angiotensin-converting enzyme
ADPKD	adult dominant polycystic disease
APCKD	adult polycystic kidney disease
BLI	β-lactamase inhibitor
BPH	benign prostatic hyperplasia
CPPS	chronic pelvic pain syndrome
CPSI	Chronic Prostatitis Symptom Index
CT	computed tomography
CAUTIs	catheter-associated urinary tract infections
DMSA	dimercaptosuccinic acid
DTPA	diethylenetriamine pentaacetate
EPS	expressed prostatic secretion
EUCAST	European Committee for Antimicrobial Susceptibility Testing
G6PD	glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
IDSA	Infectious Diseases Society of America
IL	interleukin
IPCN	International Prostatitis Collaborative Network
IVU	intravenous urography
LUTS	lower urinary tract symptom
MAG-3	mercaptoacethylglycine
MRI	magnetic resonance imaging
MRSA	methicillin-resistant Staphylococcus aureus
MSU	mid-stream sample of urine
NCCLS	National Committee for Clinical Laboratory Standards
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PCP	Pneumocystis carinii pneumonia
PSA	prostate-specific antigen
SIRS	systemic inflammatory response syndrome
SMX	sulphamethoxazole
SSI	surgical site infection
STD	sexually transmitted disease
SWL	shockwave lithotripsy
TMP	trimethoprim
TNF	tumour necrosis factor
TRUS	transrectual ultrasound
TURP	transurethral resection of the prostate
US	ultrasound
UTI	urinary tract infection
VB1	first-voided urine
VB2	mid-stream urine
VB3	voided bladder urine-3
VCU	voiding cystourethography
VUR	vesicoureteric reflux
WBC	white blood cells

Conflict of interest

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