# Guidelines on Urological Infections

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European
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of Urology

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# 1. INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent infectious diseases, with a substantial financial burden on society. Unfortunately, in Europe, there are no good data concerning the prevalence of various types of UTIs and their impact on the quality of life of the affected population; nor are there good data regarding the impact of UTIs on economics in general and that of the health care system in particular. For a well-functioning public health system, such data are urgently needed. Data obtained from other countries and societies, e.g. the USA, can only be applied with caution to the European situation.

In the USA, UTIs are responsible for over 7 million physician visits annually, including more than 2 million visits for cystitis (1). Approximately 15% of all community-prescribed antibiotics in the USA are dispensed for UTI, at an estimated annual cost of over US $1 billion (2). Furthermore, the direct and indirect costs associated with community-acquired UTIs in the USA alone exceed an estimated US $1.6 billion (1).

Urinary tract infections account for more than 100,000 hospital admissions annually, most often for pyelonephritis (1). They also account for at least 40% of all hospital-acquired infections and are in the majority of cases catheter-associated (2–4). Nosocomial bacteriuria develops in up to 25% of patients who require a urinary catheter for > 7 days, with a daily risk of 5% (5). It has been estimated that an episode of nosocomial bacteriuria adds US $500–1,000 to the direct cost of acute-care hospitalisation (6). In addition, the pathogens are fully exposed to the nosocomial environment, including selective pressure by antibiotic or antiseptic substances. Nosocomial UTIs therefore comprise perhaps the largest institutional reservoir of nosocomial antibiotic-resistant pathogens (5).

## 1.1 Pathogenesis of urinary tract infections

Micro-organisms can reach the urinary tract by haematogenous or lymphatic spread, but there is abundant clinical and experimental evidence to show that the ascent of micro-organisms from the urethra is the most common pathway that leads to a UTI, especially organisms of enteric origin (i.e. *Escherichia 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* spp., *Salmonella* spp. 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 catheterization), 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, for example, 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.

## 1.2 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 (7). 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 number of significant bacteriuria, which can be applied to all kinds of UTIs and in all circumstances. As described in Appendix 14.1, 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 a woman
- $\geq 10^4$ cfu/mL of uropathogens in an MSU in acute uncomplicated pyelonephritis in a woman

- $\geq 10^5$ cfu/mL of uropathogens in an MSU in a woman, or $\geq 10^4$ cfu/mL uropathogens in an MSU in a man, or in straight catheter urine in women, in a complicated UTI.

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

It is obvious that methods of urine collection and culture, as well as the quality of laboratory investigations, can vary. Two levels of standard must therefore be used for the management of patients. A basic standard level is necessary for routine assessment, while a higher standard level is required for scientific assessment and in special clinical circumstances, for example, fever of unknown origin in immunocompromised patients. In research, the need for a precise definition of sampling methods, the time that urine is kept in the bladder, etc., 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 might vary from country to country and institution to institution. For example, for the breakpoints for classification of a pathogen as susceptible or resistant, 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) (8–10), or the National Committee for Clinical Laboratory Standards (NCCLS) (11). Mixing results obtained by different methods, for example, 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 decision.

### 1.3 Classification of urological infections

The present version of the Guidelines uses the established classification of UTI, although the EAU infection group is working on a new classification to be presented within the frames of the International Consultations of Urological Diseases (ICUD) publication 2010 (12).

For practical reasons, the guidelines are called Guidelines on Urological Infections. This section includes the management of UTIs in men and women and infections of the male genital tract, leaving out female genital tract infections, which are clinically bound to the field of gynaecology. The guidelines focus on urology and therefore also look into the prevention of urogenital infections associated, or not, with urological interventions. For practical reasons, however, UTIs and infections of the male genital tract are classified according to the predominant clinical symptoms:

- uncomplicated lower UTI (cystitis)
- uncomplicated pyelonephritis
- complicated UTI with or without pyelonephritis
- urosepsis
- urethritis
- male genital: prostatitis, epididymitis and orchitis.

The clinical presentation and management of different UTI categories varies during life and can depend on the patient's condition. Therefore, special patient groups (older people, those with underlying diseases, and immunocompromised patients) have also to be considered.

Criteria for the diagnosis of a UTI, modified according to the guidelines of the Infectious Diseases Society of America (IDSA) (13) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (14), are summarized in Appendix 14.1. There is still an ongoing discussion about how guidelines on UTI can be improved (15).

### 1.4 Aim of guidelines

As a result of the increasing worldwide threat of microbial resistance, it has become more urgent to limit the

use of antibiotics, and consequently, to follow evidence-based treatment strategies and regimens. It is the ambition of the present working group to assist not only urologists, but also physicians from other medical specialties in their daily practice. These EAU guidelines cover the UTI categories as listed above in section 1.3 on classification, and provide some general advice on the diagnosis and management of male and female UTIs.

## 1.5 Methods

The members of the UTI Working Group [K.G. Naber (chairman), B. Bergman, M.C. Bishop, T.E. Bjerklund-Johansen, H. Botto, B. Lobel, F. Jiminez Cruz, and F.P. Selvaggi] of the EAU Guidelines Office established the first version of these guidelines in several consensus conferences. The first edition was published in 2001 in Geneva by the EAU (16) and a more condensed version was published for the first time in 2001 (17).

A Working Group [(M. Grabe (chairman), M.C. Bishop, T.E. Bjerklund-Johansen, H. Botto, M. Çek, B. Lobel, K.G. Naber, J. Palou, and P. Tenke] updated the guidelines in several subsequent consensus conferences and added several chapters, one of which deals with catheter-associated UTIs. EAU guidelines on special forms of urogenital infections, such as sexually transmitted infections (18), urogenital tuberculosis (19) and urogenital schistosomiasis (20), have been published elsewhere. Chapters 12 and 13 of the present guidelines present separate short summaries including a reference link. The present version of Chapter 2 on uncomplicated UTIs has been rewritten in view of the International Consultation on Urological Diseases (ICUD) publication on UTI, and several updates have been made.

For a literature review, PubMed was searched for published meta-analyses, which were used as far as available. Otherwise, there was a non-structured literature review process by the group members. Each member was responsible for one chapter (reporter). The first draft of each chapter was sent to the committee members asking for comments, which were then considered, discussed and incorporated accordingly. The formal agreement to each updated chapter was achieved by the EAU working group in a series of meetings.

## 1.6 Level of evidence and grade of guideline recommendations

In the updated guidelines, the studies cited from the literature were rated according to the level of evidence, and the recommendations were graded accordingly (Tables 1.1 and 1.2).

**Table 1: Levels of evidence, modified from Sackett et al. (21).**

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

**Table 2: Grades of recommendations, modified from Sackett et al. (21).**

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

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# 2. UNCOMPLICATED URINARY TRACT INFECTIONS IN ADULTS

This chapter is a summary of the ICUD initiative on urogenital infections, sections 5, 6 and 7 on uncomplicated UTIs (1).

## 2.1 Definition

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

### *2.1.1 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* spp., are isolated (3) (level of evidence [LE]: 2a).

## 2.2 Acute uncomplicated cystitis in premenopausal, non-pregnant women

### *2.2.1. Diagnosis*

2.2.1.1 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, grade B recommendation [GR]).

2.2.1.2 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 ≥ 103 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).

### *2.2.2 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 empirical therapy should be guided by:

- spectrum and susceptibility patterns of the aetiological uropathogens;
- efficacy for the particular indication in clinical studies (Appendix 1, 2, 3);
- tolerability;
- adverse effects;
- cost; and
- availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg 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).

Cotrimoxazole 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% (4,15) (LE: 1b, GR: B).

Alternative antibiotics are ciprofloxacin 250 mg bid, ciprofloxacin extended release 500 mg qd, levofloxacin 250 mg qd, norfloxacin 400 mg bid, and ofloxacin 200 mg bid, each as a 3-day course (16) (LE: 1b, GR: B). However, adverse effects have to be considered (Table 2.1.).

**Table 2.1: Recommended empirical antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy premenopausal women.**

| Antibiotic | 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 bid | 7 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 |
| Cefpodoxime proxetil | 100 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.*

*2.2.3 Follow up*

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated (17) (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).

## 2.3 Acute uncomplicated pyelonephritis in premenopausal, non-pregnant women

*2.3.1 Diagnosis*

2.3.1.1 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 cystitis symptoms (e.g. dysuria, increased frequency) (18).

2.3.1.2 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 (19) (LE: 4, GR: C).

Colony counts $\geq 10^4$ cfu/mL of uropathogens are considered to be indicative of clinically relevant bacteriuria (20) (LE: 2b, GR: C).

2.3.1.3 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).

*2.3.2 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).

2.3.2.1 Mild and moderate cases of acute uncomplicated pyelonephritis (Table 2.2)

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% (21) (LE: 1b, GR: A).

If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days (22,23) (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 (24,25) (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 (26) (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 β-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).

2.3.2.2 Severe cases of acute uncomplicated pyelonephritis (Table 2.2)

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:

| | Reference | LE |
|---|---|---|
| • 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 β-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 2.2: Recommended initial empirical antimicrobial therapy in acute uncomplicated pyelonephritis in otherwise healthy premenopausal women.**

| **I. Oral therapy in mild and moderate cases** | | | |
|---|---|---|---|
| Antibiotic | Daily dose | Duration of therapy | Reference |
| Ciprofloxacin[1] | 500–750 mg bid | 7–10 days | (21) |
| Levofloxacin[1] | 250–500 mg qd | 7–10 days | (27) |
| Levofloxacin | 750 mg qd | 5 days | (22,23) |
| 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.**<br>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 | (21) |
| Levofloxacin[1] | 250–500 mg qd | (27) |
| Levofloxacin | 750 mg qd | (22) |
| Alternatives: | | |
| Cefotaxime[2] | 2 g tid | |
| Ceftriaxone[1,4] | 1–2 g qd | (28) |
| Ceftazidime[2] | 1–2 g tid | (29) |
| Cefepime[1,4] | 1–2 g bid | (30) |
| Co-amoxiclav[2,3] | 1.5 g tid | |
| Piperacillin/tazobactam[1,4] | 2.5–4.5 g tid | (31) |
| | | |
| Gentamicin[2] | 5 mg/kg qd | |
| Amikacin[2] | 15 mg/kg qd | |
| | | |
| Ertapenem[4] | 1 g qd | (28) |
| Imipenem/cilastatin[4] | 0.5/0.5 g tid | (31) |
| Meropenem[4] | 1 g tid | (29) |
| Doripenem[4] | 0.5 g tid | (32) |

*[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).*

### *2.3.3 Follow-up*

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

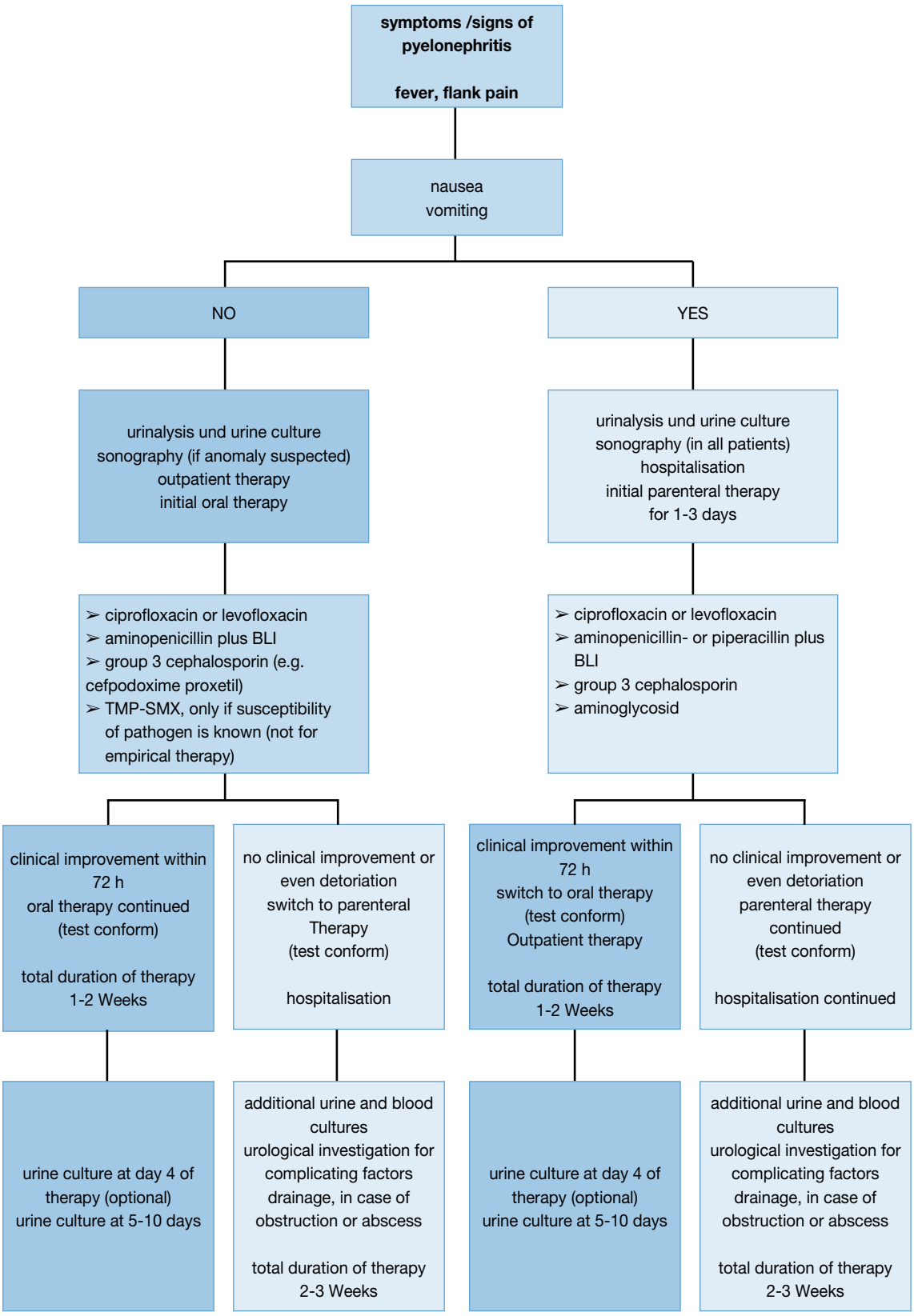
In women whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal ultrasound, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

In the patient 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 those 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 2.1.

**Figure 2.1: Clinical management of acute pyelonephritis.**




*BLI = ß-lactamase inhibitor; TMP = trimethoprim; SMX = sulphamethoxazole.*

## 2.4 Recurrent (uncomplicated) UTIs in women

*2.4.1 Diagnosis*

Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts (33) (LE: 2a).

Recurrent UTIs need to be diagnosed by urine culture (LE: 4, GR: A).

Excretory urography, cystography and cystoscopy are not routinely recommended for evaluation of women with recurrent UTIs (34) (LE: 1b, GR: B).

*2.4.2 Prevention*

Different therapeutic options can be recommended to the patient:

2.4.2.1. Antimicrobial prophylaxis:

Antimicrobial prophylaxis for prevention of recurrent UTI should be considered only after counselling and behavioural modification has been attempted (LE: 4, GR: A).

Before any prophylaxis regimen 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 postcoital antimicrobial prophylaxis should be considered to prevent recurrent uncomplicated cystitis in women in whom non-antimicrobial measures have been unsuccessful (35) (LE: 1a, GR: A). The choice of antibiotic should be based upon the identification and susceptibility pattern of the organism causing the patient's UTI and history of drug allergies. Drug regimens are shown in Tables 2.3 and 2.4.

**Table 2.3: Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs (33).**

| 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 2.4: Postcoital antimicrobial prophylaxis regimens for women with recurrent UTIs (33).**

| 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 appropriate women with recurrent uncomplicated cystitis, self-diagnosis and self-treatment with a short-course regimen of an antimicrobial should be considered (36) (LE: 2b, GR: A).

2.4.2.2 Immunoactive prophylaxis

OM-89 (Uro-Vaxomâ) 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 (37,38) (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.

#### 2.4.2.3 Prophylaxis with probiotics

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

*Lactobacillus acidophilus* and *lactobacillus crispatus* CTV05 strains are not available for prophylaxis. *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 product is available as an orally administered capsule that has been used vaginally but not for UTI prophylaxis (39,40).

Where 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 (40), and these products can be used once or twice weekly for prophylaxis (LE: 4, GR: C).

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 (40) (LE: 1b, GR: C).

#### 2.4.2.4 Prophylaxis with cranberry

Despite the lack of pharmacological data and the small number of weak clinical studies, there is evidence to suggest that cranberry (*Vaccinium macrocarpon*) is useful in reducing the rate of lower UTIs in women (41,42) (LE: 1b, GR: C).

For everyday practice, the daily consumption of cranberry products, giving a minimum of 36 mg/day proanthocyanindin A (the active compound), is recommended (LE: 1b, GR: C). The best approach is to use those compounds that have demonstrated clear bioactivity in urine.

## 2.5 Urinary tract infections in pregnancy

UTIs are common during pregnancy. Most women acquire bacteriuria before pregnancy, and 20–40% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy.

### *2.5.1 Definition of significant bacteriuria*

- in an asymptomatic pregnant woman, bacteriuria is considered significant if two consecutive voided urine specimens grow ≥ $10^5$ cfu/mL of the same bacterial species on quantitative culture; or a single catheterised specimen grows ≥ $10^5$ cfu/mL of a uropathogen (17) (LE: 2a, GR: A).
- in a pregnant woman with symptoms compatible with UTI, bacteriuria is considered significant if a voided or catheterised urine specimen grows ≥ $10^3$ cfu/mL of a uropathogen (LE: 4, GR: B).

### *2.5.2 Screening*

Pregnant women should be screened for bacteriuria during the first trimester (43) (LE: 1a, GR: A).

### *2.5.3 Treatment of asymptomatic bacteriuria*

Asymptomatic bacteriuria detected in pregnancy should be eradicated with antimicrobial therapy (43) (LE: 1a, GR: A). Recommended antibiotic regimens are shown in Table 2.5.

**Table 2.5: Treatment regimens for asymptomatic bacteriuria and cystitis in pregnancy (44).**

| Antibiotic | 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–sulfamethoxazole | q12 h, 3–5 days | Avoid trimethoprim in first trimester/term and sulfamethoxazole in third trimester/term |

*G6PD = glucose-6-phosphate dehydrogenase*

### 2.5.4 *Duration of therapy*

Short courses of antimicrobial therapy (3 days) should be considered for the treatment of asymptomatic bacteriuria and cystitis in pregnancy (44) (LE: 1a, GR: A).

### 2.5.5 *Follow-up*

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

### 2.5.6 *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 (45) (LE: 2b, GR: B).

### 2.5.7 *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 (46) (LE: 1b, GR: A). Recommended antibiotic regimens are shown in Table 2.6 (47).

**Table 2.6: Treatment regimens for pyelonephritis in pregnancy.**

| Antibiotic | 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 + | gentamicin |
| 2 g IV q6 h | 3–5 mg/kg/day IV in 3 divided doses |

### 2.5.8 *Complicated UTI*

Prolonged antibiotic therapy (7–10 days) should be considered in this patient population (LE: 4, GR: B). When indicated, ultrasonography or magnetic resonance imaging should be used preferentially to avoid radiation risk to the foetus (LE: 4, GR: B).

## 2.6 UTIs in postmenopausal women

### 2.6.1 *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 | 48 | 2a |
| • atrophic vaginitis | 48 | 2a |
| • incontinence, cystocele and post-voiding residual | 48 | 2a |
| • UTI before menopause | 48 | 2a |
| • non-secretor status of blood group antigens | 48 | 2a |

### 2.6.2 *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 are not necessarily an indication for antimicrobial treatment | 49 | 1b | B |

### 2.6.3 *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 | 50 | 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 | 17 | 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 | 51 | 1b | C |
| • alternative methods, such as cranberry and probiotic lactobacilli, can contribute but they are not sufficient to prevent recurrent UTI | 52 | 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 |

## 2.7 Acute uncomplicated UTIs in young men

### *2.7.1 Men with acute uncomplicated UTI*

| | Reference | LE | GR |
|---|---|---|---|
| • only a small number of 15 to 50-year-old men suffer from acute uncomplicated UTI | 53 | | |
| • such men should receive, as minimum therapy, a 7-day antibiotic regimen | | 4 | B |

### *2.7.2 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 | 54 | 2a | |
| • urological evaluation should be carried out routinely in adolescents and men with febrile UTI, pyelonephritis, 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. | 55 | 2a | B |

## 2.8 Asymptomatic bacteriuria

### *2.8.1 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 | 17 | 2b | B |
| • for men, a count of $\geq 10^3$ cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria | 56 | 2a | B |
| • for men with specimens collected using an external condom catheter, $\geq 10^5$ cfu/mL is an appropriate quantitative diagnostic criterion | 57 | 2a | B |
| • for patients with indwelling urethral catheters, a count of $\geq 10^5$ cfu/mL is diagnostic of bacteriuria | 17 | 2b | B |
| • for a urine specimen collected by in and out catheter, a count of $\geq$ 100 cfu/mL is consistent with bacteriuria | 17 | 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. | 17 | 2b | B |

### *2.8.2 Screening*

Screening for and treatment of asymptomatic bacteriuria is recommended:

| | Reference | LE | GR |
|---|---|---|---|
| • For pregnant women | 43 | 1a | A |
| • prior to an invasive genitourinary procedure for which there is a risk of mucosal bleeding | 17 | 1b | A |

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

| | Reference | LE | GR |
|---|---|---|---|
| • premenopausal, non-pregnant women | 17 | 1a | A |
| • postmenopausal women | 17 | 1b | A |
| • women with diabetes | 58 | 1b | A |
| • healthy men | 59 | 2b | B |

| | | | |
|---|---|---|---|
| • residents of long-term care facilities | 17 | 1a | A |
| • patients with an indwelling urethral catheter | 17 | 1b | |
| • patients with nephrostomy tubes or ureteric stents | | 4 | C |
| • patients with spinal cord injury | 60 | 2a | B |
| • patients with candiduria | 61 | 1b | A |

Screening for or treatment of asymptomatic bacteriuria in renal transplant patients beyond the first 6 months is not recommended (62) (LE: 2b, GR: B).

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

Appendix 1. **Relevant clinical trials of antimicrobial therapy of acute uncomplicated cystitis in adult non-pregnant women.**

| Test antibiotic | Dose (mg) | Duration of therapy | Comparative antibiotic | Dose (mg) | Duration of therapy | LE | First author, year | Ref | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| Co-amoxicillin/ clavulanic acid | 500/125 bid | 3 days | Ciprofloxacin | 250 bid | 3 days | 2b | Hooton 2005 | (63) | Amoxiclav was significantly inferior to ciprofloxacin |
| Cefdinir* | 100 bid | 5 days | Cefaclor | 250 tid | 5 days | 1b | Leigh 2000 | (64) | Cefdinir as effective as cefaclor 250 mg tid for 5 days, but more adverse events |
| Cefpodoxime proxetil | 100 bid | 3 days | TMP–SMX | 800/160 bid | 3 days | 1b | Kavatha 2003 | (65) | Cefpodoxime as effective and tolerable as TMP–SMX for 3 days |
| Cefuroxime axetil | 125 bid | 3 days | Ofloxacin | 100 bid | 3 days | 1b | Naber 1993° | (66) | Cefuroxime as effective and tolerable as TMP–SMX. Study underpowered to show equivalence |
| Ciprofloxacin | 500 SD | 1 day | Norfloxacin | 400 bid | 3 days | 1b | Auquer 2002 | (67) | Ciprofloxacin as effective and tolerable as norfloxacin 400 mg bid for 3 days. |
| Ciprofloxacin | 100 bid | 3 days | Ofloxacin TMP–SMX | 200 bid 800/160 bid | 3 days | 1b | McCarty 1999 | (68) | Ciprofloxacin as effective as ofloxacin and TMP–SMX, but significantly more tolerable |
| Ciprofloxacin | 100 bid | 3 days | Nitrofurantoin TMP–SMX | 100 bid 800/160 bid | 7 days 7 days | 1b | Iravani 1999 | (69) | Ciprofloxacin as effective as cotrimoxazole and nitrofurantoin |
| Ciprofloxacin | 500 SD 100-500 bid | 1 day 3-7 days | Norfloxacin | 400 bid | 7 days | 1b | Iravani 1995 | (70) | Ciprofloxacin 3 days as effective as 5–7 days and 7 days norfloxacin, but more effective than 500 mg SD |
| Ciprofloxacin | 250 bid | 3 days | Ciprofloxacin | 250 bid | 7 days | 1b | Vogel 2004 | (50) | For treatment of postmenopausal women not in long-term care and otherwise healthy, 3 days as effective as 7 days |
| Ciprofloxacin | 250 bid | 3 days | Norfloxacin TMP-SMX | 400 bid 800/160 bid | 7 days 7 days | 1b | Arredondo-Garcia 2004 | (71) | Ciprofloxacin as effective as norfloxacin and TMP–SMX. Study underpowered for equivalence. Highest drug-related adverse events in the TMP–SMX group. |
| Ciprofloxacin XR* | 500 qd | 3 days | Ciprofloxacin | 250 bid | 3 days | 1b | Henry 2002 | (72) | Ciprofloxacin XR 500 mg qd as effective and tolerable as ciprofloxacin 250 mg bid for 3 days |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ciprofloxacin XR* | 500 qd | 3 days | Ciprofloxacin | 250 bid | 3 days | 1b | Fourcroy 2005 | (73) | Ciprofloxacin XR 500 mg qd as effective as ciprofloxacin 250 mg bid for 3 days, but more tolerable |
| Enoxacin | 200 bid | 3 days | Enoxacin | 600 SD | 1 day | 1b | Backhouse 1989° | (74) | Enoxacin 3 days better than SD, but statistically underpowered |
| Fleroxacin* | 400 SD | 1 day | Fleroxacin<br>Ciprofloxacin | 200 qd<br>250 bid | 7 days<br>7 days | 1b | Iravani 1993 | (75) | Fleroxacin comparable clinical success, but decreased microbiological eradication than 7 daysYes |
| Fleroxacin* | 200 SD | 3 days | Fleroxacin<br>Ciprofloxacin | 200 qd<br>250 bid | 7 days<br>7 days | 1b | Iravani 1995° | (76) | Fleroxacin as effective and as tolerable as 7 days fleroxacin 200mg qd or ciprofloxacin 250mg bid (abstract) effective and tolerable compared to 7 days fleroxacin and compared to 7 days ciprofloxacin |
| Fosfomycin trometamol | 3000 SD | 1 day | Pipemidic acid | 400 bid | 5 days | 1b | Jardin 1990 | (77) | Fosfomycin as effective as pipemidic acid and more tolerable |
| Fosfomycin trometamol | 3000 SD | 1 day | Norfloxacin | 400 bid | 7 days | 1b | Boerema 1990 | (78) | Fosfomycin as effective as norfloxacin, but caused more adverse events (not significant). Study underpowered to show equivalence. |
| Fosfomycin trometamol | 3000 SD | 1 day | Norfloxacin | 400 bid | 5 days | 1b | De Jong 1991 | (79) | Fosfomycin as effective as norfloxacin but had significantly fewer adverse events. Study underpowered to show equivalence. |
| Fosfomycin trometamol | 3000 SD | 1 day | Nitrofurantoin | 50 q6h | 7 days | 1b | Von Pienbroek | (80) | Fosfomycin as effective as nitrofurantoin, but more gastrointestinal adverse effects with fosfomycin |
| Fosfomycin trometamol | 3000 SD | 1 day | Not applicable | - | - | 1a | Lecomte 1996<br>Lecomte 1997° | (81)<br>(11) | Meta analysis of 15 comparative studies: in general as effective and as tolerable as the comparators; long term results even better than comparators |
| Fosfomycin trometamol | 3000 SD | 1 day | Trimethoprim | 200 bid | 5 days | 1b | Minassian 1998 | (82) | Fosfomycin as effective and tolerable as trimethoprim |
| Fosfomycin trometamol | 3000 SD | 1 day | Nitrofurantoin macrocrystal | 100 bid | 7 days | 1b | Stein 1999 | (83) | Fosfomycin as effective and tolerable as nitrofurantoin |
| Fosfomycin trometamol | 3000 SD | 1 day | No comparator | - | - | 1b | Bonfiglio 2004 | (84) | Open, not comparative study by GPs, 387 female patients,18–65 years, after 8–10 days, 94.5% microbiological eradication and 88.9% clinical success (cure + improvement), GI adverse events 4.3% |
| Gatifloxacin* | 400 SD | 1 day | Gatifloxacin<br>Ciprofloxacin | 200 qd<br>250 bid | 3 days 3 days | 1b | Richard 2002 | (85) | Gatifloxacin as effective and tolerable as gatifloxacin and ciprofloxacin for 3 days each |
| Gatifloxacin* | 400 SD | 1 day | Gatifloxacin<br>Ciprofloxacin | 200 qd<br>250 bid | 3 days 3 days | 1b | Naber 2004 | (86) | Gatifloxacin as effective and tolerable as gatifloxacin and ciprofloxacin for 3 days each |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Levofloxacin | 250 qd | 3 days | Ofloxacin | 200 bid | 3 days | 1b | Richard 1998° | (87) (88) | Levofloxacin as effective as ofloxacin, but better tolerable |
| Lomefloxacin* | 400 qd | 3 days | Lomefloxacin Norfloxacin | 400 qd 400 bid | 7 days 7days | 1b | Neringer 1992 | (89) | Lomefloxacin as effective as norfloxacin, but less tolerable |
| Lomefloxacin* | 400 qd | 3 days | Lomefloxacin Norfloxacin | 400 qd 400 bid | 7 days 7days | 1b | Nicolle 1993 | (90) | Lomefloxacin as effective and tolerable as norfloxacin |
| Nitrofurantoin | 50-100 q6h MC 100 bid | 3 days | Nitrofurantoin | 50-100 q6h 100 bid (MC) | 5-7 days | 2b | Goettsch 2004° | (91) | Nitrofurantoin 3 days less effective than 5–7 days |
| Nitrofurantoin MC | 100 bid | 5 days | TMP–SMX | 800/160 bid | 3 days | 1b | Gupta 2007 | (13) | Nitrofurantoin 5 days equivalent to 3 days TMP–SMX |
| Nitrofurantoin MC | 100 bid | 7 days | Trimethoprim TMP–SMX | 200 bid 800/160 bid | 7 days 7 days | 1b | Spencer 1994 | (92) | Bacterial elimination rate was low (77–83%) for all three comparators |
| Norfloxacin | 400 bid | 3 days | Norfloxacin | 400 bid | 7 days | 1b | Inter-Nordic 1988 | (93) | Norfloxacin 3 days as effective and tolerable as 7 days, but recurrence rate higher with 3 days |
| Norfloxacin | 400 bid | 3 days | Norfloxacin | 400 bid | 7 days | 1b | Piipo 1990 | (94) | Norfloxacin 3 days as effective and tolerable as 7 days |
| Norfloxacin | 800 qd | 3 days | Norfloxacin | 400 bid | 3 days | 1b | Pimentel 1998 | (95) | Norfloxacin 3 days as effective and tolerable as 800 mg qd |
| Ofloxacin | 100 bid | 3 days | TMP–SMX | 800/160 bid | 3 days | 1b | Block 1987 | (96) | Ofloxacin as effective and tolerable as 3 days TMP–SMX |
| Ofloxacin | 200 bid | 3 days | TMP–SMX | 800/160 bid | 7 days | 1b | Hooton 1989 | (97) | Ofloxacin as effective and tolerable as 7 days TMP–SMX |
| Ofloxacin | 200 bid | 3 days | Ofloxacin TMP–SMX | 400 SD 800/160 bid | 1 day 7 days | 1b | Hooton 1991 | (98) | Ofloxacin as effective and tolerable as 7 days TMP–SMX; ofloxacin SD less effective |
| Pefloxacin* | 800 SD | 1 day | Norfloxacin TMP–SMX | 400 bid 800/160 bid | 5 days 3-7 days | 1a | Naber 1994° | (99) | Pefloxacin as effective as norfloxacin and TMP–SMX, but less tolerable. Pefloxacin should be taken with meals to reduce gastrointestinal adverse events. |
| Pefloxacin* | 400 bid | 5 days | Ofloxacin | 200 bid | 5 days | 1b | Kadiri 1999 | (100) | Pefloxacin as effective as ofloxacin, but study underpowered to show equivalence |
| Pivmecillinam* | 200 bid | 7 days | Cephalexin | 250 q6h | 7 days | 1b | Menday 2000 | (101) | Pivmecillinam as effective and tolerable as cephalexin |
| Pivmecillinam* | 200 bid | 3 days | Pivmecillinam | 200 bid | 7 days | 1a | Nicolle 2000° | (12) | 3 days less effective than 7 days (review) |
| Pivmecillinam* | 400 bid | 3 days | Norfloxacin | 400 bid | 3 days | 1b | Nicolle 2002 Menday 2002 | (102) (103) | Pivmecillinam clinically as effective as norfloxacin, but bacteriologically less effective; significantly less *Candida* vaginitis with pivmecillinam |
| Pivmecillinam* | 200 bid-tid 400 bid | 7 days 3 days | Placebo | – | 7 days | 1b | Ferry 2007 | (104) | Pivmecillinam 7 days more effective than 3 days, and both significantly more effective than placebo |
| Rufloxacin* | 400 SD | 1 day | Pefloxacin | 800 SD | 1 day | 1b | Jardin 1995 | (105) | Rufloxacin as effective as pefloxacin and norfloxacin but less tolerable (more CNS adverse events) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sparfloxacin* | 400, 200, 200 qd | 3 days | Ofloxacin | 200 bid | 3 days | 1b | Henry 1998 | (106) | Sparfloxacin as effective as ofloxacin 200 mg bid for 3 days, but higher rate of phototoxicity; ofloxacin higher rate of sleeplessness |
| Sparfloxacin* | 400, 200, 200 qd | 3 days | Ciprofloxacin | 250 bid | 7 days | 1b | Henry 1999 | (107) | Sparfloxacin as effective as ciprofloxacin 250 mg bid for 7 days, and better than SD, but higher rate of phototoxicity |
| Trimethoprim | 200 bid | 5–7 days | (meta-analysis) | – | – | 1a | Warren 1999 | (14) | Trimethoprim recommended as standard, if *E. coli* resistance < 20% |
| Trimethoprim | 200 bid | 3 days | Trimethoprim | 200 bid | 5–7 days | 2b | Goettsch 2004° | (91) | 3 days less effective than 5–7 days |
| Trimethoprim | 200 bid | 3 days | Trimethoprim | 200 bid | 10 days | 1b | Gossius 1985° | (108) | Trimethoprim 3 days less adverse events than 10 days |
| Trimethoprim | 200 bid | 3 days | Trimethoprim | 200 bid | 5 days | 1b | Van Merode 2005 | (109) | Trimethoprim 3 days no different to 5 days, but follow-up too short. In the abstract, number of patients and dose are missing.Yes |
| TMP-SMX | 320/ 1600 SD | 1 day | TMP-SMX | 160/800 bid | 3 days 10 days | 1b | Gossius 1984 | (110) | TMP–SMX SD as effective as 3–10 days, but fewer adverse effects |
| TMP-SMX | 160/800 bid | 3 days | (metaanalysis) | - | - | 1a | Warren 1999 | (14) | TMP–SMX recommended as standard if *E. coli* resistance is < 20%; 3-day course tends to higher recurrence rate, but more tolerable than longer treatment |
| TMP-SMX *E. coli S* | 160/800 bid | 3 days | TMP-SMX *E. coli R* | 160/800 bid | 3 days | 2a | Raz 2002 | (111) | Clinical and microbiological success in female patients with infection caused by suceptible *E. coli* about twice as high as for resistant *E. coli* |

**not available in all countries.*

*° not found in Warren 1999 and MEDLINE search 1998 until 2008.*

**Appendix 2:. Relevant clinical trials of therapy of acute uncomplicated pyelonephritis. In some trials patients with acute uncomplicated pyelonephritis were treated with the same protocol as patients with complicated pyelonephritis or UTIs (substratification not possible)**

| Test antibiotic | Dose | Duration of therapy | Comparative antibiotic | Dose | Duration of therapy | LE | Author, year | Ref | IV/ oral | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| Ampicillin | 30 g/day for 3 days, then 20 g/ day for 4 days | 7 days | Ampicillin | Moderate doses | 1 month | 1b | Ode 1980 | (112) | IV | Ampicillin in excessive high dosage was inferior to normal dosage; conventional therapy relatively bad results (cure 9/21), low number |
| Cefepime | 1 g bid | 8.5 days (mean) | No comparator | – | – | 4 | Giamarellou 1993 | (30) | IV | Cefepime 1g bid is as safe and effective as other parenteral cephalosporins for the treatment of acute bacterial UTI and serious bacterial infections (historical comparison) |
| Cefixime Initial ceftriaxone IV | 400 mg qd 1 g | 10 days | Ceftriaxone | 1 g qd | 10 days | 1b | Sanchez 2002 | (113) | IV/ oral | After initial IV ceftriaxone, oral cefixime as effective as ceftriaxone 1g qd IV for 10 days in women with acute uncomplicated pyelonephritis |
| Ciprofloxacin oral ± ciprofloxacin IV | 500 mg bd ± 400 mg IV bd | 7 days | TMP–SMZ ± cetriaxone IV | 800/160 mg bid + 1 g IV qd | 14 days | 1b | Talan 2000 | (21) | IV/ oral | Ciprofloxacin significantly more effective than ceftriaxone/cotrimoxazole for 10 days; also a trend towards better tolerance |
| Ciprofloxacin XR* | 1000 mg qd | 7–14 days | Ciprofloxacin | 500 mg bid | 7–14 days | 1b | Talan 2004 | (114, 115) | oral | Cefpodoxime as effective and tolerable as 7–10 days ciprofloxacin 500 mg bid |
| Cefpodoxime proxetil | 200 mg bid | 10 days | Ciprofloxacin | 500 mg bid | 10 days | 1b | Naber 2001 | (25) | oral | Clinically, but not microbiologically as effective as ciprofloxacin 500 mg bid |
| Ceftibuten + initial cefuroxime | 200 mg bid + 750 mg bid | 10 days | Norfloxacin + initial cefuroxime | 400 mg bid + 750 mg bid | 10 days | 1b | Cronberg 2001 | (24) | IV/ oral | Clinically, but not microbiologically as effective as norfloxacin 400 mg bid for 10 days. Both treatment regimens after initial IV cefuroxime. |
| Doripenem IV + followed by oral (optional) levofloxacin | 0.5 g tid + 250 mg qd | 10 days | Levofloxacin IV + followed by oral (optional) levofloxacin | 250 mg qd | 10 days | 1b | Naber 2009 | (32) | IV/ oral | Doripenem 0.5 g tid as effective as levofloxacin 250 mg qd for treatment of uncomplicated pyelonephritis and complicated UTI |
| Ertapenem (after > 3 days, possible oral therapy, usually ciprofloxacin) | 1.0 g qd | 4 (2–14) days | Ceftriaxone (after > 3 days, possible oral therapy, usually ciprofloxacin) | 1 g qd | 4 (2–14) days | 1b | Wells 2004 | (28) | IV/ oral | Ertapenem 1 g qd as effective as ceftriaxone 1 g qd for treatment of uncomplicated pyelonephritis and complicated UTI followed by appropriate oral therapy |
| Gatifloxacin* | 400 mg qd vs 200 mg qd | 10 (5–14) days | Ciprofloxacin | 500 mg bid | 10 (5–14) days | 1b | Naber 2004 | (116) | oral | Levofloxacin as effective and tolerable as ciprofloxacin 500mg bid |
| Levofloxacin | 250 mg qd | 10 days | Ciprofloxacin | 500 mg bid | 10 days | 1b | Richard 1998 | (27) | oral | Levofloxacin as effective and tolerable as ciprofloxacin 500 mg bid (underpowered) |
| Levofloxacin | 250 mg qd | 10 days | Lomefloxacin | 400 mg qd | 10 days | 1b | Richard 1998 | (27) | oral | Levofloxacin as effective and tolerable as lomefloxacin 400 mg qd (underpowered) |
| Levofloxacin IV/oral (IV optional) | 750 mg qd | 5 days | Ciprofloxacin IV/oral (IV optional) | 400/500 mg bid | 10 days | 1b | Klausner 2007 Peterson 2008 | (22) (23) | IV/ oral IV/ oral | Levofloxacin as effective and tolerable as ciprofloxacin 400/500 mg bid for 10 days. Both treatment regimens after initial IV therapy. Both studies refer to the same cohort. |
| Meropenem | 1 g tid | ? | Ceftazidime + Amikacin | 2 g tid 15 mg/kg/ day | ? | 4 | Mouton 1995 | (29) | IV | Meropenem as well tolerated and effective as combination of ceftazidime plus amikacin for treatment of serious infections (including pyelonephritis) |
| Piperacillin/ tazobactam | 2/0.5 g tid | 5-14 days | Imipenem/ cilastatin | 0.5/0.5 g tid | 5–14 days | 1b | Naber 2002 | (31) | IV | Piperacillin/tazobactam 2/0.5 g tid is as effective as imipenem/cilastatin 0.5/0.5 g tid for treatment of uncomplicated pyelonephritis and complicated UTI |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pivampicillin (PA)/ pPivmecillinam (PM) | 0.5 g PA/0.4 g PM tid | 1 week | PA/PM | 0.5 g PA/0.4 g PM tid | 3 weeks | 1b | Jernelius 1988 | (117) | oral | 1 week treatment is too short. Side effects more common with 3 weeks treatment (0.5 g PA/0.4 g PM tid 1 week + 0.25 g PA/0.2 g PM tid 2 weeks) and bacteriological success still low (69%). |
| TMP–SMX | 160/800 mg bid | 14 days | TMP–SMX | 160/800 mg bid | 6 weeks | 1b | Stamm 1987 | (26) | oral | As effective as TMP–SMX for 6 weeks, but more tolerable |
| TMP–SMX + initial gentamicin | 160/800 mg bid IV for 3 days, then oral + gentamcin tid | 14 days | Ampicillin + initial gentamicin | IV 1 g q6h for 3 days, then oral 500 mg q6h + gentamicin tid | 14 days | 1b | Johnson 1991 | (118) | oral | Cotrimoxazole more effective than ampicillin because of: (1) more resistant strains and (2) increased recurrence even with susceptible strains |

**not available in all countries*

**Appendix 3: Efficacy of antibiotics for preventing recurrent UTI in non-pregnant women*.**

| Substance | Dose | n/N | Comparator | Dose | n/N | Weight (%) | Relative risk (95% CI) | | Author, Year | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| **Antibiotic vs placebo** | | | | | | | | | | |
| Cinoxacin | 250 mg/24 h | 1/23 | Placebo | | 17/22 | 5.4 | 0.06 | (0.01–0.39) | Martens 1995 | (119) |
| Cinoxacin | 500 mg/24 h | 8/21 | Placebo | | 17/19 | 24.2 | 0.43 | (0.24–0.75) | Martorana 1984 | (120) |
| Cinoxacin | 500 mg/24 h | 2/15 | Placebo | | 4/13 | 7.9 | 0.43 | (0.09–1.99) | Schaeffer 1982 | (121) |
| Cinoxacin | 500 mg/24 h | 1/20 | Placebo | | 8/21 | 5.1 | 0.13 | (0.02–0.96) | Scheckler 1982 | (122) |
| Norfloxacin | 200 mg/24 h | 0/11 | Placebo | | 10/13 | 2.9 | 0.06 | (0.00–0.85) | Nicolle 1989 | (123) |
| Norfloxacin | 200 mg/24 h | 4/18 | Placebo | | 13/17 | 16.0 | 0.29 | (0.12–0.72) | Rugendorff 1987 | (124) |
| Nitrofurantoin | 100 mg/24 h | 1/13 | Placebo | | 5/6 | 5.5 | 0.09 | (0.01–0.63) | Stamm 1980 | (125) |
| Nitrofurantoin | 50 mg/24 h | 3/25 | Placebo | | 15/25 | 12.5 | 0.20 | (0.07–0.61) | Bailey 1971 | (126) |
| Cephalexin | 125 mg/24 h | 1/20 | Placebo | | 13/23 | 5.3 | 0.09 | (0.01–0.62) | Gower 1975 | (127) |
| TMP–SMX | 40/200 mg/24 h | 1/13 | Placebo | | 5/7 | 5.3 | 0.11 | (0.02–0.75) | Stamm 1980 | (125) |
| TMP–SMX | 40/200 mg postcoital | 2/16 | Placebo | | 9/11 | 9.8 | 0.15 | (0.04–0.58) | Stapleton 1990 | (128) |
| **Total** | | **24/195 (12.3%)** | | | **116/177 (65.5%)** | | **0.21** | **(0.13–0.34)** | | |
| | | | | | | | | | | |
| **Antibiotic vs antibiotic** | | | | | | | | | | |
| Cefaclor | 250 mg/ 24 h | 8/49 | Nitrofurantoin | 50 mg/24 h | 8/48 | 20.0 | 0.98 | (0.40–2.40) | Brumfitt 1995 | (129) |
| Norfloxacin | 400 mg/ 24 h | 2/26 | Nitrofurantoin | 100 mg/24 h | 0/26 | 7.2 | 5.00 | (0.25–99.4) | Nunez 1990 | (130) |
| Trimethoprim | 100 mg/24 h | 16/38 | Nitrofurantoin | 100 mg/24 h | 4/34 | 19.2 | 3.58 | (1.33–9.66) | Brumfitt 1985 | (131) |
| TMP-SMX | 40/200 mg/24 h | 1/13 | Nitrofurantoin | 100 mg/24 h | 1/13 | 8.5 | 1.00 | (0.07–14,3) | Stamm 1980 | (125) |
| Trimethoprim | 100 mg/24 h | 1/12 | Cinoxacin | 500 mg/24 h | 2/14 | 10.3 | 0.58 | (0.06–5.66) | Seppanen 1988 | (132) |
| Pefloxacin | 400 mg/weekly | 17/185 | Pefloxacin | 400 mg/mo | 52/176 | 22.6 | 0.31 | (0.19–0.52) | Guibert 1995 | (133) |
| Ciprofloxacin | 125 mg postcoital | 2/70 | Ciprofloxacin | 125 mg/24 h | 2/65 | 12.2 | 0.93 | (0.13–6.40) | Melekos 1997 | (134) |
| **Total** | | **47/393 (12.0%)** | | | **69/376 (18.4%)** | | | | | |
| | | | | | | | | | | |
| **Antibiotics vs non-antibiotics** | | | | | | | | | | |
| Nitrofurantoin | 50 mg/12 h | 4/43 | Methanamine hippurate | 1 g/12 h | 19/56 | | 0.27 | (0.10–0.75) | Brumfitt 1981 | (135) |
| Trimethoprim | 100 mg/24 h | 8/20 | Povidone iodine | Topical | 10/19 | | 0.76 | (0.38–1.51) | Brumfitt 1983 | (136) |
| Trimethoprim | 100 mg/24 h | 8/20 | Meth. hippurate | 1 g/12 h | 10/25 | | 1.00 | (0.49–2.05) | Brumfitt 1983 | (136) |

**modified according Nicolle LE, Ronald AR. Recurrent urinary tract infectionin adult women: diagnosis and treatment. Infect Dis Clin North Am 1987;1:793-806. with a study period of at least 6 months.*

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# 3. URINARY TRACT INFECTIONS IN CHILDREN

## 3.1 Summary and recommendations

Urinary tract infection (UTI) in children is a frequent health problem, with the incidence of UTIs only a little lower than the incidences for 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, being 3% in girls and 1.1% in boys. Paediatric UTI is the most common cause of fever of unknown origin in boys less than 3 years. The clinical presentation of a UTI in infants and young children can vary from fever to gastrointestinal, lower or upper urinary tract symptoms.

Investigation should be undertaken after two episodes of a 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.

Vesicoureteric reflux 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).

In the treatment of a 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).

## 3.2 Background

The urinary tract is a common source of infection in children and infants. It represents the most common bacterial infection in children less than 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, requiring dialysis treatment in a significant number of adults (2) (LE: 2a).

The risk of a 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 under 3 months of age, when it is more common in males. The incidence of asymptomatic bacteriuria is 0.7-3.4% in neonates, 0.7-1.3% in infants under 3 months of age and between 0.2% and 0.8% in preschool boys and girls, respectively (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 less than 6 months. The overall recurrence rate for the neonatal period has been reported to be 25% (3,4).

## 3.3 Aetiology

The common pathogenic sources are Gram-negative, mainly enteric, organisms. Of these, *Escherichia coli* is

responsible for 90% of episodes of UTIs (5). Gram-positive organisms (particularly enterococci and staphylocci) represent 5-7% of cases. Hospital-acquired infections show a wider pattern of aggressive organisms, such as *Klebsiella, Serratia* and *Pseudomonas* spp. Groups A and B streptococci are relatively common in the newborn (6). There is an increasing trend towards the isolation of *Staphylococcus saprophyticus* in UTIs in children, although the role of this organism is still debatable (7).

### 3.4 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 colonize the preputial sac, glandular surface and the distal urethra. Among these organisms are strains of *E. coli* expressing 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, pelvi-ureteric junction obstruction or non-obstructive urinary stasis (e.g. prune belly syndrome, 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 (spina bifida, sphincter dyssynergia, etc) may lead to postvoid 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 where there is VUR. Almost certainly the necessary components include VUR, intrarenal reflux and a 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 developed in utero (13).

### 3.5 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 in a boy, testicular torsion has to be considered.

A UTI in neonates may be non-specific and with no localization. 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 will be the presentation. Signs of a 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.

### 3.6 Classification

Urinary tract infections may be classified either 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 3.1).

**Table 3.1: Clinical classification of urinary tract infections (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 |

*3.6.1 Severe UTI*

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

*3.6.2 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.

## 3.7 Diagnosis

*3.7.1 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.

*3.7.2 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 more than 100,000 cfu/mL of one pathogen. The urine specimen may be difficult to obtain in a child less than 4 years old and different methods are advised since there is a high risk of contamination (17,18).

3.7.2.1 Collection of the urine

*3.7.2.1.1 Suprapubic bladder aspiration*

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

*3.7.2.1.2 Bladder catheterization*

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

*3.7.2.1.3 Plastic bag attached to the genitalia*

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

3.7.2.2 Quantification of bacteriuria

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

The presence of pyuria (more than 5 leucocytes per field) and bacteriuria in a fresh urine sample will reinforce the clinical diagnosis of UTI (17).

In boys, when the urine is obtained by bladder catheterization, the urine culture is considered positive with more than 104 cfu/mL. Even though Hoberman (20) identified a micro-organism 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 more than $10^5$ cfu/mL is considered positive (16) (Table 3.2).

**Table 3.2: Criteria of UTI in children.**

| Urine specimen from suprapubic bladder puncture | Urine specimen from bladder catheterization | 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<br>≥ $10^5$ cfu/mL without symptoms |

3.7.2.3 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 leucocyte esterase usually combined in a dipstick test.

*3.7.2.3.1 Nitrite*

This is the degradation product of the nitrates of bacterial metabolism, particularly of 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. Pseudomonas aeruginosa, 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).

*3.7.2.3.2 Leucocyte esterase*

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

A combination of nitrite and leucocyte 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 leucocyte 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 colonization (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 hours 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 *Mycobacterium 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 under 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 catheterization are significant for a UTI and discriminate between infection and contamination (20,25).

*3.7.2.3.3 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 above 20 µg/mL.

*3.7.2.3.4 Urinary N-acetyl-ß-glucosaminidase*

This is a marker of tubular damage. It is increased in a febrile UTI and may become a reliable diagnostic test for UTIs, although it is also elevated in VUR (27).

*3.7.2.3.5 Interleukin-6*

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

### *3.7.3 Imaging of the urinary tract*

A 'gold standard' imaging technique has to be cost-effective, painless, safe, with minimal or nil radiation, and an ability to detect any significant structural anomaly. Current techniques do not fulfil all such requirements.

#### 3.7.3.1 Ultrasonography

Ultrasonography (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 technetium-99m dimercaptosuccinic acid (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).

#### 3.7.3.2 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 hours. This technique is helpful in determining functional renal mass and ensures an accurate diagnosis of cortical scarring by showing areas of hypoactivity indicating 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).

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

The use of Tc-99m DMSA scans can be helpful in the early diagnosis of acute pyelonephritis. About 50-85% of children will show positive findings in the first week. Minimal parenchymal defects, when characterized by a slight area of hypoactivity, can resolve with antimicrobial therapy (39,40). However, defects lasting longer than 5 months are considered to be renal scarring (41) (LE: 2a).
Tc-99m DMSA scans are considered more sensitive than excretory urography and ultrasonography in the detection of renal scars (42-45). It remains questionable whether radionuclide scans could substitute for echography as a first-line diagnostic approach in children with a UTI (46,47).

#### 3.7.3.3 Cystourethrography

##### *3.7.3.3.1 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 less than 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 in order to minimize radiological exposure (49). Voiding cystourethrography is mandatory in the assessment of febrile childhood UTI, even in the presence of normal ultrasonography. Up to 23% of these patients may reveal VUR (50).

##### *3.7.3.3.2 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 a 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 a poor image resolution and difficulty in detecting lower urinary tract abnormalities (51,52).

##### *3.7.3.3.3 Cystosonography*

Contrast material-enhanced voiding ultrasonography 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.

#### 3.7.3.4 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 requiring 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.

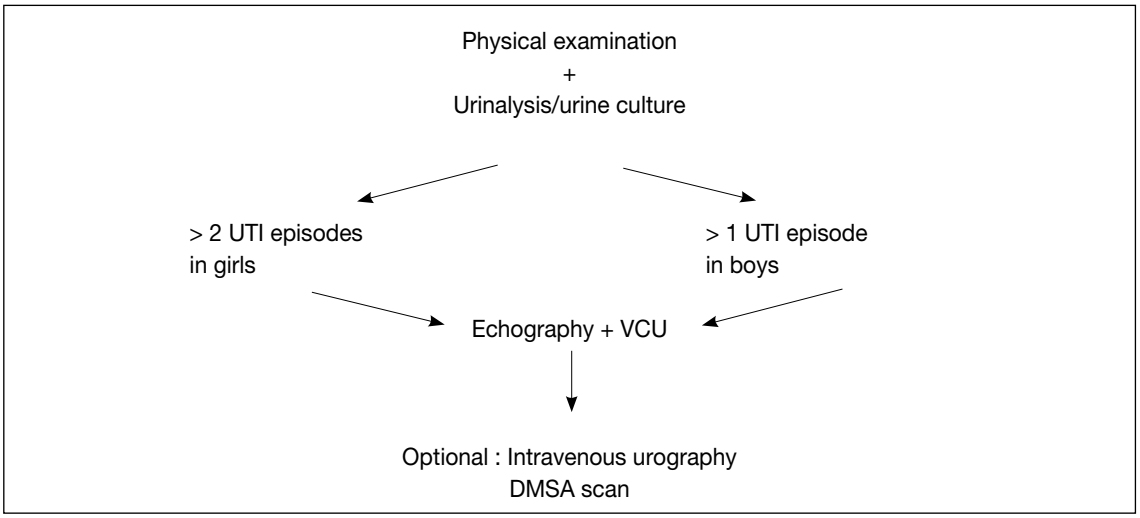
3.7.3.5 Urodynamic evaluation

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.

## 3.8 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 episode in a boy, investigations should be undertaken (Figure 3.1), but not in the case of asymptomatic bacteriuria (51-58). The need for DTPA/MAG-3 scanning is determined by the ultrasound findings, particularly if there is suspicion of an obstructive lesion.

**Figure 3.1: Schedule of investigation of a UTI in a child.**




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

## 3.9 Treatment

Treatment has four main goals:

1. elimination of symptoms and eradication of bacteriuria in the acute episode
2. prevention of renal scarring
3. prevention of a recurrent UTI
4. correction of associated urological lesions.

### *3.9.1 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.

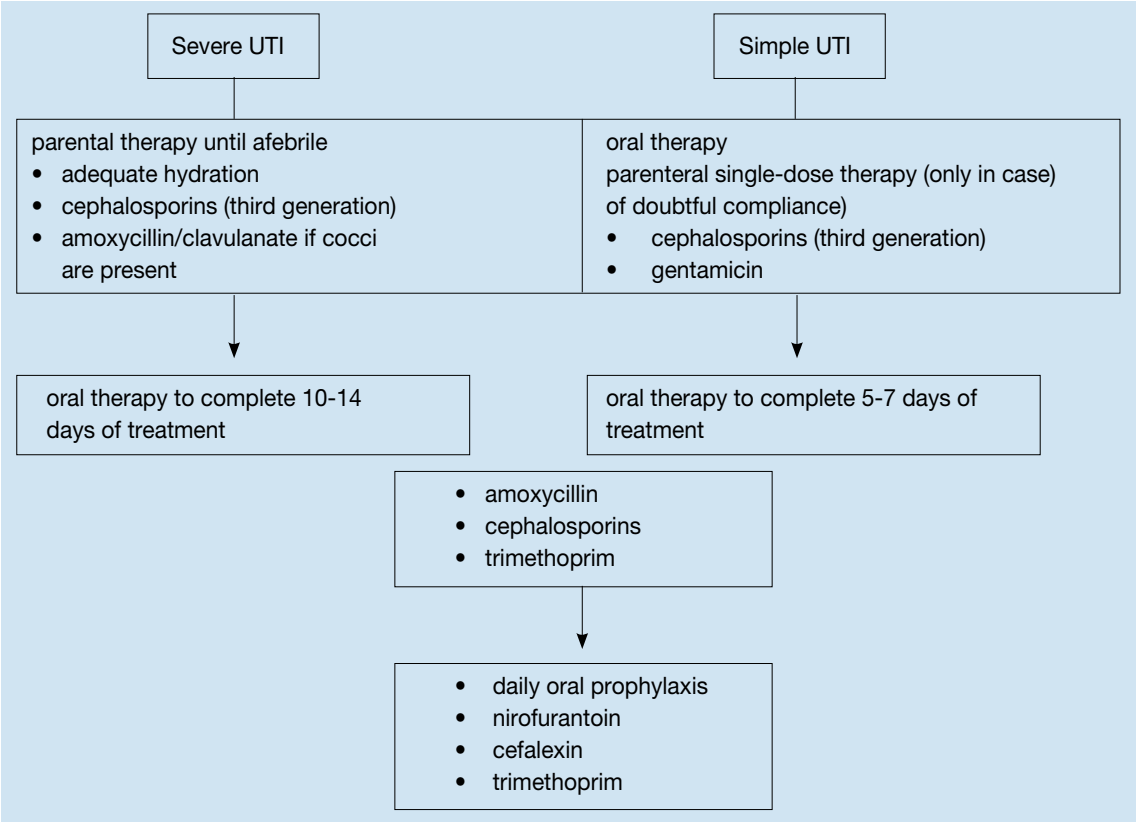
A wide variety of antimicrobials can be used in older children, with the exception of tetracyclines (because of teeth staining). Fluorinated quinolones may produce cartilage toxicity (58), but if necessary may be used as second-line therapy in the treatment of serious infections, since musculoskeletal adverse events are of moderate intensity and transient (60,61). For a safety period of 24-36 hours, 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 indication for TMP is declining in areas with increasing resistance.

In children less than 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, 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 3.2 and the dosing of antimicrobial agents is outlined in Table 3.3 (63).

Figure 3.2. Treatment of febrile UTIs in children.




### *3.9.2 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).

### *3.9.3 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).

## 3.10 Acknowledgement

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

**Table 3.3: Dosing of antimicrobial agents in children aged 3 months to 12 years*.**

| Antimicrobial agent | Application | Age | Total dosage per day | Doses per day |
|---|---|---|---|---|
| Ampicillin | Intravenous | 3-12 months | 100-300 mg/kg BW | 3 |
| Ampicillin | Intravenous | 1-12 years | 60-150 (-300) mg/kg BW | 3 |
| Amoxycillin | Oral | 3 months to 12 years | 50-100 mg/kg BW | 2-3 |
| Amoxycillin/clavulanate | Intravenous | 3 months to 12 years | 60-100 mg/kg BW | 3 |
| Amoxycillin/clavulanate | Oral | 3 months to 12 years | 37.5-75 mg/kg BW | 2-3 |
| Cephalexin | | | | |
| Treatment | Oral | 3 months to 12 years | 50-100 mg/kg BW | 3 |
| Prophylaxis | Oral | 1-12 years | 10 mg/kg BW | 1-2 |
| Cefaclor | | | | |
| • Treatment | Oral | 3 months to 12 years | 50-100 mg/kg BW | 3 |
| • Prophylaxis | Oral | 1-12 years | 10 mg/kg BW | 1-2 |
| Cefixime | Oral | 3 months to 12 years | 8-12 mg/kg BW | 1-2 |
| Cetriaxone | Intravenous | 3 months to 12 years | 50-100 mg/kg BW | 1 |
| Aztreonam | Intravenous | 3 months to 12 years | (50)-100 mg/kg BW | 3 |
| Gentamicin | Intravenous | 3-12 months | 5-7.5 mg/kg BW | 1-3 |
| Gentamicin | Intravenous | 1-2 years | 5 mg/kg BW | 1-3 |
| Trimethoprim | | | | |
| • Treatment | Oral | 1-12 years | 6 mg/kg BW | 2 |
| • Prophylaxis | Oral | 1-12 years | 1-2 mg/kg BW | 1 |
| Nitrofurantoin | | | | |
| • Treatment | Oral | 1-12 years | 3-5 mg/kg BW | 2 |
| • Prophylaxis | Oral | 1-12 years | 1mg/kg BW | 1-2 |

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

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# 4. UTIS IN RENAL INSUFFICIENCY, TRANSPLANT RECIPIENTS, DIABETES MELLITUS AND IMMUNOSUPPRESSION

## 4.1 Summary

*4.1.1 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 in the adult, the kidney is normal beforehand, chronic renal damage is most unlikely. There is no evidence that more prolonged or intensive antibiotic treatment of acute pyelonephritis will shorten the episode or prevent complications.

In diabetes mellitus, overwhelming infection can predispose to pyogenic infection with intrarenal perinephric abscess formation, emphysematous pyelonephritis, and, very rarely, a specific form of infective interstitial nephropathy. Papillary necrosis is a common consequence of pyelonephritis in diabetics. Females are more prone to asymptomatic bacteriuria than diabetic men 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 I and type II 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).

*4.1.2 Chronic renal disease and UTI*

There are several factors of general potential importance predisposing to infection in uraemia, including the loss of several urinary defence mechanisms and a degree of immunosuppression. Typically, adult polycystic kidney disease (APCKD), gross vesicoureteric reflux (VUR) and endstage obstructive uropathy will harbour infective foci or promote ascending infection, but not invariably so. Clearly, severe urinary tract infection (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 (C).

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

4.1.2.1 Adult polycystic kidney disease (APCKD)

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 utilized as a last resort (GR: B).

#### 4.1.2.2 Calculi and UTI

Management is similar to that for patients without renal impairment, i.e. to clear the stones if possible and to minimize 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).

#### 4.1.2.3 Obstruction 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, upper tract pressure flow studies.

### *4.1.3 UTI in renal transplantation and immunosuppression*

The need to correct uropathy or to remove a potential focus of infection in a diseased endstage kidney is more pressing in a patient 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, immunosuppression will promote, at least, persistent bacteriuria, which may become symptomatic. In the context of renal transplantation, UTI is very common, but immunosuppression is only one of many factors which 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 have reduced progression to endstage renal disease.

### *4.1.4 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, is discussed in the text and summarized in Tables 3.1-3.4.

## 4.2 Background

Whenever UTI is present in patients with renal insufficiency, problems arise in both the treatment of infection and the management of the 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?

## 4.3 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 nephropathies, although the distribution and extent of the lesions may be different (3-5) (LE: 2a).

### *4.3.1 Vesicoureteric 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 urinary infection or asymptomatic bacteriuria specifically in the progression of scar formation is tenuous. Prophylactic antibiotics will therefore offer little benefit in preserving renal tissue in reflux nephropathy in the older child and adult, 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.

### *4.3.2 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 will 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 which is permanently damaged from any cause will have 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 tracts, which can cause subtle and persistent damage.

#### *4.3.3 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 will further reduce host defences (8).

#### *4.3.4 Acute effects of UTI on the normal kidney*

The acute effects of UTI on the normal kidney are complex. They are worth reviewing as 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.

*Escherichia coli* is the commonest of the Gram-negative organisms 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 organisms cause direct cellular injury, usually after colonizing the renal pelvis. Damage can also occur indirectly from the effects of inflammatory mediators. Metastatic infection will rarely cause renal infection, presenting as cortical abscesses and usually only in susceptible individuals (see the sections below on Diabetes mellitus and 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 interleukin-6 (IL-6) and interleukin-8 (IL-8) are elevated (12,13) (LE: 2b). Tissue damage is reflected by urinary secretion of tubular proteins and enzymes, such as $\alpha$2-macroglobulin, ß2-microglobulin and N-acetyl-ß-D-glucosaminadase enzyme (NDMA). In functional terms, there may be a loss of concentrating power which can persist 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 micro-organism is regarded as evidence of an immune response and therefore of exposure to micro-organisms which 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 will 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 which are secreted by the host urothelium. In practical terms, *E. coli* micro-organisms which are pathological to the kidney appear to express P (or pyelonephritis-associated) or type 2 fimbriae, at least in children where 90% of individuals with acute pyelonephritis express these micro-organisms 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 micro-organism, as its attachment may mean that it is easier for host defence mechanisms to localize and abolish it (19). The cellular and humeral inflammatory host response is also a critical part of host defence. Various cytokines (e.g. IL-6, IL-8) are responsible for inducing leucocyte migration and may be intrinsically deficient in converting asymptomatic bacterial colonization 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 an 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).

#### *4.3.5 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 dimercaptosuccinic acid (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 3-6 months later at follow-up in 77% of patients (9) (LE: 3).

An earlier study by Alwall (21) described 29 women followed for 20-30 years with evidence of increasing renal damage and chronic pyelonephritis upon biopsy (LE: 3). As this study would have used cruder diagnostic techniques, which might not have identified pre-existing disease, 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 the 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 very alarming and dramatic results, but in practical terms the observed changes will 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 the 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 causing complicated UTI.

### *4.3.6 Specific conditions in which an acute UTI causes renal damage*

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

#### 4.3.6.1 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 I diabetes were particularly at risk if they had had diabetes for a long time or complications had developed, particularly peripheral neuropathy and proteinuria. Risk factors in patients with type II 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 originating in the lower urogenital tract. *Klebsiella* infection is particularly common (25% compared with 12% in non-diabetics).

Asymptomatic bacteriuria is common in female diabetics (though not in males). 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 an underlying diabetic nephropathy (25) and autonomic neuropathy causing voiding dysfunction. Impaired host resistance is thought to predispose to the 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 leucocyte concentration (although polymorph function is normal). Interestingly, poor glycaemic control has not been shown to increase the risk of bacteriuria (26).

It has always been recognized 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 randomized trial (27) (LE: 1b), which concluded that treatment did 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 were subsequently recognized 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 is sometimes infected by gas-forming organisms, with a high mortality (emphysematous pyelonephritis) (29). This is characterized histologically by acute pyogenic infiltrate with microabscesses 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 which ruptures leading to a perinephric collection and a psoas abscess. The presentation can occasionally be quite 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 in the treatment of asymptomatic bacteriuria is probably required (GR: C).

#### 4.3.6.2 Tuberculosis

Tuberculosis can cause both acute and chronic renal damage through bilateral renal infiltration. Rarely, this can lead to endstage 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 also of a form of proliferative glomerulonephritis (32,33). (LE: 2b). For more details see EAU guidelines on genitourinary tuberculosis (34).

## 4.4 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 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 persisting 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.

### *4.4.1 Adult dominant polycystic kidney disease (ADPK)*

Urinary tract infection is a prominent complication of ADPK, 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 liposolubility 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 ADPK and control groups (42) (LE: 2a). However, despite close monitoring of patients, UTI and septicaemic episodes are still a significant cause of morbidity, so that bilateral nephrectomy may be the only option.

Polycystic disease is not to be confused with acquired renal cystic disease of the endstage 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 UTI may indicate an adverse prognosis, particularly in males with ADPK.

### *4.4.2 Renal calculi*

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

It is disappointing that, as yet, there are few studies providing long-term serial data identifying renal damage and its causal relationship with infection. In this respect, it is of some interest that a study of 100 patients undergoing 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.

## 4.5 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 of prophylactic antibiotics (45).

### *4.5.1 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 containing the excised kidney should ideally be cultured as micro-organisms 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 micro-organism within the mucous biofilm covering the foreign body. Infection in the native kidneys may worsen considerably as a result of maximum immunosuppression.

In patients with a renal transplant 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 uropathies, 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-catheterization 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, though 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, obstruction). Infarction, either of the whole kidney or of a segment due to arterial damage, can promote UTI through bacterial colonization 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.

### *4.5.2 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) and free radicals as part of the inflammation cascade (45). Urinary tract infections 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 an antiviral agent (cidofovir) (49) (LE: 2a).

### *4.5.3 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 minimized if urodynamic abnormalities, e.g. obstruction, are identified and corrected well in advance of the transplant procedure (50) (LE: 3).

## 4.6 Antibiotic therapy in renal failure/transplantation

Much of the detailed information on antibiotic prescribing in renal failure is summarized in Tables 4.1-4.5 and appendix 14.3. It is important to note that peritoneal dialysis and haemodialysis will clear certain antibiotics, which should either be avoided or given in much higher dosage. Secondly, there are important interactions to consider between immunosuppressive agents and antibiotics.

**Table 4.1: 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 a dialysis treatment |
| • Combination of loop diuretics, e.g. furosemide and a cephalosporin, is nephrotoxic |
| • Nitrofurantoin and tetracyclines are contraindicated, but not doxycyclin |

*GFR = glomerular filtration rate.*

**Table 4.2: Clearance of antibiotics at haemodialysis.**

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

** Drugs cleared by peritoneal dialysis.*

**Table 4.3: Treatment of tuberculosis in renal failure.**

| |
|---|
| Rifampicin and INAH not cleared by dialysis. Give pyridoxine. |
| Ethambutol not dialyzed. Reduce dose if GFR < 30 mL/min |
| Avoid rifampicin with cyclosporine |

**Table 4.4: 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. |
| • 6-month low-dose TMP-SMX (co-trimoxazole) (LE: 1b, GR: A) |
| • Empirical treatment of overt infection (quinolone, TMP-SMX for 10-14 days) |

*TMX = trimethoprim-sulphamethoxazole.*

**Table 4.5: Drug interactions with cyclosporin and tacrolimus.**

| |
|---|
| Rifampicin |
| Erythromycin |
| Aminoglycosides |
| TMP-SMX |
| Amphotericin B |

*TMP-SMX = trimethoprim-sulphamethoxazole.*

*4.6.1 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 will be 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 6 months after renal transplantation (51) (LE: 2a). Patients must be investigated for a surgical complication.

In most units, the combination of trimethoprim and sulphamethoxazole (TMP-SMX, 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 6 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 will result in synergistic

nephrotoxicity with trimethoprim.

A number of other drug interactions need to be considered, e.g. gentamicin, TMP-SMX and amphotericin B promote cyclosporin and tacrolimus toxicity. Rifampicin and eythromycin 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.

#### *4.6.2 Fungal infections*

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

#### *4.6.3 Schistosomiasis*

Schistosomiasis is a familiar problem for patients treated for endstage 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) are recommended for 1 month. In a trial comparing infected patients with those free of schistosomiasis, there is no difference between the incidences of acute and chronic rejection. However, UTI and urological complications occurred in the infected group and a higher cyclosporin dosage 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).

### 4.7 Immunosuppression

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

#### *4.7.1 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 randomized 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 endstage 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 where there is a close relationship between CD4 counts and the risk of bacteriuria, particularly in patients whose counts are less than 200 cells/mL (57). About 40% of patients with bacteriuria will be 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.

#### *4.7.2 Viral and fungal infections*

Viral and fungal infections are relatively common in immunosuppressed patients.

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### 4.8.1 *Further reading*

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


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# 5. COMPLICATED UTIS DUE TO UROLOGICAL DISORDERS

## 5.1 Summary and recommendations

A complicated urinary tract infection (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.

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 *Escherichia 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. Hospitalization 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 ß-lactam 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 has sometimes 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 the completion of therapy and also 4-6 weeks later (GR: B).

## 5.2 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 5.1.

**Table 5.1: 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 catheterization |
| • | A 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 post-operative UTI |
| • | Renal insufficiency and transplantation, diabetes mellitus and immunodeficiency |

Complicated UTI can arise in a heterogeneous group of patients. But neither patient age nor gender 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):

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

*5.2.1 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 may vary from severe obstructive acute pyelonephritis with imminent urosepsis to a catheter-associated post-operative UTI, which might disappear spontaneously as soon as the catheter is removed. It also has to be recognized that symptoms, especially lower urinary tract sympoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as benign prostatic hyperplasia (BPH), TURP, etc.

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 details in Sections 4.1.3 and 4.1.4 on UTIs in renal insufficiency, transplant recipients, diabetes mellitus and immunosuppression.

*5.2.2 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 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 hours apart) yielding $\geq 10^5$ cfu/mL of the same micro-organism are required. The requirement for pyuria is $\geq$ 10 WBC per high-power field (x 400) 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 leucocyte esterase test, haemoglobin and probably a nitrite reaction.

## 5.3 Microbiology

*5.3.1 Spectrum and antibiotic resistance*

Patients with a complicated UTI, both community and hospital-acquired, tend to show a diversity of micro-organisms 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. *Escherichia coli, Proteus, Klebsiella, Pseudomonas, Serratia* spp. 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 from time to time and from one hospital to another.

*5.3.2 Complicated UTIs associated with urinary stones*

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

Of the urease-producing organisms, *Proteus, Providencia, Morganella* spp., and *Corynebacterium urealyticum* are predominant, but *Klebsiella, Pseudomonas, Serratia* 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 resulting increase in ammonia in the urine injures the glycosaminoglycan (GAG) 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).

*5.3.3 Complicated UTIs associated with urinary catheters*

In catheter-associated UTIs, the distribution of micro-organisms 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 UTI.

## 5.4 Treatment

*5.4.1 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. Hospitalization is often necessary depending on the severity of the illness.

*5.4.2 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. Most important for the prognosis is still the severity of the associated illness and of the underlying urological condition.

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 characterization 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 micro-organisms in subsequent infections. Whenever possible, empirical therapy should be replaced by a therapy adjusted for the specific infective organism(s) identified in the urine culture. Therefore, a urine specimen for culture must be obtained prior to initiating therapy and the selection of an antimicrobial agent should be re-evaluated once culture results are available (7). So far, it has not been shown that any agent or class of agents is superior in a case where 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.

If empirical treatment is necessary, fluoroquinolones with mainly renal excretion are recommended because they have a large spectrum of antimicrobial activity covering most of the expected pathogens and they reach high concentration levels both in 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 randomized trial, has been shown to be as effective as ceftriaxone (17).

In most countries, *E. coli* shows a high rate of resistance against TMP-SMX (18% in the last US evaluation) (16) 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 institutionalized or hospitalized 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. hospitalized 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 summarized in Table 5.2 and Appendix 12.2 (Recommendations for antimicrobial therapy in urology).

*5.4.3 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).

*5.4.4 Complicated UTIs associated with urinary stones*

If a nidus of either 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 can not be achieved (21).

*5.4.5 Complicated UTIs associated with indwelling catheters*

Current data do not support the treatment of asymptomatic bacteriuria, either during short-term catheterization (< 30 days) or during long-term catheterization, because it will promote the emergence of resistant strains (22,23). In short-term catheterization, 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 both too short as well as too long may cause the emergence of resistant strains. A 7-day course may be a reasonable compromise.

*5.4.6 Complicated UTIs in spinal-cord injured patients*

It is generally accepted that asymptomatic bacteriuria in these patients should not be treated (25), even in cases of intermittent catheterization. For symptomatic episodes of infection in the spinal-cord injured patient, only a few studies have investigated the most appropriate agent and the most appropriate 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 summarized in Table 5.2.

**Table 5.2: Antimicrobial treatment options for empiric 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 = ß-lactam inhibitor*

*5.4.7 Follow-up after treatment*

The greater likelihood of the involvement of resistant micro-organisms 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, prior to and after the completion of the antimicrobial treatment, urine cultures must be obtained for the identification of the micro-organisms and the evaluation of susceptibility testing.

## 5.5 Conclusions

Until predisposing factors are completely removed, true cure (i.e. without recurrent infection) is usually not possible. Correction of these abnormalities must be performed, whenever possible, as an essential part of treatment. Recurrent infection is the rule when the underlying urological abnormality cannot be removed: either relapse (e.g. with the same micro-organism) or a re-infection (e.g. with a new micro-organism). For this reason, a urine culture has to be carried out between 5 and 9 days after the completion of therapy and repeated between 4 and 6 weeks later.

## 5.6 References


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# 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 European Society for Infection in Urology (the ESIU is 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 urinary tract infections (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. 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 more than 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 catheterization 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 or more 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 |
| *Diagnostics* | | |
| 14. | Routine urine culture in asymptomatic catheterised patients is not recommended. | B |

| | | |
|---|---|---|
| 15. | Urine, and in septic patients also blood for culture must be taken before any antimicrobial therapy is started. | C |
| 16. | 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* | | |
| 17. | Whilst the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended, except in certain circumstances, especially prior to traumatic urinary tract interventions. | A |
| 18. | 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 |
| 19. | Antimicrobial treatment is recommended only for symptomatic infection. | B |
| 20. | 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 |
| 21. | For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns. | C |
| 22. | After culture results are available, antibiotic therapy has to be adjusted according to sensitivities of the pathogens. | B |
| 23. | In case of candiduria associated with urinary symptoms, or if candiduria is the sign of a systemic infection, systemic therapy with antifungals is indicated. | B |
| 24. | Elderly female patients may need treatment if bacteriuria does not resolve spontaneously after catheter removal. | C |
| *Alternative drainage systems* | | |
| 25. | There is limited evidence that postoperative intermittent catheterisation reduces the risk of bacteriuria compared with indwelling catheters. No recommendation can be made. | C |
| 26. | In appropriate patients, a suprapubic, condom drainage system or intermittent catheter is preferable to an indwelling urethral catheter. | B |
| 27. | 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* | | |
| 28. | Patients with urethral catheters in place for 10 years or more should be screened for bladder cancer. | C |

**GR = grade of recommendation*

### 6.3 Reference

1. Tenke P, Kovacs B, Bjerklund Johansen TE, Matsumoto T, Tambyah PA, Naber KG. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 2008;31S: S68-S78. http://www.ischemo.org/abstracts/TenkeIJAA2008.pdf

# 7. SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

### 7.1 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, hyperleucocytosis or leucopenia, tachycardia, tachypnoea), is recognized as the first event in a cascade to multi-organ failure. Mortality is considerably increased when severe sepsis or septic shock are present, though the prognosis of urosepsis is globally better than sepsis due to 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, recombinant activated protein C) 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 can due to both community- or nosocomial-acquired 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 catheterizations, correct use of closed catheter systems and attention to simple daily asepsis techniques in order to avoid cross-infection (LE: 2a, GR: B).

## 7.2 Background

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

Severe sepsis is a severe situation with a reported mortality rate ranging from 20% to 42% (1). Most severe sepsis reported in the literature is related to pulmonary (50%) or abdominal infections (24%), with UTIs accounting for only 5% (2). Sepsis is commoner 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 suggesting improved management of patients (the total in-hospital mortality rate fell from 27.8% to 17.9% during the period 1995-2000) (4). Globally (this is not true for urosepsis), the rate of sepsis due to fungal organisms increased while Gram-positive bacteria became the predominant pathogen in sepsis even if in urosepsis Gram-negative bacteria remain predominant.

In urosepsis, as in other types of sepsis, the severity of sepsis 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 acquired immunodeficiency syndrome. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathies, neurogenic bladder disorders or endoscopic manoeuvres. However, all patients can be affected by bacterial species capable of inducing inflammation within the urinary tract. Moreover, it is now recognized that SIRS may be present without infection (pancreatitis, burns, non-septic shock, etc) (5).

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

## 7.3 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 leucocyturia. The following definitions apply (Table 7.1):

- 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 sepsis 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 7.1: 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 |
| Systemic 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, pancreatitis). This systemic response is manifested by two or more of the following conditions:<br>Temperature > 38°C or < 36°C<br>Heart rate > 90 beats min<br>Respiratory rate > 20 breaths/min or PaCO2 < 32mmHg (< 4.3kPa)<br>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 | A systolic blood pressure of < 90mmHg or a reduction of > 40mmHg 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 an 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 an 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 last for more than 1 hour and does not respond to fluid administration or pharmacological intervention |

## 7.4 Physiology and biochemical markers

Micro-organisms 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 bacteriaemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis (ABP), and is facilitated by obstruction. *Escherichia coli* remains the most prevalent micro-organism. Particularly in several countries, some bacterial strains can be resistant to quinolones or third-generation cephalosporins. Some micro-organisms are multi-resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and *Serratia* spp. and therefore difficult to treat. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or the immunosuppressed) with typical signs of generalized sepsis associated with local signs of infection. A fatal outcome is described in 20-40% of all patients.

### *7.4.1 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 immunodepressive phasis follows the initial pro-inflammatory mechanism. Other cytokines are involved such as interleukins. Tumour necrosis factor-$\alpha$ (TNF-9 pt), interleukin-1 (IL-1), IL-6, and IL-8 are cytokines that are associated with sepsis. 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. A genetic predisposition is more than likely to explain sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood (2).

### *7.4.2 Procalcitonin is a potential marker of sepsis*

Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally in healthy humans, levels are undetectable. During severe generalized 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).

## 7.5 Prevention

Septic shock is the most frequent cause of death for patients hospitalized for both community and nosocomial acquired infection (20-40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for the combination of treatment of the cause (obstruction), 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.

### *7.5.1 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, both in prophylaxis and in 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 in-patient periods prior to 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 catheterization as well as by ureteral stenting (11). Antibiotic prophylaxis does not prevent stent colonization, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimization of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least invasive method to release urinary tract obstruction until the patient is stabilized.
- 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.

*7.5.2 Appropriate peri-operative antimicrobial prophylaxis*

For appropriate peri-operative antimicrobial prophylaxis, see Section 11. The potential side effects of antibiotics must be considered prior to their administration in a prophylactic regimen.

*7.5.3 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.

*7.5.4 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 catheterized 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.

## 7.6 Treatment

*7.6.1 Relief of obstruction*

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

*7.6.2 Antimicrobial therapy*

Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the basis of culture results. The dosage of the antibiotic substances is of paramount importance in patients with sepsis syndrome and should generally be high, with exception of patients in renal failure. The antibacterial treatment options are summarized in Appendix 12.

*7.6.3 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. An early goal-directed therapy has been shown to reduce mortality (14). Volaemic expansion and vasopressor therapy have considerable impact on the outcome. Early intervention with appropriate measures to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilization 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 (ACTH test) (15).

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

Recombinant activated protein C (dotrecogin alpha) is a new drug that has been approved for therapy of severe sepsis since November 2002. This expensive treatment has been proven to be more effective in patients with more severe disease, as assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II scores $\geq$ 25 or the presence of $\geq$ two organ dysfunctions (17).

The best strategy has been summarized and graded according to a careful evidence-based

methodology in the recently published 'Surviving Sepsis Guidelines' (18).

## 7.7 Conclusion

Sepsis syndrome in urology remains a severe situation with a mortality rate as high as 20-40%. A recent campaign, 'Surviving Sepsis Guidelines', aimed at reducing mortality by 25% in the next few years has been published recently (18). Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, urolithiasis. Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patients' 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.

## 7.8 Acknowledgement

The authors are thankful to Jean M. Carlet, Head of Intensive Care, Hôpital Saint Joseph, Paris, France, for reviewing this manuscript on urosepsis.

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# 8. URETHRITIS

## 8.1 Definition

Primary urethritis has to be differentiated from secondary urethritis, which can be found in patients with indwelling catheters or urethral strictures, and can be caused by uropathogens or by staphylococci. Besides infective causes of urethritis, chemical, mechanical and non-infective inflammatory causes also have to be considered, such as Reiter's, Behçet's and Wegener's diseases (1). Only selected aspects of primary urethritis will be discussed in this chapter (2). For further details, see also the EAU guidelines on sexually transmitted diseases (STDs) (3).

## 8.2 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 socio-economic status and the frequency of infections due to *Neisseria gonorrhoeae* and *C. trachomatis*. Infection is spread by sexual contact.

## 8.3 Pathogens

Pathogens include *N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium* and *Trichomonas vaginalis*. The frequency of the different species varies between patient populations (4–8). 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.

## 8.4 Route of infection and pathogenesis

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae, C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the genito-urinary tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women. Recent evidence has suggested that *M. genitalum* can also cause cervicitis and pelvic inflammatory disease in women (9) (LE: 3)

## 8.5 Clinical course

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

## 8.6 Diagnosis

A Gram stain of a urethral discharge or a urethral smear that shows more than five leucocytes per high power field (× 1,000) and eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis (10)(LE: 3, GR: B). The Gram strain is the preferred rapid diagnostic test for evaluating urethritis. It is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. A positive leucocyte 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 spp*. can usually be identified microscopically.

## 8.7 Therapy

### *8.7.1. Treatment of gonorrheal urethritis*

The following guidelines for therapy comply with the recommendations of the US Centers for Disease Control and Prevention (9–11). The following antimicrobials can be recommended for the treatment of gonorrhoea:

**As first-choice treatment**

- cefixime, 400 mg orally as a single dose or 400 mg by suspension (200 mg/5 mL)
- ceftriaxone, 1g intramuscularly (with local anaesthetic) 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 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 gonorrhea in the United States. In Europe, knowledge of local susceptibility patterns is mandatory for the correct treatment of gonorrhoeal urethritis.

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

### *8.7.2. 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 *M. genitalium* may respond better to azithromycin (14). 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.

## 8.8 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 until 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.

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# 9. PROSTATITIS AND CHRONIC PELVIC PAIN SYNDROME

## 9.1 Summary and recommendations

Bacterial prostatitis is a disease entity diagnosed clinically and by evidence of inflammation and infection localized 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 defeverescence and normalization 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, a fluoroquinolone or trimethoprim should be given orally for 2 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. Despite the existence of some scientifically valid studies, no specific recommendations have been made until now. This has been because patients with CPPS probably represent a heterogeneous group of diseases and therapeutic outcome is always uncertain.

## 9.2 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 localized to the prostate (1). A causative pathogen, however, is detected by routine methods in only 5-10% of cases (2), 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 systematization of treatment (3-5).

This chapter will review documented or suspected bacterial infections of the prostate.

## 9.3 Diagnosis

### *9.3.1 History and symptoms*

According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, the latter being defined by symptoms persisting for at least 3 months (3-5). The predominant symptoms are pain at various locations and lower urinary tract symptoms (LUTS) (Tables 9.1 and 9.2) (6-8). Chronic bacterial prostatitis is the most frequent cause of recurrent urinary tract infections in the male (9).

**Table 9.1: Localization of pain in prostatitis and CPPS***

| 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 9.2: Lower urinary tract symptoms in prostatitis and CPPS***

| |
|---|
| • 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. (8).*

9.3.1.1 Symptom questionnaires

Symptoms appear to have the strongest basis for use as a classification parameter in bacterial prostatitis as well as in CPPS (10). Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms (10,11). They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH (USA) (12). Although the CPSI has been validated, so far its benefit in clinical studies is still uncertain. The questionnaire contains four questions regarding pain or discomfort, two questions regarding urination and three questions related to quality of life (see Appendix 11.4).

*9.3.2 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 differential diagnoses, such as other diseases in the urogenital organs and anorectal disorders. Clinical examination should include evaluation of the pelvic floor musculature.

*9.3.3 Urine cultures and expressed prostatic secretion*

The most important investigations in the evaluation of the patient with prostatitis are quantitative bacteriological localization cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey (1) (see Appendix 12.6).

According to the classification developed by the NIDDK/NIH (Table 9.3), the presence of leucocytes in post-massage urine and ejaculate are also included in the definition of inflammatory chronic prostatitis or CPPS (group IIIA) (3). The inclusion of leucocytes in the ejaculate as part of the new consensus CPPS concept allows almost twice as many patients to be reclassified into group IIIA as were formerly included in the category ‘abacterial prostatitis‘ using the earlier Drach’s classification (13).

**Table 9.3: Classification of prostatitis and CPPS according to NIDDK/NIH (3-5).**

| Type | Name and description |
|---|---|
| I | Acute bacterial prostatitis |
| II | Chronic bacterial prostatitis |
| III | Chronic abacterial prostatitis - chronic pelvic pain syndrome (CPPS) |
| | A. Inflammatory CPPS (white cells in semen/EPS/VB3) |
| | B. 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).*

The Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in bacterial prostatitis (Table 9.4) (14). The significance of intracellular bacteria, such as *Chlamydia trachomatis*, is uncertain (15). In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *Mycobacterium tuberculosis, Candida* spp. and rare pathogens, such as *Coccidioides immitis, Blastomyces dermatitidis* and *Histoplasma capsulatum* (16).

**Table 9.4: The most common pathogens in prostatitis.**

| |
|---|
| **Aetiologically recognized pathogens*** |
| *Escherichia coli* |
| *Klebsiella* spp. |
| *Proteus mirabilis* |
| *Enterococcus faecalis* |
| *Pseudomonas aeruginosa* |
| |
| **Organisms of debatable significance** |
| Staphylococci |
| Streptococci |
| *Corynebacterium* spp. |
| *Chlamydia trachomatis* |
| *Ureaplasma urealyticum* |
| *Mycoplasma hominis* |

**Adapted from Weidner et al. (2) and Schneider et al. (14).*

There is no correlation between leucocyte and bacterial counts and the severity of symptoms in men with chronic prostatitis/CPPS (17). It has also been shown that culture, leucocyte and antibody status does not predict antibiotic response in this group of prostatitis (18). In both studies, however, patients with clearly defined chronic bacterial prostatitis were excluded.

### *9.3.4 Perineal biopsy*

Perineal biopsies may be taken to help in the detection of difficult-to-culture micro-organisms, but perineal biopsy should be reserved for research purposes and cannot be recommended as part of the routine work-up. Bacteria have been cultured from perineal prostate biopsies in 36% of men with CPPS, but these results do not differ from the findings in asymptomatic controls (19).

### *9.3.5 Other tests*

The main parameter for diagnosis of inflammation in the male urogenital tract is increased leucocyte counts in the prostatic fluid, post-prostate massage urine, and seminal fluid.

Prostatic biopsy is not indicated in the routine management of prostatitis/CPPS. However, histological prostatitis is frequently diagnosed in biopsies taken for suspected prostate cancer. If such patients are asymptomatic, they are classified in the new category of 'asymptomatic prostatitis' (type IV) (Table 9.3).

Other inflammatory markers include elevated pH, lactate dehydrogenase (LDH) and immunoglobulins (20). The cytokines, interleukin (IL)-1ß and tumour necrosis factor (TNF)-$\alpha$, may be identified in EPS (20) and complement C3, coeruloplasmin or polymorphonuclear (PMN) elastase in the ejaculate. These tests, however, cannot be considered to be part of routine diagnostic work-up (21).

Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate and dilatation in the seminal vesicles. However, TRUS is not an important classification parameter in prostatitis (22), as it is unreliable in the diagnosis of prostatitis.

### *9.3.6 Classification systems*

The purpose of the culture technique described by Meares and Stamey in 1968 was to decide whether bacteriuria originated from the urethra, the prostate or the bladder. Ten years, later Drach et al. (23) suggested a classification of prostatitis based on the work of Meares and Stamey, in which various types of prostatitis were differentiated according to the number of leucocytes and positive cultures in EPS and in segmented urine samples, i.e. first voided bladder urine-1 (VB1), mid-stream urine (second voided bladder urine-2, VB2) and urine following prostatic massage (third voided bladder urine-3, VB3). This has been the most widely used classification of prostatitis for almost three decades (Table 9.5) and is still included in the latest WHO classification of diseases (ICD 10) (24).

**Table 9.5: Classification of prostatitis according to Drach et al. (23)**

| Classification | Clinical and laboratory findings |
|---|---|
| Acute bacterial prostatitis | Clinically significant infection of the prostate |
| Chronic bacterial prostatitis | Significant inflammation of the prostate<br>Isolation of an aetiologically recognized organism from the prostatic fluid/urine |
| Chronic abacterial prostatitis | Significant prostatic inflammation<br>Failure to isolate an organism from the prostatíc fluid/urine, or isolation of an organism whose aetiological significance is debatable |
| Prostatodynia | No significant prostatic inflammation<br>Failure to isolate an organism from the prostatic fluid/urine |

In 1995, the NIDDK of the NIH (USA) convened a workshop to 'develop a plan which would enable clinicians and research investigators to effectively diagnose, treat, and eventually prevent the prostatitis syndrome' (4). The NIDDK recommended a new classification of the prostatitis syndrome, which has been accepted by the IPCN. The terms 'abacterial prostatitis' and 'prostatodynia' were exchanged for 'chronic pelvic pain syndrome (CPPS)', with or without inflammation, respectively. Seminal secretion was added to segmented urine and EPS as an additional parameter. A new category (type IV) of asymptomatic prostatitis (histological prostatitis) was added (Table 9.3). This classification is now used as a logical basis for choice of treatment.

*9.3.7 Diagnostic evaluation*

The content and order of procedures in the diagnostic evaluation of a patient with suspected prostatitis will depend on previous examinations undertaken by the GP, the established routines in different hospitals and countries and the distance from the patient's home to the urologist. A suggested algorithm for diagnostic evaluation is presented in Table 9.6.

**Table 9.6: Algorithm for diagnostic urological work-up in prostatitis.**

| |
|---|
| • Clinical evaluation |
| • Urinalysis and urine culture |
| • Exclude sexually transmitted diseases |
| • Micturition chart, uroflowmetry and residual urine |
| • Four-glass test according to Meares and Stamey |
| • Microscopy |
| • Culture |
| • Try antibiotics if signs of inflammation |

*9.3.8 Additional investigations*

The EAU working group believes that guidelines on prostatitis should not contain a set of minimum 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. If suspected, bladder cancer must be excluded with urine cytology and cystoscopy. A ureteric calculus is ruled out by unenhanced spiral computerized tomography or intravenous pyelography. Interstitial cystitis is diagnosed by means of a micturition chart, cystoscopy and biopsy. Anorectal examination is carried out whenever indicated.

Microscopic examination of ejaculate is inferior to microscopy of EPS. It is difficult to differentiate between spermatocytes and leucocytes, unless specific methods are applied, e.g. peroxidase staining (25), and the detection rate for positive cultures is significantly reduced (26).

Video-urodynamics and advanced urodynamic examination with measurement of urethral closing pressure are not justified in the routine evaluation of a prostatitis patient, although intriguing results have been obtained in some studies (27).

The measurement of cytokines, biofilms, etc. in EPS has research interest only (6,28). Prostate-specific antigen (PSA) values may be elevated in both symptomatic and asymptomatic prostatitis (29). If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalize after antimicrobial treatment for 4 weeks in about 50% of patients (30). A delay of at least 3 months should be allowed before it can be assumed a stable level of PSA has been reached. Measurement of free and total PSA adds no practical diagnostic information in prostatitis (31).

## 9.4 Treatment

### *9.4.1 Antibiotics*

Antibiotics are life-saving in acute bacterial prostatitis, recommended in chronic bacterial prostatitis and may be tried in inflammatory CPPS.

Acute bacterial prostatitis can be 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, may be administered. For initial therapy, these regimens may be combined with an aminoglycoside. After defeverescence and normalization of infection parameters, oral therapy can be substituted and continued for a total of about 2-4 weeks (32). In less severe cases, a fluoroquinolone may be given orally for 10 days (5) (IVC).

The recommended antibiotics in chronic bacterial prostatitis and inflammatory CPPS (NIH type IIIA), together with their advantages and disadvantages, are listed in Table 9.7 (33). Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties (33) (LE: 2b, GR: B), their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including *Pseudomonas aeruginosa*. In addition, levofloxacin is active against Gram-positive and 'atypical' pathogens, such as *C. trachomatis* and genital mycoplasmas (LE: 2b, GR: B).

The duration of antibiotic treatment is based on experience and expert opinion and is supported by many clinical studies (34). In chronic bacterial prostatitis and in inflammatory CPPS, antibiotics should be given for 2 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics continued only if cultures are positive or the patient reports positive effects from the treatment. A total treatment period of 4-6 weeks is recommended. Relatively high doses are needed and oral therapy is preferred (33,34) (LE: 3, GR: B).

The reason for administration of antibiotics in inflammatory CPPS is that there may be a bacterial infection, even though bacteria have not been detected by routine methods (35,36). Furthermore, many clinical studies report a beneficial effect of antibiotics in inflammatory CPPS (37,38) (LE: 2a, GR: B). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given (33,38) (LE: 2b, GR: B).

### *9.4.2 Antibiotics and α-blockers in combination therapy*

Urodynamic studies have shown increased urethral closing pressure in patients with chronic prostatitis (5). A combination treatment of α-blockers and antibiotics is reported to have a higher cure rate than antibiotics alone in inflammatory CPPS (Type IIIA+B) (39) (LE: 1b, GR: B). This is a treatment option favoured by many urologists.

However, in a recent, randomized, double-blind placebo-controlled multicentre study, it was shown that neither ciprofloxacin, tamsulozin, nor the combination of both ciprofloxacin and tamsulozin were superior to placebo in reducing symptoms in men with moderate to severe symptoms (40) (LE: 1b, GR: B). However, in this latter study, many patients were included who had already been heavily pretreated with different drug regimens.

**Table 9.7: Antibiotics in chronic bacterial prostatitis***

| Antibiotic Advantages | Disadvantages | Recommendation |
|---|---|---|
| **Fluoroquinolones**<br>• Favourable pharmacokinetics<br>• Excellent penetration into the prostate<br>• Good bioavailability<br>• Equivalent oral and parenteral pharmacokinetics (depending on the substance)<br>• Good activity against 'typical' and atypical pathogens and *Pseudomonas aeruginosa*<br>• In general, good safety profile | Depending on the substance:<br>• Drug interactions<br>• Phototoxicity<br>• Central nervous system adverse events | Recommend |
| **Trimethoprim**<br>• Good penetration into prostate<br>• Oral and parenteral forms available<br>• Relatively cheap | • No activity against *Pseudomonas*, some enterococci and some Enterobacteriaceae | Consider |

| | | |
|---|---|---|
| • Monitoring unnecessary<br>• Active against most relevant pathogens | | |
| **Tetracyclines**<br>• Cheap<br>• Oral and parenteral forms available<br>• Good activity against *Chlamydia* and *Mycoplasma* | • No activity against *Ps. aeruginosa*<br>• Unreliable activity against coagulase-negative staphylococci, *E.coli*, other Enterobacteriaceae, and enterococci<br>• Contraindicated in renal and liver failure<br>• Risk of skin sensitization | Reserve for special indications |
| **Macrolides**<br>• Reasonably active against Gram-positive bacteria<br>• Active against Chlamydia<br>• Good penetration into prostate<br>• Relatively non-toxic | • Minimal supporting data from clinical trials<br>• Unreliable activity against Gram-negative bacteria | Reserve for special indications |

**Adapted from Bjerklund Johansen et al. (33).*

*9.4.3 Other oral medication*

The α-blocker, terazosin, was found to be superior to placebo in reducing symptoms for patients with CPPS (41) (LE: 1b, GR: B). Pentosan polysulphate sodium may reduce symptoms and improve quality of life in patients with CPPS (42) (LE: 2a, GR: B). Finasteride will provide some improvement for patients with category IIIA prostatitis (43) (LE: 1b, GR: B).

*9.4.4 Intraprostatic injection of antibiotics*

This treatment has not been evaluated in controlled trials and should be considered only if oral treatment fails to eradicate the infection (44,45).

*9.4.5 Surgery*

In acute prostatitis, some patients need bladder drainage, preferably with a suprapubic catheter. A positive effect of transurethral resection of the prostate (TURP) and transurethral needle ablation has been observed in patients with severe discomfort (46,47) (LE: 2a, GR: B). Even radical prostatovesiculectomies have been carried out to relieve the pain of chronic prostatitis, the results of which are dubious (48). In general, surgery should be avoided in the treatment of prostatitis patients, except for drainage of prostatic abscesses.

*9.4.6 Other treatment forms*

Microwave energy delivered from Prostatron 2.0 has an in-vitro bactericidal effect on laboratory-cultured *E. coli* and E. cloacae (49), and transurethral microwave thermotherapy (TUMT) in inflammatory CPPS was proven superior to sham-treated controls (50) (LE: 1b, GR: B). However, TUMT is still considered an experimental treatment option in patients with a suspected infection.

A number of other medical and physical treatment modalities have been suggested in non-inflammatory CPPS. Since in this condition there is no evidence of an infection, a full coverage of this topic lies beyond the scope of this review and the reader is referred to other publications. It should be recalled, however, that symptoms will resolve within 1 year in about 30% of men with CPPS (51) (2).

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# 10. EPIDIDYMITIS AND ORCHITIS

## 10.1 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 testis is 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).

## 10.2 Incidence and prevalence

There are no new data available concerning the incidence and prevalence of epididymitis. According to older data, acute epididymitis was a major cause for admission to hospitals of military personnel (2) (LE: 3). Acute epididymitis in young males 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 undergoing mumps infection. The incidence depends upon the vaccination status of the population (4). A primary chronic orchitis is the granulomatous disease, a rare condition with uncertain aetiology reported in about 100 cases in the literature (5).

## 10.3 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.

## 10.4 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, auto-immune phenomena are assumed to trigger chronic inflammation (5,7). Orchitis of the child and mumps-orchitis are of haematogenous origin (7).

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

## 10.5 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 results from sexually transmitted organisms have a history of sexual exposure, which can lie dormant for months before the onset of symptoms. If the patient is examined immediately after obtaining a 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 an infection of *N. gonorrhoeae*. The presence of only WBC on a urethral smear indicates the presence of non-gonorrhoic urethritis. *C. trachomatis* will be isolated in approximately two-thirds of these patients (2,6) (LE; 3).

Ejaculate analysis according to WHO criteria including leucocyte analysis may indicate persistent inflammatory activity. In many cases, transient decreased sperm counts and forward motility can be found. Azoospermia due to a complete obstruction of both epididymis 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).

### *10.5.1 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.

### *10.6 Treatment*

Only a few studies have been performed measuring the penetration of antimicrobial agents into epididymis and testis in human. 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 comparing microbiological results from puncture of the epididymis and from urethral swabs as well as urine have shown very good correlation. Therefore, prior to 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 a total treatment

period of at least 2 weeks. Macrolides may be used as alternative agents (GR: C).

Supportive therapy includes bed rest, uppositioning of the testes and antiphlogistic therapy. Since, for young men, epididymitis can lead to permanent occlusion of the epididymal ducts and thus to infertility, 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.

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# 11. PERIOPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

### 11.1 Summary


The aim of antimicrobial prophylaxis in urological surgery is to prevent infective complications that result from diagnostic and therapeutic procedures. However, the evidence on the best choice of antibiotics and prophylactic regimens is limited (Table 11.1).


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 extracorporeal shockwave lithotripsy (ESWL), although it is recommended in complicated procedures and patients with identified risk factors.

For open and laparoscopic surgery, the same rules as in abdominal surgery can be applied. No antibiotic prophylaxis is recommended for clean operations, whereas a single or 1-day dose is recommended in clean–contaminated/contaminated operations. 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/sulphamethoxazole (TMP-SMZ), second-generation cephalosporins, fluoroquinolones, aminopenicillins plus a β-lactam inhibitor (BLI), 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 11.1. Level of evidence and grade of recommendation for standard urological procedures.**
*(The consequences in terms of antibiotic prophylaxis are given in Table 11.5)*

| Procedure | LE | GR | Remarks |
|---|---|---|---|
| *Diagnostic procedures* | | | |
| Cystoscopy | 1b | A | Low frequency of infections<br>Contradictory findings |
| Urodynamic study | 1a | A | Low frequency of infections<br>Contradictory findings |
| Transrectal core biopsy of prostate | 1b | A | High risk of infection<br>Assess carefully risk factors |
| Diagnostic ureteroscopy | 4 | C | No available studies |
| *Therapeutic procedures* | | | |
| TURB | 2b | C | Poor data. No concern given to burden of tumor, necrosis |
| TURP | 1a | A | Good documentation |
| ESWL | 1a/1b | A | Low frequency of infections<br>Contradictory findings |
| Ureteroscopy stone | 2b | B | Literature does not distinguish between severity of stone management |
| Percutaneous stone management | 2b | B | High risk of infection |
| *Open and laparoscopic surgery* | | | |
| *Clean operations (no opening of urinary tract)* | | | |
| Nephrectomy | 3 | C | SSI poorly documented<br>Catheter-related UTI |
| Scrotal surgery | 3 | C | Review studies contradictory |
| Prosthetic implants | 3 | B | Limited documentation<br>Regimen not defined |
| *Clean–contaminated (opening of urinary tract)* | | | |
| Nephroureterectomy | 3 | B | Poor documentation |
| Pelvio-ureteric junction repair | 4 | C | No studies detected |
| Total (radical) prostatectomy | 2a | B | No RCT, poor 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 |

*ESWL = extracorporeal shockwave lithotripsy; TURB = transurethral resection of the bladder; TURP = transurethral resection of the prostate; RCT= Randomised Controlled Trials*

## 11.2 Introduction

Antibiotic prophylaxis in urology has been controversial for many years. Most studies in the past have been poorly designed and have 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 opinions 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) and of 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 more than 200 urological services or units. The survey found that 9.7% of patients had a healthcare-(nosocomial-)associated urinary tract infection (NAUTI) (10). The survey illustrates 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.

## 11.3 Goals of perioperative antibacterial prophylaxis

Antibiotic prophylaxis and antibiotic therapy are two different issues. Antibiotic prophylaxis aims at preventing 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. On the other hand, antibiotic therapy is the treatment of a clinically suspected or microbiologically proven infection.

There are some clinical situations, however, that are not easily classified as either prophylaxis or therapy, e.g. patients with long-term indwelling catheters and bacteriuria. These patients must receive antibiotics at the time of surgery, regardless of how they are classified.

There is also a dilemma regarding the definition of infections. The US Centers for Disease Control and Prevention (CDC) have presented definitions that are currently the most comprehensive and are recommended for the evaluation of infectious complications (11). These definitions have also been used in the recent Pan-European study on NAUTI (*see* above) (10). Revision of definitions and recommendations are ongoing in some countries (12). Table 11.2 illustrates the different types of infectious complications encountered in urological surgery.

**Table 11.2: Main types of healthcare-associated infections encountered in urological practice.**

| Site of infection | Minor | Major |
|---|---|---|
| Surgical wound<br>Incision (SSI) | Superficial wound infection | Deep wound infection<br>Wound rupture (abdominal dehiscence)<br>Deep abdominal or surgical site abscess |
| UTI or organ-specific infection | Asymptomatic bacteriuria (bacterial colonization)<br>Symptomatic lower UTI | Febrile genitourinary infection<br><br>Pyelonephritis<br>Renal abscess |
| Other urogenital sites<br>Blood stream<br>Other sites | Epididymitis Bacteraemia | Acute bacterial prostatitis (type I)<br>Sepsis<br>Pneumonia<br>Septic embolism |

SSIs 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 genitourinary infections such as acute pyelonephritis, prostatitis, epididymitis and urosepsis, as well as serious wound infections (Table 11.2). 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. On the other hand, 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. Obviously, perioperative antibacterial prophylaxis in urology has to go beyond the traditional aim of prophylaxis in surgery, which is the prevention of wound infections.

## 11.4 Risk factors

Risk factors (Table 11.3) are underestimated in most trials. However, they are important in the pre-operative 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 (13) into clean, clean–contaminated, contaminated, and 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 and 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 (6,14,15).

**Table 11.3: 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 genitourinary 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 NAUTI (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 clearcut recommendations. Furthermore, the bacterial load, the duration and difficulty of the operation, the surgeon's skill and peri-operative bleeding may also influence the risk of infection (6).

## 11.5 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 (15,16). It is essential to individualise the choice of antibiotic prophylaxis according to each patient's cumulative risk factors (17). Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection (18–20).

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

### *11.5.1 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 from 2 h before but not later than 3 h after the start of an intervention (21–23). 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 (24). It is worth noting that a bloodstream infection can develop in less than an hour (21).

### *11.5.2 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 between 1 and 2 h before intervention. Administration of the drug several hours before surgery is probably less effective. In other cases, intravenous administration is recommended. Local irrigation of the operating field with antibiotics is not recommended.

### *11.5.3 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 11.4)

### *11.5.4 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 fourfold difference in sales of antibiotics (25). 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. TMP-SMZ, 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.

## 11.6 Prophylactic regimens in defined procedures

The list of major urological diagnostic and therapeutic procedures is given in Table 11.4 and the empirical relationship between the level of invasiveness and risk for infective complications is illustrated in Figure 11.1.

**Table 11.4. List of urological interventions.**

| |
|---|
| **Diagnostic procedures** |
| • Fine-needle biopsy of the prostate |
| • Core-needle biopsy of the prostate |
| • Cystoscopy |
| • Urodynamic examination |
| • Radiological diagnostic intervention of the urinary tract |
| • Ureteroscopy |
| **Deviation procedures** |
| • Insertion of indwelling catheter |
| • Insertion of suprapubic catheter |
| • Insertion of nephrostomy tube |
| • Insertion of ureteric stent |
| **Endourological operations** |
| • Resection of bladder tumour |

- Resection of prostate
- Minimal invasive prostatic operation, i.e. microwave thermotherapy
- Ureteroscopy for stone or tumour fulguration
- Percutaneous stone or tumour surgery

**Extracorporeal shockwave lithotripsy**

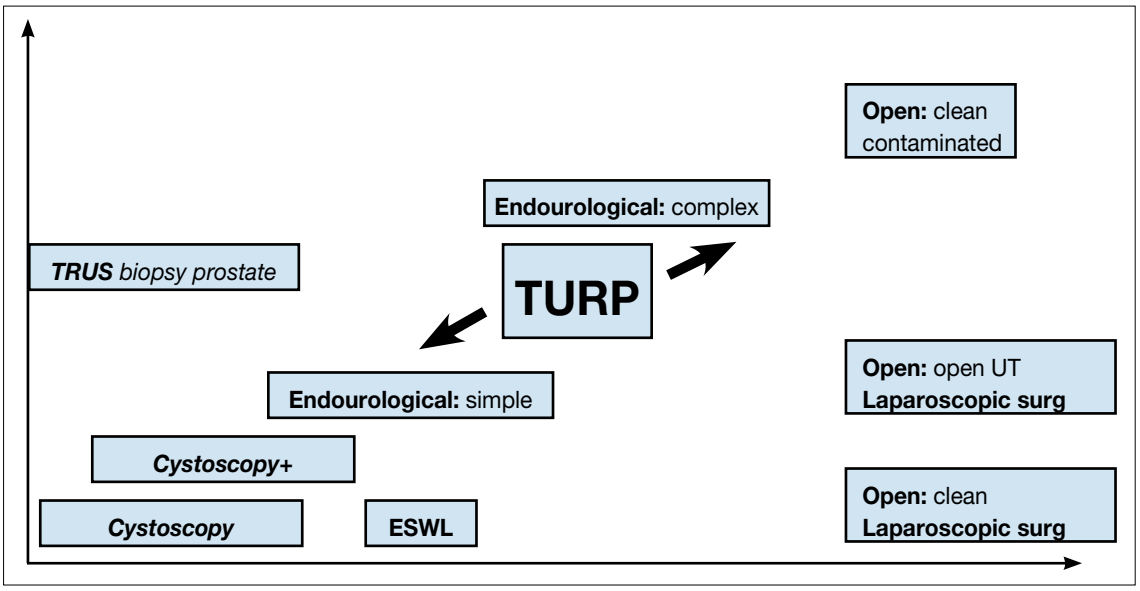
**Laparoscopic surgery**

- Radical prostatectomy
- Pyeloplasty
- Nephrectomy and nephron-sparing surgery of the kidney
- Other major laparoscopic surgery, including bowel surgery

**Open surgery**

- Open surgery of the prostate, i.e. enucleation of prostatic adenoma
- Open stone surgery
- Pyeloplasty
- Nephrectomy and nephrone-sparing surgery of the kidney
- Nephro-ureterectomy including bladder resection
- Bladder resection
- Urethroplasty
- Implantation of prosthetic devices
- Urinary diversion procedures using intestinal segments

**Figure 11.1 Level of invasiveness and risk of infection in urological procedures (empirical scheme) (5)**




The recommendations for antibiotic prophylaxis in standard urological surgery are summarised in Table 11.5 and Appendix 14.4.

*11.6.1. Diagnostic procedures*

Antimicrobial prophylaxis in core biopsy of the prostate is generally recommended (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 (26–41) (LE: 1b, GR: A).

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 view of the very large number of cystoscopic examinations and the potential adverse effect on bacterial sensitivity, antibiotic prophylaxis is not recommended in standard cases. However, bacteriuria, indwelling catheter and a history of genitourinary infection are risk factors that must be considered (42–56) (LE: 1b, GR: A).

*11.6.2. Endo-urological treatment procedures (urinary tract entered)*

There is little evidence for benefit of antibiotic prophylaxis in TURB. However, antibiotic prophylaxis should be considered in large tumours with a prolonged resection time, in large necrotic tumours and in patients with risk factors (43,57,58) (LE: 2b, GR: C).

TURP 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 (15,59-61) (LE: 1a, GR: A). There is a difference between smaller resections in healthy patients and large resections in at-risk patients (Figure 11.1).

There are few studies that have defined the risk of infection following ureteroscopy and percutaneous stone removal and no clear-cut evidence exists (62). 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 11.1) (5). Other risk factors (i.e. size, length, bleeding, and surgeon's experience) also need to be considered in the choice of regimen (63–70) (LE: 2b, GR: B).

ESWL 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, and infectious stones) (71–79) (LE: 1a-1b, GR: A).

Most antibiotic groups have been evaluated, such as fluoroquinolones, BLIs, including cephalosporins, as well as TMP-SMZ, but comparative studies are limited.

*11.6.3. Laparoscopic surgery*

There is 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).

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

No standard antibiotic prophylaxis is recommended in clean operations (80-84) (LE: 3, GR: C).

*11.6.5. Open or laparoscopic urological operations with open urinary tract (clean–contaminated procedures)*

In a case of opening of the urinary tract, a single perioperative parenteral dose of antibiotic is recommended (LE: 3, GR: C). This is valuable for standard procedures such as total (radical) prostatectomy (85–88) In open enucleation of prostatic adenoma, the risk of postoperative infection is particularly high (89) (LE: 2b, GR: B).

*11.6.6. 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 (90–92) (LE: 2a, GR: B).

*11.6.7. Post-operative 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 prior to surgery or after removal of the drainage tube (LE: 3, GR: B).

*11.6.8. 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 (94–97) (LE: 2a, GR: B).

**Table 11.5: Recommendations for antibiotic prophylaxis in standard urological surgery.**

| Procedure | Pathogens (expected) | Prophylaxis | Antibiotics | Remarks |
|---|---|---|---|---|
| ***Diagnostic procedures*** | | | | |
| Transrectal biopsy of the prostate | Enterobacteriaceae<br>Anaerobes? | All patients | Fluoroquinolones<br>TMP ± SMX<br>Metronidazole?[1] | Single dose effective in low-risk patients. Consider prolonged course in high-risk patients |
| Cystoscopy<br>Urodynamic examination | Enterobacteriaceae<br>Enterococci<br>Staphylococci | No | TMP ± SMX<br>Cephalosporin 2nd Generation | Consider in high-risk patients |
| Ureteroscopy | Enterobacteriaceae<br>Enterococci<br>Staphylococci | No | TMP ± SMX<br>Cephalosporin 2nd generation | |
| ***Endourological surgery and ESWL*** | | | | |
| ESWL | Enterobacteriaceae<br>Enterococci | No | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLIa | In patients with stent or nephrostomy tube or other risk factor |
| Ureteroscopy for uncomplicated distal stone | Enterobacteriaceae<br>Enterococci<br>Staphylococci | No | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI<br>Fluoroquinolones | Consider in risk patients |
| Ureteroscopy of proximal or impacted stone and percutaneous stone extraction | Enterobacteriaceae<br>Enterococci<br>Staphylococci | All patients | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI<br>Fluoroquinolones | Short course<br>Length to be determined<br>Intravenous suggested at operation |
| TUR of the prostate | Enterobacteriaceae<br>Enterococci | All patients | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI | Low-risk patients and small-size prostate require no prophylaxis |
| TUR of bladder tumour | Enterobacteriaceae<br>Enterococci | No | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI | Consider in high-risk patients and large tumours |
| ***Open or laparoscopic urological surgery*** | | | | |
| Clean operations | Skin-related pathogens, e.g. staphylococci<br>Catheter-associated uropathogens | No | | Consider in high-risk patients Short postoperative catheter requires no treatment |
| Clean–contaminated (opening of urinary tract) | Enterobacteriaceae<br>Enterococci<br>Staphylococci | Recommended | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI | Single peri-operative course |
| Clean–contaminated/ contaminated (use of bowel segments) | Enterobacteriaceae<br>Enterococci<br>Anaerobes<br>Skin-related bacteria | All patients | Cephalosporin 2nd or 3rd generation<br>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

*BLI = beta-lactamase inhibitor; ESWL = extracorporeal shockwave lithotripsy;TMP ± SMX = trimethoprim with or without sulphametoxazole (co-trimoxazole); TUR = transurethral resection.*

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# 12. SPECIFIC INFECTIONS

Urogenital tuberculosis and bilharziasis are two infections that may affect the urogenital tracts. 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 infectious have been published elsewhere. Following the abstract printed hereby, there is a direct link to these published Guidelines, free for consultation.

## 12.1. Urogenital Tuberculosis

Nearly one third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Moreover, tuberculosis is the most common opportunistic infection in AIDS patients. Genitourinary tuberculosis is not very common but it is considered as a severe form of extra-pulmonary tuberculosis. The diagnosis of genitourinary tuberculosis is made based on culture studies by isolation of the causative organism; however, biopsy material on conventional solid media may occasionally be required. Drug treatment is the first line therapy in genitourinary tuberculosis. Treatment regiments of 6 months are effective in most of the 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 2 months of intensive chemotherapy.

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## 12.2. Urogenital Schistosomiasis

More than 100 million people worldwide are affected by bilharziasis, caused by Schistosoma heamatobium. For travellers precaution is most important. For the population in endemic areas, an integrated approach including health education is necessary. Effective pharmacologic treatment is available.

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# 13. SEXUALLY TRANSMITTED INFECTIONS

The classical bacteria that cause venereal diseases, e.g. gonorrhea, syphilis, chancroid and inguinal granuloma only account for a small proportion of all known 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 sexually transmitted infections (STI) comprise more than 30 relevant STD pathogens. However, not all pathogens

that can be sexually transmitted manifest diseases in the genitals and not all infections of the genitals are exclusively sexually transmitted. Concise information and tables summarising the diagnostic and therapeutic management of STDs in the field of Urology allow a synoptic overview and are in agreement with recent international guidelines of other specialities.

Special considerations (i.e. HIV infection, pregnancy, infants, allergy) and recommended regimens may be looked up here.

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# 14. APPENDICES

## 14.1 Criteria for the diagnosis of a UTI, as modified according to IDSA/ESCMID 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 | $\geq$ 10 WBC/mm$^3$<br>$\geq 10^3$ cfu/mL* |
| 2 | Acute uncomplicated pyelonephritis | Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urological abnormalities (ultrasonography, radiography) | $\geq$ 10 WBC/mm$^3$<br>$\geq 10^4$ 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) | $\geq$ 10 WBC/mm$^3$<br>$\geq 10^5$ cfu/mL* in women<br>$\geq 10^4$ cfu/mL* in men, or in straight catheter urine in women |
| 4 | Asymptomatic bacteriuria | No urinary symptoms | $\geq$ 10 WBC/mm$^3$<br>$\geq 10^5$ cfu/mL* in two consecutive MSU cultures<br>$\geq$ 24 hours apart |

| | | | |
|---|---|---|---|
| 5 | Recurrent UTI (antimicrobial prophylaxis) | At least three episodes of uncomplicated infection documented by culture in last 12 months: women only; no structural/functional abnormalities | < $10^3$ cfu/mL* |

*MSU = mid-stream sample of urine; UTI = urinary tract infection; WBC = white blood cells. All pyuria counts refer to unspun urine.*
**Uropathogen in MSU culture.*

14.1.1 References


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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


## 14.2 Recommendations for antimicrobial therapy in urology

| Diagnosis | Most frequent pathogen/species | Initial, empirical antimicrobial therapy | Therapy duration |
|---|---|---|---|
| Cystitis | • *E. coli* | | |
| acute, | • *Klebsiella* | | |
| uncomplicated | • *Proteus* | • Fosfomycin trometamol | 1 day |
| | • *Staphylococci* | • Pivmecillinam | (3-)7 days |
| | | • Nitrofurantoin | (5-)7 days |
| | | | |
| | | Alternatives | |
| | | • Fluoroquinolone* | (1-)3 days |
| | | Cepodoxime proxetil | 3 days |
| | | If local resisstance rate of E. coli < 20% | |
| | | • Trimethoprim-sulphamethoxazole | 3 days |
| | | • Trimethoprim | 5 days |
| Pyelonephritis | • *E. coli* | • Fluoroquinolone* | 7-10 days |
| acute, | • *Proteus* | • Cephalosporin (group 3a) | |
| uncomplicated | • *Klebsiella* | Alternatives: | |
| | • Other enterobacteria | • Aminopenicillin/BLI | |
| | • Staphylococci | • Aminoglycoside | |
| | | | |
| UTI with | • *E. coli* | • Fluoroquinolone* | 3-5 days after |
| Complicating | • Enterococci | • Aminopenicillin/BLI | defeverescence or |
| Factors | • *Pseudomonas* | • Cephalosporin (group 2) | control/elimination |
| | • Staphylococci | • Cephalosporin (group 3a) | of complicating |
| Nosocomial UTI | • *Klebsiella* | • Aminoglycoside | factor |
| | • *Proteus* | In case of failure of initial therapy | |

| | | | |
|---|---|---|---|
| Pyelonephritis | • *Enterobacter* | within 1-3 days or in clinically severe | |
| acute, | • Other enterobacteria | cases: | |
| complicated | • *(Candida)* | Anti-*Pseudomonas* active: | |
| | | • Fluoroquinolone, if not used initially | |
| | | • Acylaminopenicillin/BLI | |
| | | • Cephalosporin (group 3b) | |
| | | • Carbapenem | |
| | | • ± Aminoglycoside | |
| | | In case of *Candida*: | |
| | | • Fluconazole | |
| | | • Amphotericin B | |
| | | | |
| Prostatitis | • *E. coli* | • Fluoroquinolone* | Acute: |
| acute, chronic | • Other enterobacteria | Alternative in acute bacterial prostatitis: | 2-4 weeks |
| | • *Pseudomonas* | • Cephalosporin (group 3a/b) | |
| Epididymitis | • Enterococci | In case of *Chlamydia* or *Ureaplasma*: | Chronic: |
| acute | • Staphylococci | • Doxycycline | 4-6 weeks or longer |
| | • *Chlamydia* | • Macrolide | |
| | • *Ureaplasma* | | |
| | | | |
| Urosepsis | • E. coli | • Cephalosporin (group 3a/b) | 3-5 days after |
| | • Other enterobacteria | • Fluoroquinolone* | defeverescence or |
| | After urological | • Anti-*Pseudomonas* active | control/elimination |
| | interventions – multi- | acylaminopenicillin/BLI | of complicating |
| | resistant pathogens: | • Carbapenem | factor |
| | • *Pseudomonas* | • ± Aminoglycoside | |
| | • *Proteus* | | |
| | • *Serratia* | | |
| | • *Enterobacter* | | |

*BLI = ß-lactamase inhibitor; UTI = urinary tract infection.*
**Fluoroquinolone with mainly renal excretion (see text).*
*°Only in areas with resistance rate < 20% (for E. coli).*
*bid = twice daily; GFR; glomerular filtration rate; HD = haemodialysis; IV = intravenous; od = once daily; po = by mouth; qid = four times daily; SBE = subacute bacterial endocarditis*

## 14.3 Recommendations for antibiotic prescribing in renal failure

| Antibiotic | GFR (ml/min | | | Comments |
|---|---|---|---|---|
| | **Mild** 50-20 | **Moderate** 20-10 | **Severe** <10 | |
| *Aciclovir | normal dose every 12h | normal dose every 24h | 50% of normal dose every 24h | Give post HD |
| Aciclovir po | normal | Simplex: normal<br>Zoster: 800mg tds | Simplex: 200mg bd<br>Zoster: 800mg bd | Give post HD |
| Amikacin | 5-6mg/kg 12h | 3-4mg/kg 24h<br><br>HD: 5mg/kg post HD and monitor levels | 2mg/kg 24-48h | Give post HD<br>Monitor pre and 1hr post-dose levels after 3rd dose &adjust dose as required |
| Amoxicillin po | normal | normal | 250mg 8h (normal) | Give post HD |
| Amphotericin | normal | normal | normal | |
| (Liposonal + Lipid complex) | Amphotericin is highly NEPHROTOXIC.<br>Consider using liposomal/lipid complex amphotericin.<br>Daily monitoring of renal function (GFR) essential. | | | |
| Ampicillin IV | normal | 250-500mg 6h | 250mg 6h<br>(500mg 6h) | Give post HD |
| Benzylpenicillin | normal | 75% | 20-50%<br>Max. 3.6g/day<br>(1.2g.qds) | Give post HD<br>Refer to microbiology for dosing in SBE |
| Caspofungin | normal | normal | normal | |
| Cefotaxime | normal | normal | 1g stat then 50% | Give post HD |
| Cefradine | normal | Normal | 250mg 6h | Give post HD |
| Ceftazidime | 1g 12h | 1g 24h | 500mg 24h (1g 24h) | Give post HD |
| Ceftriaxone | normal | normal | normal<br>Max 2g/day | |
| Cefuroxime IV | normal | 750mg-1.5g 12h | 750mg 24h<br>(750mg 12h) | 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% 12h<br>(1.2g 12h) | 1.2 stat then 50% 24h<br>(1.2g stat then 600mg 12h) | Give post HD |
| Co-Amoxiclav po (Augmentin) | normal | 375mg-625mg 12h<br>(375mg 8h) | 375mg 12h<br>(375mg 8h) | 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<br>Max. 1.5g/day<br>(500mg qds) | |
| *Ethambutol | normal | 24-36h | 48h | Give post HD |

| | | | | |
|---|---|---|---|---|
| | Monitor levels if GFR < 30ml/min (contact Mirco) | | | |
| Flucloxacillin IV + po | normal | normal | normal Max 4g/day | |
| Fluconazole | normal | normal | 50% | Give post HD. No adjustments in single dose therapy required |
| *Flucytosine | 50mg/kg 12h | 50mg/kg 24h | 50mg/kg stat then dose according to levels | Give post HD. Levels should be monitored pre-dialysis. |
| Fusidic acid | normal | normal | Normal | |
| 1) Gentamicin<br><br>ONCE DAILY | **GFR 10-40ml/min**<br>3mg/kg stat (max 300mg)<br>Check pre-dose levels 18-24 hours after first dose.<br>Redose only when level < 1mg/L. | | **GFR < 10mL/min**<br>2mg/kg (max 200mg) redose according to levels | BOTH METHODS<br>Give post HD<br><br>Monitor blood levels: |
| 2) Gentamicin<br><br>CONVENTIONAL | 80mg 12h | 80mg 24h | 80mg 48h<br>HD: 1-2 mg/kg<br>Post HD: redoes According to levels | Once daily: pre only<br>Conventional: pre and 1hr post level required. |
| Imipenem | 500mg 8-12h | 250-500mg bd | Risk of convulsions – use Meropenem: *see below* | Give post HD |
| Isoniazid | normal | normal | 200mg-300mg 24h | Give post HD |
| Itraconazole | normal | normal | normal | |
| Levoflaxacin | 500mg stat Then 250mg bd** | 500mg stat then 125mg bd** | 500mg stat then 125mg od | **applies if full dose is 500mg bd. If full dose 500mg od five reduced dose daily |
| Linezolid | normal | normal | normal | Give post HD |
| Meropenem | 12h | 50% 12h | 50% 24h | Give post HD |
| Metronidazole | normal | normal | 12h (normal) | Give post HD |
| Nitrofurantoin | Do **NOT** use in renal impairment | | | |
| Penicillin V | normal | normal | normal | Give post HD |
| Piperacillin/ Tazobactam (Tazocin) | 4.5g 8h | 4.5g 12h | 4.5g 12h | Give post HD |
| Pyrazinamide | normal | normal | normal | |
| Rifampicin | normal | normal | 50-100% | |
| *Teicoplanin | 100% 48h | 100% 72h | 100% 72h | Dose reduction after day 3 of therapy |
| Tetracycline | See **Doxycycline** | | | |
| Trimethoprim | normal | Normal for 3/7 then 50% 18h | 50% 24h | Give post HD |
| Vancomycin | 1g od<br>Check pre-dose level before 3rd dose | 1g 48h<br>Check pre-dose level before 2nd dose | 1g stat (or 15mg.kg, up to max 2 g).<br>Recheck level after 4-5 days.<br>ONLY give subsequent dose when level < 12mg/L. | Monitor pre-dose levels & adjust dose as required. |
| Vorinconazole | normal | normal | normal | Give post HD |

*bid = twice daily; GFR; glomerular filtration rate; HD = haemodialysis; IV = intravenous; od = once daily; po = by mouth; qid = four times daily; SBE = subacute bacterial endocarditis*

### 14.4 Recommendations for peri-operative antibacterial prophylaxis in urology

| Procedure | Pathogens (expected) | Prophylaxis | Antibiotics | Remarks |
|---|---|---|---|---|
| ***Diagnostic procedures*** | | | | |
| Transrectal biopsy of the prostate | Enterobacteriaceae<br>Anaerobes? | All patients | Fluoroquinolones<br>TMP ± SMX<br>Metronidazole?[1] | Single dose effective in low-risk patients. Consider prolonged course in high-risk patients |
| Cystoscopy<br>Urodynamic examination | Enterobacteriaceae<br>Enterococci<br>Staphylococci | No | TMP ± SMX<br>Cephalosporin 2nd Generation | Consider in high-risk patients |
| Ureteroscopy | Enterobacteriaceae<br>Enterococci<br>Staphylococci | No | TMP ± SMX<br>Cephalosporin 2nd generation | |
| ***Endourological surgery and ESWL*** | | | | |
| ESWL | Enterobacteriaceae<br>Enterococci | No | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLIa | In patients with stent or nephrostomy tube or other risk factor |
| Ureteroscopy for uncomplicated distal stone | Enterobacteriaceae<br>Enterococci<br>Staphylococci | No | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI<br>Fluoroquinolones | Consider in risk patients |
| Ureteroscopy of proximal or impacted stone and percutaneous stone extraction | Enterobacteriaceae<br>Enterococci<br>Staphylococci | All patients | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI<br>Fluoroquinolones | Short course<br>Length to be determined<br>Intravenous suggested at operation |
| TUR of the prostate | Enterobacteriaceae<br>Enterococci | All patients | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI | Low-risk patients and small-size prostate require no prophylaxis |
| TUR of bladder tumour | Enterobacteriaceae<br>Enterococci | No | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI | Consider in high-risk patients and large tumours |
| ***Open or laparoscopic urological surgery*** | | | | |
| Clean operations | Skin-related pathogens, e.g. staphylococci<br>Catheter-associated uropathogens | No | | Consider in high-risk patients Short postoperative catheter requires no treatment |
| Clean–contaminated (opening of urinary tract) | Enterobacteriaceae<br>Enterococci<br>Staphylococci | Recommended | TMP ± SMX<br>Cephalosporin 2nd or 3rd generation<br>Aminopenicillin/BLI | Single peri-operative course |
| Clean–contaminated/ contaminated (use of bowel segments) | Enterobacteriaceae<br>Enterococci<br>Anaerobes<br>Skin-related bacteria | All patients | Cephalosporin 2nd or 3rd generation<br>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) | |

*BLI = beta-lactamase inhibitor; TMP ± SMX = trimethoprim with or without sulphametoxazole (co-trimoxazole); TUR = transurethral resection.*

## 14.5 Chronic Prostatitis Symptom Index (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

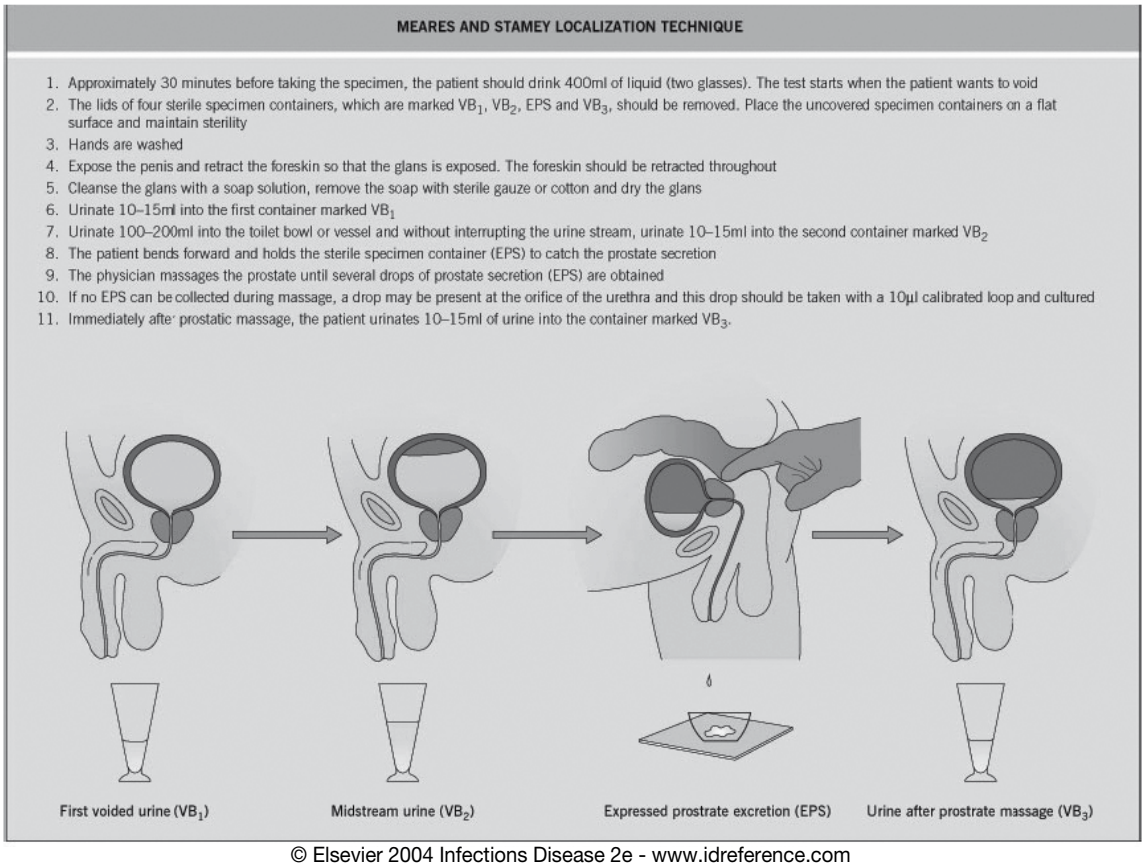
Domain

*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 = _____

## 14.6 Meares & Stamey Localization 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.

## 14.7 Antibacterial agents

| Groups | Agents |
|---|---|
| **Trimethoprim-sulphonamide combinations** | Trimethoprim, co-trimoxazole (TMP-SMX), co-tetroxoprime (TXP-SDX), trimethoprim plus sulfametrol |
| | |
| **Fluoroquinolones**[1,2] | |
| • Group 1 | Norfloxacin, pefloxacin |
| • Group 2 | Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin |
| • Group 3 | Levofloxacin |
| • Group 4 | Gatifloxacin, moxifloxacin |
| | |
| **Macrolides** | Erythromycin, roxithromycin, clarithromycin, azithromycin |
| | |
| **Tetracyclines** | Doxycycline, minocycline, tetracycline |
| | |
| **Fosfomycin** | Fosfomycin-sodium, fosfomycin trometamol[3] |
| | |
| **Nitrofuran**[4] | Nitrofurantoin |
| | |
| **Penicillins** | |
| Benzylpenicillin | Penicillin G |
| Phenoxypenicillins | Penicillin V, propicillin, azidocillin |
| Isoxazolylpenicillins | Oxacillin, cloxacillin, dicloxacillin, flucloxacillin |
| Aminobenzylpenicillins[5] | Ampicillin, amoxycillin, bacampicillin |
| Aminopenicillins/BLI[6] | Ampicillin/sulbactam, amoxycillin/clavulanic acid[7] |
| Acylaminopenicillins | Mezlocillin, piperacillin |
| ±BLI[6] | Piperacillin/tazobactam, sulbactam[6] |
| | |
| **Cephalosporins**[1] | |
| • Group 1 (oral) | Cefalexin, cefadroxil, cefaclor |
| • Group 2 (oral) | Loracarbef, cefuroxime axetile |
| • Group 3 (oral) | Cefpodoxime proxetile, cefetamet pivoxile, ceftibuten, cefixime |
| • Group 1 (parenteral) | Cefazolin |
| • Group 2 (parenteral) | Cefamandole, cefuroxime, cefotiame |
| • 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 |

*BLI = ß-lactamase inhibitors; INH = isoniazid.*

*[1] Classification according to the Paul Ehrlich Society for Chemotherapy (1, 2, 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 the newborn.*

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

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

*[7] In solution, storage instability.*

### *14.7.1 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 from country to country. 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.

#### *14.7.1.1 Aminopenicillins*

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

Aminopenicillins are sensitive to ß-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, 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.

#### *14.7.1.2 Acylaminopenicillins*

The acylaminopenicillins include apalcillin, azlocillin, mezlocillin and piperacillin. They are characterized by their high activity against enterococci, enterobacteria and *Pseudomonas* (weaker activity of mezlocillin). Acylaminopenicillins are hydrolyzed by ß-lactamases and are therefore active only against ß-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.

#### *14.7.1.3 Isoxazolylpenicillins*

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

### *14.7.2 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 14.7.2).

#### *14.7.2.1 Group 1 cephalosporins*

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

#### *14.7.2.2 Group 2 cephalosporins*

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

#### *14.7.2.3 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.

#### *14.7.2.4 Group 3b cephalosporins*

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

*14.7.2.5 Group 4 cephalosporins*

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

*14.7.2.6 Group 5 cephalosporins*

The Group 5 cephalosporins are characterized 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 14.7.2: Classification of parenteral cephalosporins (2.)**

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

*14.7.3 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 14.7.3).

**Table 14.7.3: Classification of oral cephalosporins (1).**

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

14.7.3.1 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. Since their activity against enterobacteria is limited, 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.

14.7.3.2 Group 2 oral cephalosporins

The activity of cefprozil against *Staph. aureus, S. pyogenes, S. pneumoniae, H. influenzae* and *M. catarrhalis* is somewhat higher than that of cefaclor. However, cefprozil is less active than cefaclor against *E. coli, Klebsiella pneumoniae* and *P. 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 ß-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.

14.7.3.3 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 proxetile is intermediate, whereas cefetamet pivoxile, 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 the treatment of gonorrhoea.

### *14.7.4 Monobactams*

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

### *14.7.5 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 *Ps. aeruginosa*. However, ertapenem is not active against Ps. aeruginosa. Ertapenem has a longer half-life than the imipenem/cilastatin and meropenem and is therefore suitable for once-daily dosing.

### *14.7.6 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 14.7.4).

**Table 14.7.4: Classification of fluoroquinolones, as modified according to the Paul Ehrlich Society for Chemotherapy (33).**

| 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 |

| | |
|---|---|
| | Ciprofloxaci |
| **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 |

*UTI = urinary tract infections.*

** 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.*

14.7.6.1 Group 1 fluoroquinolones

The indications for group 1 fluoroquinolones is 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.

14.7.6.2 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 and enterococci and 'atypical' pathogens, e.g. *Chlamydia, Legionella* and *Mycoplasma*. Their activity against *Ps. aeruginosa* varies, with ciprofloxacin being most active *in vitro*. In addition, ciprofloxacin, ofloxacin and fleroxacin are also available for parenteral use.

14.7.6.3 Group 3 fluoroquinolones

The main difference in the spectrums of activity of group 3 fluoroquinolones (levofloxacin) and of group 4 fluoroquinolones (gatifloxacin, moxifloxacin) is that group 3 fluoroquinolones 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* spp. 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, so far, no parenteral fluoroquinolone of this group has been made available.

Apart from respiratory tract infections, these broad-spectrum fluoroquinolones are appropriate for the treatment of skin and soft-tissue infections, of intra-abdominal infections, and of the 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. The urinary excretion of moxifloxacin after oral administration is only in the range of about 20%.

### *14.7.7 Co-trimoxazole (trimethoprim-sulphamethoxazole, TMP-SMX)*

The treatment of UTIs is the main indication for trimethoprim (TMP) alone or in combination with a sulphonamide, e.g. sulphamethoxazole (SMX). TMP with or without SMX can also be used for the prophylaxis of recurrent cystitis. The resistance rate against E. coli can vary from country to country. 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, TMP-SMX should only be used in accordance with sensitivity testing. TMP, especially in combination with SMX, can lead to severe although rare adverse events, such as Lyell syndrome, Stevens-Johnson syndrome and pancytopenia.

### *14.7.8 Fosfomycin*

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

### *14.7.9 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, Ps. 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.

### *14.7.10 Macrolides*

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

### *14.7.11 Tetracyclines*

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

### *14.7.12 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. the treatment of UTIs), aminoglycosides should only be used in combination with another appropriate antibiotic. Ideal partners are ß-lactam antibiotics, as 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.

### *14.7.13 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.

### *14.7.14 Oxazolidinones*

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

### *14.7.15 References*

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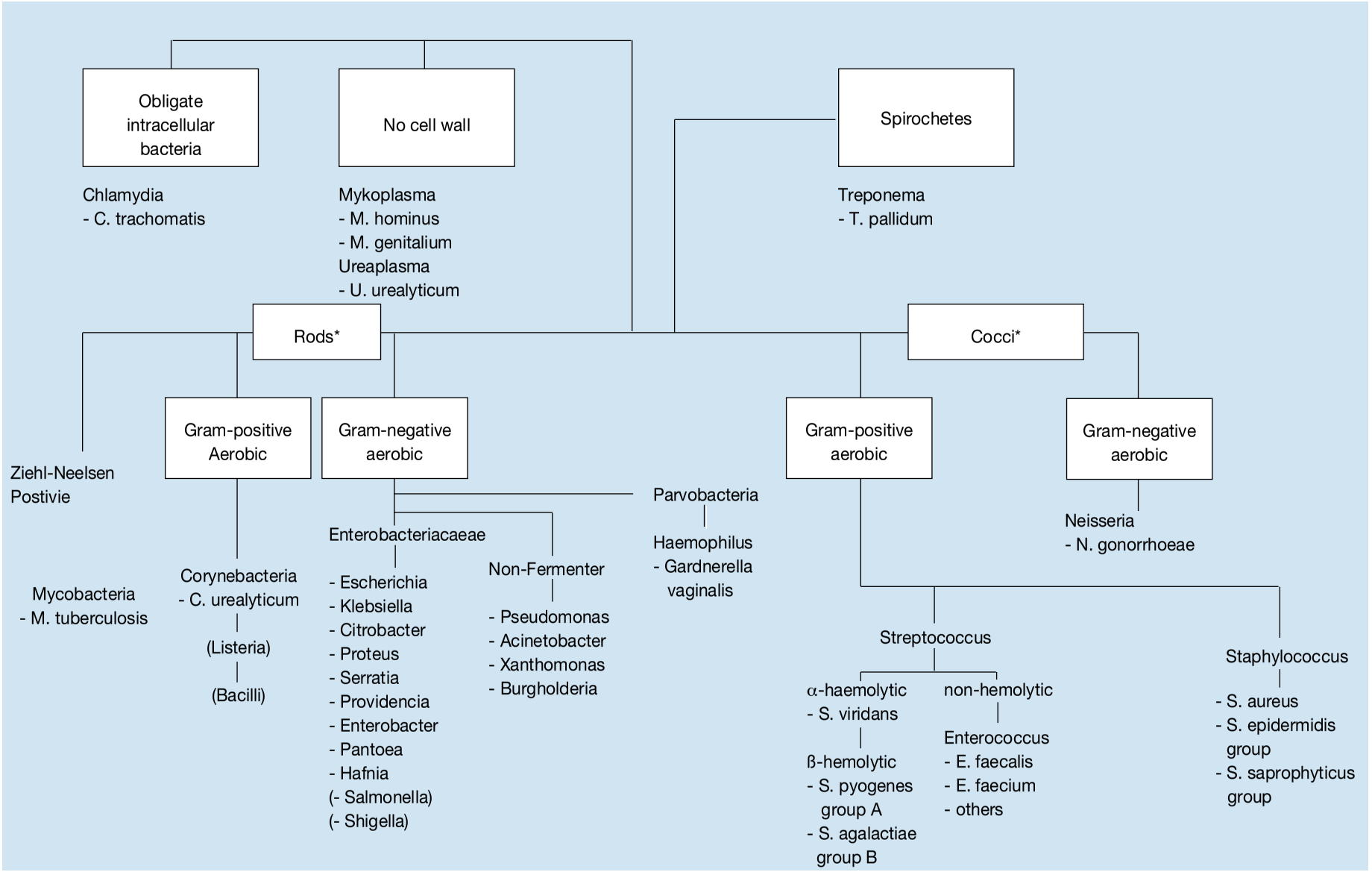
## 14.8 Relevant bacteria for urological infections




*Anaerobic bacteria not considered.*

# 15. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations.*

| | |
|---|---|
| ABP | acute bacterial prostatitis |
| ACE | angiotensin-converting enzyme |
| ACTH | adrenocorticotropic hormone test |
| ADPK | adult dominant polycystic disease |
| APACHE | acute physiology and chronic health evaluation |
| APCKD | adult polycystic kidney disease |
| AUA | American Urological Association |
| BLI | ß-lactamase inhibitor |
| BPH | benign prostatic hyperplasia |
| CBP | chronic bacterial prostatitis |
| CDC | centres for disease control and prevention |
| cfu | colony-forming unit |
| CPPS | chronic pelvic pain syndrome |
| CPSI | Chronic Prostatitis Symptom Index |
| CRP | C-reactive protein |
| CT | computed tomography |
| DMSA | dimercaptosuccinic acid |
| DRE | digital rectal examination |
| DTPA | diethylenetriaminepentaacetate |
| EMG | electromyography |
| EPS | expressed prostatic secretion |
| ESCMID | European Society of Clinical Microbiology and Infectious Diseases |
| ESR | erythrocyte sedimentation rate |
| ESWL | extracorporeal shockwave lithotripsy |
| EUCAST | European Committee for Antimicrobial Susceptibility Testing |
| G6PD | glucose-6-phosphate dehydrogenase |
| GAG | glucosaminoglycan |
| G-CSF | granulocyte-colony stimulating factor |
| GFR | glomerular filtration rate. |
| GM-CSF | granulocyte-macrophage-colony stimulating factor |
| HCO | Health Care Office of the EAU |
| HIV | human immunodeficiency virus |
| HMO | health maintenance organization |
| IC | intermittent catheterization |
| IDSA | Infectious Diseases Society of America |
| IL | interleukin |
| IPCN | International Prostatitis Collaborative Network |
| IVU | intravenous urogram |
| LDH | lactate dehydrogenase |
| LUTS | lower urinary tract symptoms |
| MAG-3 | mercaptoacethylglycine |
| MRI | magnetic resonance imaging |
| MRSA | methicillin-resistant Staphylococcus aureus |
| MRSE | methicillin-resistant coagulase-negative staphylococci |
| MSU | mid-stream sample of urine |
| NAUTI | nosocomial urinary tract infection |
| NCCLS | National Committee for Clinical Laboratory Standards |
| NDMA | N-acetyl-ß-D-glucoseaminadase enzyme |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| NIH | National Institutes of Health |
| PaCO2 | partial pressure of carbon dioxide in alveolar gas |
| PCP | *Pneumocystis carinii* pneumonia |
| PL | placebo |
| PMN | polymorphonuclear |
| PSA | prostate-specific antigen |
| SIRS | systemic inflammatory response syndrome |
| SMX | sulphamethoxazole |

| | |
|---|---|
| SR | sustained release |
| STD | sexually transmitted disease |
| Tc | technetium |
| TMP | trimethoprim |
| TNF | tumour necrosis factor |
| TRUS | transrectual ultrasound |
| TURP | transurethral resection of the prostate |
| UTI | urinary tract infection |
| VB1 | first-voided urine |
| VB2 | mid-stream urine |
| VB3 | voided bladder urine-3 |
| VCU | voiding cysto-urethography |
| VUR | vesicoureteric reflux |
| WBC | white blood cells |
| WHO | World Health Organisation |

**Bacterial names**

| | |
|---|---|
| *B. fragilis* | *Bacteriodes fragilis* |
| *C. trachomatis* | *Chlamydia trachomatis* |
| *E. coli* | *Escherichia coli* |
| *H. influenzae* | *Haemophilus influenzae* |
| *M. catarrhalis* | *Moraxella catarrhalis* |
| *M. tuberculosis* | *Mycobacterium tuberculosis* |
| *N. gonorrhoeae* | *Neisseria gonorrhoeae* |
| *Ps. aeruginosa* | *Pseudomonas aeruginosa* |
| *P. mirabilis* | *Proteus mirabilis* |
| *S. aureus* | *Staphylococcus aureus* |
| *S. saprophyticus* | *Staphylococcus saprophyticus* |
| *S. pyogenes* | *Streptococcus pyogenes* |
| *T. vaginalis* | *Trichomonas vaginalis* |

**Conflict of interest**

All members of the Urological Infections guidelines writing panel have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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.