Guidelines on The Management of Urinary and Male Genital Tract Infections

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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 is there good data regarding the impact of UTIs on economics in general and that of the health care system especially. 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 requiring 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 hospitalization (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 leading 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 catheterization 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 preventing 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, 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 specialized virulence factors, e.g. different types of pili, which facilitate the ascent of bacteria from the faecal flora, introitus vaginae or periurethral area up the urethra into the bladder, or, less frequently, allow the organisms to reach the kidneys to induce systemic inflammation.

1.2 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 (≥ 10^5 cfu) in the context of pyelonephritis in pregnancy (7). Although this concept introduced quantitative microbiology into the diagnostics 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 12.1, the following bacterial counts are clinically relevant:

- ≥ 10^3 colony-forming units (cfu) of uropathogen/mL of a mid-stream sample of urine (MSU) in acute uncomplicated cystitis in a woman
- ≥ 10^4 cfu uropathogen/mL of MSU in acute uncomplicated pyelonephritis in a woman

- $\geq 10^5$ cfu uropathogen/mL of MSU in a woman, or $\geq 10^4$ cfu uropathogen/mL of 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 10^2 cfu uropathogen/mL. Asymptomatic bacteriuria is diagnosed if two cultures of the same bacterial strain (in most cases the species only is available) taken $\geq$ 24 hours apart show bacteriuria of $\geq 10^5$ cfu uropathogen/mL.

It is obvious that methods of urine collection and culture, as well as the quality of laboratory investigations, may vary. Two levels of standard must therefore be used for the management of patients. A basic standard level is necessary for routine assessment, while a higher standard level is required for scientific assessment and in special clinical circumstances, e.g. fever of unknown origin in immunocompromised patients. In research, the need for a precise definition of sampling methods, the time that urine is kept in the bladder, etc., must be recognized 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 microbes 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 concerning specimen transport, pathogen identification and antimicrobial susceptibility testing. Since these methods, and also microbiological definitions, may vary from country to country and institution to institution, e.g. 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, e.g. the European Committee for Antimicrobial Susceptibility Testing (EUCAST) (8-10), the National Committee for Clinical Laboratory Standards (NCCLS) (11). Mixing results obtained by different methods, e.g. rates of bacterial resistance, can be problematic and requires careful interpretation. Histological investigation sometimes shows the presence of non-specific inflammation. Only in some cases, such findings (e.g. prostatitis in patients who have elevated levels of prostate-specific antigen [PSA]) may help determine the appropriate treatment, whereas in more specific inflammations, such as tuberculosis, actinomycosis, etc., histology may be diagnostic. In general, however, histological findings usually contribute very little to the treatment decision.

1.3 Classification of urinary and male genital tract infections

Infections can be classified according to their location within the urogenital tract, e.g. pyelonephritis, cystitis, prostatitis, urethritis, epididymitis or orchitis. The different parts of the urinary tract, however, communicate with each other to some degree. As a result, bacteria in one area are probably also present elsewhere. For practical clinical 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
- special forms: prostatitis, epididymitis and orchitis.

The clinical presentation and management of different UTI categories may vary during life and may depend on the patient's condition. Therefore, special patient groups (the elderly, those with underlying diseases and the immunocompromised) 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) (12) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (13), are summarized in Appendix 12.1.There is still an ongoing discussion about how guidelines on UTI could be improved (14).

1.4 Aim of guidelines

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 urinary UTIs. It is hoped that the guidelines may assist not only the urologist, but also physicians from other medical specialities in their daily practice.

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, F.P. Selvaggi) of the EAU Health Care Office has established the first version of these guidelines in several consensus conferences. The first edition was published in 2001 in Geneva by the EAU (15) and in a more condensed version in 2001 (16).

The members of the current UTI Working Group (K.G. Naber (chairman), M.C. Bishop, T.E. Bjerklund-Johansen, H. Botto, M. Cek, B. Lobel, J. Palou, P. Tenke) of the EAU Guidelines Office updated the guidelines in several consensus conferences thereafter and added one chapter on catheter-associated UTI. EAU guidelines on special forms of urogenital infections, such as sexual transmitted infections (17), urogenital tuberculosis (18) and urogenital schistosomiasis (19), have been published elsewhere and are therefore not included in the present guidelines.

For 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 at three plenary meetings: the first in Paris on 10 December 2004, the next in Istanbul on 15 March 2005, and finally in Florence on 22 October 2005. Each chapter was reviewed by three committee members (editorial group) for consistency and compatibility in two editorial meetings: one meeting took place in Straubing, 22-24 April 2005, and one in Stavern, 9-11 Sept 2005, and the chapters were revised accordingly.

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 1.1: Levels of evidence, according to (20).

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized trials
Ib	Evidence obtained from at least one randomized trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
IV	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 1.2: Grades of guideline recommendations, modified according to (20).

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies, but without randomized 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 ADULT

2.1 Summary and recommendations

2.1.1 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 who have none of the factors known to increase the risk of complications or of treatment failure.

2.1.2 Aetiological spectrum

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

2.1.3 Acute uncomplicated cystitis in pre-menopausal, non-pregnant women

Besides physical examination, urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis (B). Colony counts $\geq 10^3$ cfu uropathogen/mL are considered to be a clinically relevant bacteriuria (IIb).

Short courses of antimicrobials are highly effective and are desirable because of the improved compliance that they promote, their lower cost and lower frequency of adverse reactions. Single-dose therapy (with some exceptions) is generally less effective than the same antibiotic used for a longer duration. However, with most suitable antimicrobials, there is little to be gained from treatment given beyond 3 days and the risk of adverse events is higher (IaA).

Trimethoprim (TMP) or TMP-sulphamethoxazole (SMX) can only be recommended as first-line drugs for empirical therapy in communities with rates of uropathogen resistance to TMP of less than 20% (IbA). Otherwise, fluoroquinolones, fosfomycin trometamol, pivmecillinam and nitrofurantoin are recommended as alternative oral drugs for empirical therapy. However, in some areas, the rate of fluoroquinolone-resistant *E. coli* is also increasing.

Urinalysis, including a dipstick method, is sufficient for routine follow-up. Post-treatment cultures in asymptomatic patients may not be indicated. In women whose symptoms do not resolve, or which resolve and

then recur within 2 weeks, urine culture and antimicrobial susceptibility testing should be performed (IVC).

2.1.4 Acute uncomplicated pyelonephritis in pre-menopausal, non-pregnant women

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness. It may occur in the absence of cystitis symptoms, e.g. dysuria, frequency. Besides physical examination, urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis (C). Colony counts ≥ 10^4 cfu uropathogen/mL can be considered to be a clinically relevant bacteriuria (IIb).

An evaluation of the upper urinary tract with ultrasound should be performed to rule out urinary obstruction or renal stone disease (C). Additional investigations, such as an unenhanced helical computed tomography (CT), an excretory urogram, or dimercaptosuccinic acid (DMSA) scan, should be considered if the patients remain febrile after 72 hours of treatment to rule out further complicating factors, e.g. urolithiasis, renal or perinephric abscesses (C).

As first-line therapy in mild cases, an oral fluoroquinolone for 7 days is recommended in areas where the rate of fluoroquinolone-resistant *E. coli* is still low (<10%) (IbA). If a Gram-positive organism is seen on the initial Gram stain, an aminopenicillin plus a ß-lactamase inhibitor (BLI) could be recommended (IIbB). More severe cases of acute uncomplicated pyelonephritis should be admitted to hospital and treated according to the patient's condition parenterally with a fluoroquinolone (ciprofloxacin or levofloxacin), a third-generation cephalosporin or an amino/acylaminopenicillin plus a BLI according to the local susceptibility pattern (IIbB). With improvement, the patient can be switched to an oral regimen using a fluoroquinolone or TMP-SMX (if active against the infecting organism) to complete the 1- or 2-week course, respectively (IIbB). In areas with increased resistance rate of *E. coli* against fluoroquinolones and in situations in which fluoroquinolones are contraindicated (e.g. pregnancy, lactating women, adolescence), a second- or third-generation oral cephalosporin is recommended (IIbB).

Routine post-treatment cultures in an asymptomatic patient may not be indicated; routine urinalysis using a dipstick method is sufficient (IIbB). In women whose symptoms of pyelonephritis resolve but then recur within 2 weeks, it is important to carry out a repeat urine culture, antimicrobial susceptibility testing, and an appropriate investigation to rule out urinary tract abnormalities (C).

2.1.5 Recurrent (uncomplicated) UTIs in women

Recurrent UTIs (RUTIs) are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts. The following prophylactic antimicrobial regimens are recommended:

- long-term, low-dose prophylactic antimicrobials taken at bedtime (IaA)
- post-intercourse prophylaxis for women in whom episodes of infection are associated with sexual intercourse (IbA)
- a patient-initiated treatment may also be suitable for management of RUTIs in well-informed, young women (IIaB).

Prophylactic alternative methods include immunotherapy (IaB) and probiotic therapy (IIaC), acidification (IIaC), and cranberry juice (IIaC). These regimens are not yet as effective as antimicrobial prophylaxis, though directly comparative studies have not been performed.

2.1.6 UTIs in pregnancy

Urinary tract infections are common during pregnancy. Most women acquire bacteriuria before pregnancy, while 20-40% of women with asymptomatic bacteriuria will develop pyelonephritis during pregnancy. Treatment of asymptomatic bacteriuria lowers this risk (IIa).

Most symptomatic UTIs in pregnant women present as acute cystitis. Short-term therapy is not as established as in non-pregnant women. For a recurrent UTI, low-dose cephalexin (125-250 mg) or nitrofurantoin (50 mg) at night is recommended for prophylaxis against re-infection (IbA). Post-intercourse prophylaxis may be an alternative approach (IbA).

For acute pyelonephritis, second- or third-generation cephalosporins, an aminoglycoside, or an aminopenicillin plus a BLI may be recommended antibiotics (IIbB). During pregnancy, quinolones, tetracyclines and TMP are contraindicated in the first trimester, while sulphonamides should not be used in the last trimester (IIbB). In cases of delayed defervescence and upper tract dilatation, a ureteral stent may be indicated and antimicrobial prophylaxis should be considered until delivery (IIbB).

2.1.7 UTIs in post-menopausal women

In acute cystitis, the antimicrobial treatment policy in post-menopausal women is similar to that in pre-menopausal women. However, short-term therapy in post-menopausal women is not as well documented as that in younger women. In the case of a recurrent UTI, urological or gynaecological evaluation should be

performed in order to eliminate a tumour, obstructive problems, detrusor failure or a genital infection (IIIB).

In post-menopausal women with a recurrent UTI, therapy with intravaginal oestriol is able to reduce significantly the rate of recurrences (IbA). For the remainder of patients, an antimicrobial prophylactic regimen should be recommended in addition to hormonal treatment (IIIB).

For acute pyelonephritis, the same treatment modalities are recommended as for pre-menopausal, non-pregnant women (see section 2.1.3).

2.1.8 Acute uncomplicated UTIs in young men

Only a small number of 15 to 50-year-old men suffer from acute uncomplicated UTI. Such men should receive, as minimum therapy, a 7-day antibiotic regimen (IIaB). Most men with febrile UTI have a concomitant infection of the prostate, as measured by transient increases in serum PSA and prostate volume (IIa). Urological evaluation should be carried out routinely in adolescents and men with febrile UTI, pyelonephritis, recurrent infections, or whenever a complicating factor is suspected (IIIB). A minimum treatment duration of 2 weeks is recommended (IIIB), preferably with a fluoroquinolone since prostatic involvement is frequent.

2.1.9 Asymptomatic bacteriuria

Asymptomatic bacteriuria is common. Populations with structural or functional abnormalities of the genitourinary tract may have an exceedingly high prevalence of bacteriuria, but even healthy individuals frequently have positive urine cultures. Asymptomatic bacteriuria is seldom associated with adverse outcomes. Screening for, or treatment of, asymptomatic bacteriuria is not recommended for the following persons:

- pre-menopausal, non-pregnant women (IbA)
- diabetic women (IbA)
- older persons living in community (IIB)
- elderly institutionalized subjects (IIaB)
- persons with spinal cord injury (IIaB)
- catheterized patients while the catheter remains *in situ* (IbA).

Screening for asymptomatic bacteriuria and treatment is recommended only for selected groups where benefit has been shown: pregnant women (IbA); before transurethral resection of the prostate (TURP) (IbA) and other traumatic urological interventions (IIIB). Antimicrobial therapy should be initiated shortly before the procedure (IIIB).

2.2 Background

Acute, uncomplicated UTIs in adults include episodes of acute cystitis and acute pyelonephritis occurring in otherwise healthy individuals. These UTIs are seen mostly in women who have no risk factors, i.e. no structural or functional abnormalities within the urinary tract and the kidneys and no underlying disease known to increase the risks of acquiring infection or of failing therapy (1). Uncomplicated UTIs are extremely common infections. Approximately 25-35% of women between the ages of 20 and 40 years have experienced an episode described by their physician as an uncomplicated UTI (2).

2.3 Definition

The distinction between an uncomplicated and a complicated UTI is important because of implications with regard to pre- and post-treatment evaluation, the type and duration of antimicrobial regimens, and the extent of the evaluation of the urinary tract. In contrast to an uncomplicated UTI (see above), a complicated UTI is an infection associated with a condition that increases the risks of acquiring an infection or of failing therapy. At the time of presentation with an acute onset of urinary tract symptoms, it is usually not possible to classify definitively patients as having a complicated or an uncomplicated UTI. Several factors have been identified, however, that are markers for a potential complicated UTI (Table 2.1).

Table 2.1: Factors that suggest a potential complicated UTI

- Male sex
- Elderly
- Hospital-acquired infection
- Pregnancy
- Indwelling urinary catheter
- Recent urinary tract intervention
- Functional or anatomical abnormality of the urinary tract
- Recent antimicrobial use
- Symptoms for > 7 days at presentation
- Diabetes mellitus
- Immunosuppression

These factors only provide guidance to the clinician who must decide, based on limited clinical information, whether to embark on a more extensive evaluation and treatment course. It is generally safe to assume that a pre-menopausal, non-pregnant woman with acute onset of dysuria, frequency or urgency, who has not recently been instrumented or treated with antimicrobials and who has no history of a genitourinary tract abnormality, has an uncomplicated lower (cystitis) or upper (pyelonephritis) UTI (1). Recurrent UTIs are common among pre-menopausal, sexually active, healthy women, even though they generally have anatomically and physiologically normal urinary tracts.

Whether a UTI in pregnancy by itself is to be classified as an uncomplicated or a complicated UTI remains debatable. Although data on UTIs in healthy post-menopausal women without genitourinary abnormalities are limited, it is likely that most UTIs in such women are also uncomplicated. Data on UTIs in healthy adult men are sparse and much less is known about the optimal diagnostic and therapeutic approaches to UTIs in men.

2.4 Aetiological spectrum

The spectrum of aetiological agents is similar in uncomplicated upper and lower UTIs, with *E. coli* being the causative pathogen in approximately 70-95% of cases and *S. saprophyticus* in about 5-19% of cases, whereas *S. saprophyticus* is less frequently found in pyelonephritis than in cystitis. Occasionally, other Enterobacteriaceae, such as *P. mirabilis* and *Klebsiella* spp., or enterococci (mostly in mixed cultures indicating contamination), are isolated from such patients. In as many as 10-15% of symptomatic patients, bacteriuria cannot be detected using routine methods (1,3).

2.5 Acute uncomplicated cystitis in pre-menopausal, non-pregnant women

At this stage in life, the incidence of acute uncomplicated cystitis is high and this infection is associated with considerable morbidity. Therefore, even small improvements in diagnostics, therapy or prophylaxis have a high impact on public health.

2.5.1 Incidence, risk factors, morbidity

A prospective study at a university health centre or a health maintenance organization (HMO) revealed an incidence of 0.7 per person-year in the university cohort and 0.5 per person-year in the HMO cohort (4). Cohort and case control studies in young women showed that the risk is strongly and independently associated with recent sexual intercourse, recent use of diaphragm with spermicide, preceding asymptomatic bacteriuria, a history of recurrent UTI, the age of first UTI and history of UTI in the mother (4-6). On average, each episode of this type of UTI in pre-menopausal women was shown to be associated with 6.1 days of symptoms, 2.4 days of restricted activity, 1.2 days in which they were not able to attend classes or work and 0.4 days in bed (7).

2.5.2 Diagnosis

A non-pregnant pre-menopausal woman presenting with acute dysuria usually has one of three types of infection (1):

- acute cystitis
- acute urethritis, caused by *Chlamydia trachomatis, Neisseria gonorrhoeae*, or herpes simplex virus
- vaginitis caused by *Candida* spp. or *Trichomonas vaginalis*.

A distinction between these three entities can usually be made with a high degree of certainty from the history and physical examination (1).

Acute cystitis is more likely if the woman complains of urgency and suprapubic pain; has suprapubic tenderness; is a diaphragm-spermicide user; has symptoms that mimic those of previously confirmed cystitis; or has recently undergone urethral instrumentation. Although approximately 40% of women with cystitis have haematuria, this is not a predictor of a complicated infection. Urethritis caused by *N. gonorrhoeae or C. trachomatis* is relatively more likely if a women has had a new sexual partner in the past few weeks or if her sexual partner has urethral symptoms; there is a past history of a sexually transmitted disease (STD); symptoms were of gradual onset over several weeks and there are accompanying vaginal symptoms such as vaginal discharge or odour. Vaginitis is suggested by the presence of vaginal discharge or odour, pruritus, dyspareunia, external dysuria and no increased frequency or urgency.

Urinalysis (e.g. using a dipstick method) to look for pyuria, haematuria and nitrites is indicated if a UTI is suspected. Pyuria is present in almost all women with an acutely symptomatic UTI and in most women with urethritis caused by *N. gonorrhoeae* or *C. trachomatis*; its absence strongly suggests an alternative diagnosis. The definitive diagnosis of a UTI is made in the presence of significant bacteriuria, the definition of which remains somewhat controversial. The traditional standard for significant bacteriuria is $\geq 10^5$ cfu uropathogen/mL in voided MSU, based on studies of women with acute pyelonephritis and asymptomatic bacteriuria that were carried out four decades ago (8). Several more recent studies have shown that this is an

insensitive standard when applied to acutely symptomatic women and that approximately one-third to one-half of cases of acute cystitis have bacteriuria < 10^5 cfu/mL (9) (II). For practical purposes, colony counts ≥ 10^3 cfu/mL should be used for the diagnosis of acute uncomplicated cystitis (10,11).

The determination of a urine culture is generally not necessary in women with uncomplicated cystitis because the causative organisms and their antimicrobial susceptibility profiles are predictable. Also, culture results become available only after the patient's symptoms have resolved or are considerably improved. Voided MSU or straight catheter (by trained urological personnel) urine cultures should probably be performed if the patient's symptoms are not characteristic of a UTI. The laboratory must be instructed to look for 'low count' bacteriuria if such UTIs are to be detected.

A pelvic examination is indicated if any of the factors suggesting urethritis or vaginitis listed above are present or if there is doubt as to the diagnosis. A pelvic examination should include a careful evaluation for evidence of vaginitis, urethral discharge, or herpetic ulcerations; a cervical examination for evidence of cervicitis and cervical and urethral cultures for *N. gonorrhoeae* and *C. trachomatis* (or other sensitive and specific tests in first-voided urine in the morning, such as polymerase chain reaction tests).

2.5.3 Treatment

There seems to be no long-term adverse effects with respect to renal function or increased mortality associated with acute uncomplicated cystitis, even in women who experience frequent recurrences, and in the non-pregnant population. Untreated cystitis rarely progresses to symptomatic upper tract infection. Thus, the significance of lower tract infection in non-pregnant women seems to be limited to the morbidity of symptoms caused by the infection, which can lead to substantial disruption of the lives of affected individuals. In fact, most lower UTIs (50-70%) clear spontaneously if untreated, although symptoms may persist for several months. In a prospective, placebo-controlled study (12) (Ib), 288 patients were treated with placebo for 7 days, of whom 39% dropped out after the first follow-up visit (8-10 days). The spontaneous cure rate of symptoms was 28% after the first week, while 37% had neither symptoms nor bacteriuria after 5-7 weeks. In another study (13) (Ib), symptomatic improvement and cure occurred in 52% of 33 placebo-treated patients with bacteriologically proven urinary tract infection after 1 week, but only 20% of these patients showed bacteriological eradication as well. Both parameters were significantly lower than in the group of patients treated with nitrofurantoin (100 mg four times daily for 3 days).

Knowledge of the antimicrobial susceptibility profile of uropathogens causing uncomplicated UTIs in the community should guide therapeutic decisions, although the trend away from routinely culturing patients with uncomplicated cystitis may unfortunately lead to the lack of such data. The resistance pattern of *E. coli* strains causing an uncomplicated UTI, however, may vary considerably between European regions and countries, so that no general recommendations are suitable throughout Europe. In an international survey of the antimicrobial susceptibility of uropathogens from uncomplicated UTI, the overall resistance rate was lowest in the Nordic countries and Austria and highest in Portugal and Spain (3,14) (IIb).

Short courses of antimicrobials are highly effective in the treatment of acute uncomplicated cystitis in pre-menopausal women (15,16) (Ia). Short-course regimens are desirable because of the improved compliance that they promote, their lower cost, and lower frequency of adverse reactions. However, in assessing the potential cost advantages of short-course regimens, it is necessary to consider the potential added expense associated with treatment failures or recurrences arising from short-course therapy. It is also important to consider the potential psychological aspects of single-dose therapy; as symptoms may not subside for 2 or 3 days, the patient may have misgivings during this time about the 'insufficient' treatment provided to her. Such a scenario may result in unnecessary visits or calls to the physician.

A wide variety of antimicrobial regimens comprising different drugs, doses, schedules and durations have been used to treat these common bacterial infections. Only a few of these regimens have been compared directly in adequately designed studies. To develop evidence-based guidelines for the antimicrobial therapy of uncomplicated acute bacterial cystitis and pyelonephritis in women, a committee of the IDSA systematically reviewed the English medical literature up to 1997 and developed guidelines for the antimicrobial treatment of acute uncomplicated bacterial cystitis and pyelonephritis in women (16). The UTI Working Group of the EAU Guidelines Office has used this database and more recent publications to develop the following, updated, guidelines on antimicrobial therapy.

The following antimicrobials were considered by the UTI Working Group: trimethoprim (TMP), trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones (ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, levofloxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin), ß-lactams (amoxycillin, ampicillin-like compounds, cefadroxil, cefuroxime axetil, cefpodoxime proxetil, ceftibuten, pivmecillinam, ritipenem axetil), fosfomycin trometamol, and nitrofurantoin.

The following conclusions about antimicrobial therapy can be made:

i) Treatment duration

In otherwise healthy, adult, non-pregnant women with acute uncomplicated cystitis, single-dose therapy (with some exceptions) is significantly less effective in eradicating initial bacteriuria than are longer durations of treatment with antimicrobials tested in this manner, such as TMP-SMX, TMP, norfloxacin, ciprofloxacin, fleroxacin, and as a group ß-lactams. However, TMP-SMX, TMP, norfloxacin, ciprofloxacin, and fleroxacin given for 3 days are as effective as the same antimicrobials used over longer durations. Longer treatment usually shows a higher rate of adverse events (Ib).

Although not examined in controlled trials, cystitis caused by *S. saprophyticus* may respond better to longer treatment durations, e.g. 7 days (16) (IIIB).

ii) Trimethoprim, co-trimoxazole

TMP-SMX was the most studied drug (30 studies). A 3-day regimen with TMP-SMX can therefore be considered to be the standard therapy (IaA). TMP alone was equivalent to TMP-SMX with regard to eradication and adverse effects. However, a recent study on more than 10,000 Dutch women revealed that better results were obtained for trimethoprim prescribed for 5-7 days than for 3 days (17) (IIaB). Considering possible rare, but serious, adverse effects caused by sulphonamides, TMP alone may be considered the preferred drug over TMP-SMX (IIIC). TMP or TMP-SMX can be recommended as first-line drugs for empirical therapy, but only in communities with rates of uropathogen resistance to TMP < 10-20% because there is a close correlation between susceptibility and the eradication of *E. coli* on the one hand and resistance and persistence of the uropathogen on the other (18,19) (Ib). The risk of emerging resistant uropathogens in the case of recurrence was also much higher when using TMP as a first-line drug than when using pivmecillinam or ciprofloxacin (20) (III), which had the lowest risk of the drugs investigated.

iii) Fluoroquinolones

The fluoroquinolones (ciprofloxacin, fleroxacin, norfloxacin and ofloxacin) are equivalent to TMP-SMX when given as a 3-day regimen (IbA). Pefloxacin and rufloxacin, each as single-day therapies, are interesting options and may be equivalent to TMP-SMX in the eradication of bacteriuria and its recurrence. Questions remain as to the possibility of a higher incidence of adverse effects with these agents than with other recommended therapies (21-24) (IbB). Two more recent studies investigated short-term therapy with levofloxacin and with the extended-release formulation of ciprofloxacin (CiproXR). A 3-day regimen with levofloxacin, 250 mg once daily, was similarly effective to a 3-day regimen of ofloxacin 200 mg twice daily, but with levofloxacin there was a trend to lesser adverse events (25) (IbA). A 3-day course with CiproXR (500 mg) once daily was equivalent in regard to efficacy and safety as a course of conventional ciprofloxacin (250 mg twice daily) (26) (IbA).

Fluoroquinolones are more expensive than TMP and TMP-SMX, and are thus not recommended as first-line drugs for empirical therapy except in communities with rates of uropathogen resistance to TMP > 10-20%. Concern about fluoroquinolone resistance led practitioners to be appropriately hesitant about the widespread use of fluoroquinolones for the routine treatment of uncomplicated UTIs, although there are no published studies demonstrating that short-course fluoroquinolone therapy for acute cystitis in women results in the selection of fluoroquinolone-resistant flora (27-29) (III). In some countries, however, the resistance of *E. coli* to fluoroquinolones has already increased to more than 10%. In this situation, alternative oral drugs should be considered for empirical therapy (see Table 2.3). Treatment with any of these agents should result in more than 90% eradication of the bacteriuria.

iv) ß-lactam antibiotics

In general, ß-lactams as a group are less effective than the aforementioned drugs (III). No sufficiently large comparative studies between one of the above recommended regimens (3-day TMP, TMP-SMX, or one of the above-mentioned fluoroquinolones) and second- and third-generation oral cephalosporins or an aminopenicillin plus a BLI were available for the IDSA analysis (16). Only one study of adequate size compared a 3-day course of ß-lactam antimicrobial (pivmecillinam) with treatment for a longer duration (30) (Ib). The study found that 3 days of therapy were equivalent to 7 days of therapy with regard to the eradication of the initial bacteriuria, although the shorter treatment was associated with an increased incidence of recurrence. Pooled bacteriological outcomes from more recent studies showed that 7 days of pivmecillinam, 200 mg twice daily, and 3 days of norfloxacin, 400 mg twice daily, have similar results (31,32) (IbA). With pivmecillinam, however, the rate of vaginal candidiasis was significantly lower than with norfloxacin (33) (Ib). Pivmecillinam also shows low resistance rates for *E. coli* and other Enterobacteriaceae, without cross-resistance to other antimicrobials used for the treatment of UTI (14,34) (IIb).

In general, first- and second-generation oral cephalosporines are not recommended as first-line antimicrobials for a 3-day treatment of uncomplicated UTI (16,35,36) (IbA). However, among third-generation oral cephalosporins, a 3-day course with cefpodoxime-proxetil (200 mg twice daily) was as safe and effective as that of TMP-SMX in 133 evaluable patients (37) (IbA). In contrast, a more recent study of 370 women (38)

showed that a 3-day regimen of amoxycillin-clavulanate (500 mg/125 mg twice daily) was not as effective as a 3-day regimen of ciprofloxacin (250 mg twice daily) even in women infected with susceptible strains (Ib). This difference may be due to the inferior ability of amoxycillin-clavulanate to eradicate vaginal *E. coli*, facilitating early re-infection.

v) Fosfomycin

Fosfomycin trometamol was evaluated as single-dose (3 g) therapy by a meta-analysis comprising 15 comparative trials on 2048 patients (39) (IaA), in whom short-term bacteriological eradication was identified in 1540 patients with confirmed UTI, and obtained with fosfomycin trometamol in 85.6% of cases and with other treatments (single dose and 3-7 day regimens) in 86.7% of cases. In patients who completed long-term follow-up, the overall eradication rate with fosfomycin trometamol (84.6%) was significantly ($p<0.05$) higher than with other treatments (79.6%). In a more recent large trial (18) (IbA) on 547 female patients, single-dose fosfomycin trometamol and a 5-day course of trimethoprim (200 mg twice daily) showed equivalent microbiological cure rates (83% by either drug). As regards safety, in the meta-analysis, the single-dose and the 3-7 day regimens were found to be equivalent concerning the number of adverse events. Considering that fosfomycin trometamol has been extensively used in several European countries for single-dose therapy of uncomplicated UTI since 1988, the resistance rate for *E. coli* remained very low without cross-resistance to other antimicrobials used for the treatment of UTI (14,34,40) (IIb).

vi) Nitrofurantoin

Nitrofurantoin (50-100 mg four times daily, or sustained release formulation 100 mg twice daily) cannot be considered a suitable drug for short-term therapy (up to 3 days) of acute uncomplicated cystitis. A course of 5-7 days is recommended if nitrofurantoin is used for this indication (17) (IIaB). Despite the clinical use of nitrofurantoin for many years, the resistance rate for *E. coli* and *S. saprophyticus* is still low throughout Europe (3) (IIb), although in some areas a two-fold increase in nitrofurantoin resistance has already been observed for *E. coli* within the last 10 years (40). Nitrofurantoin is, however, not active against *P. mirabilis* and *Klebsiella* spp., the second and third most frequently isolated Gram-negative uropathogens (3) (IIb). There is also some concern about the safety of nitrofurantoin, especially the acute and chronic pulmonary syndromes, which are common in the elderly (41,42). These severe adverse events, however, were not observed when nitrofurantoin was used for long-term and low-dose prophylaxis for recurrent UTIs in girls and women (43,44) (III).

In Table 2.2, the pivotal clinical studies with various oral antimicrobial treatment options of acute uncomplicated bacterial cystitis in adult pre-menopausal non-pregnant women are summarized according to the level of evidence and grade of recommendations as defined in the Introduction (Section 1.1 and 1.2). See also the recommendations in Appendix 12.2.

Table 2.2: Oral treatment options of acute uncomplicated bacterial cystitis in adult pre-menopausal non-pregnant women according to level of evidence and grade of recommendation

Substance	Dosage	Duration	LE	GR	Reference	Ref	Remarks
Cefpodoxime proxetil	100 mg bid	3 days	Ib	A	Kavatha 2003	37	Cefpodoxime proxetil for 3 days was as safe and effective as TMP-SMX for 3 days
Ciprofloxacin	250 mg bid	3 days	Ib	A	Iravani 1995 Vogel 2004	45 46	Also for treatment of post-menopausal non-institutionalized women
Cipro XR	500 mg od	3 days	Ib	A	Henry 2002	26	Efficacy and tolerance of extended release ciprofloxacin (ciproXR) 500 mg od was equivalent to 3-day conventional ciprofloxacin 250 mg bid
Enoxacin	200 mg bid	3 days	Ib	B	Backhouse 1987	47	3-day therapy (85% cure rate) better than single dose (77%); insufficient statistical power; abstract only
Fleroxacin	400 mg	SD	Ib	B	Iravani 1993	48	Single dose showed a comparable clinical response, but inferior bacteriological eradication when compared to a 7-day course (200 mg od)
Fleroxacin	200 mg od	3 days	Ib	B	Iravani 1995	49	3-day fleroxacin 200 mg od was equivalent to 7-day course of fleroxacin 200 mg od or ciprofloxacin 250 mg bid (abstract)
Fosfomycin	3000 mg	SD	Ia Ib	A	Lecomte 1997 Minassian 1998	39 18	Meta-analysis of 15 comparative trials: overall results indicated that single-dose fosfomycin trometamol had equivalent efficacy with comparators (single dose and 3-7 day treatment regimens) at short-term follow-up, but significantly better results were obtained at long-term follow-up with fosfomycin trometamol
Gatifloxacin	200 mg od	3 days	Ib	A*	Richard 2002 Naber 2004	50 51	Efficacy and tolerance were equivalent with single-dose gatifloxacin 400 mg vs 3-day therapy with gatifloxacin 200 mg od or ciprofloxacin 250/100 mg bid; not available in Europe
Gatifloxacin	400 mg	SD	Ib	A*	Richard 2002 Naber 2004	50 51	Efficacy and tolerance were equivalent with single-dose gatifloxacin 400 mg vs 3-day therapy with gatifloxacin 200 mg od or ciprofloxacin 250/100 mg bid; not available in Europe
Levofloxacin	250 mg od	3 days	Ib	A	Richard 1998	25	Levofloxacin (250 mg od) showed equivalent efficacy compared with ofloxacin (200 mg bid), with levofloxacin showing a trend to less AE than with ofloxacin
Lomefloxacin	400 mg od	3 days	Ib	B	Neringer 1992 Nicolle 1993	52 53	With lomefloxacin, there were significantly more AE than with norfloxacin
Nitrofurantoin	50-100 mg qid; 100 mg SR bid	5-7 days	IIa	B	Spencer 1994 Goettsch 2004	54 17	Sustained release (SR) formulation; eradication rates for all three comparative drugs (nitrofurantoin, TMP, TMP-SMX) were low (77-83%) in Spencer (1994), while 5- and 7-day therapy were more effective than 3-day therapy (Goettsch 2004)
Norfloxacin	400 mg bid	3 days	Ib	A	Inter-Nordic 1988 Piipo 1990	55 56	Recurrence rates with 3-day were significantly higher than with 7-day therapy
Ofloxacin	200 mg bid	3 days	Ib	A	Block 1987 Hooton 1989, 1991	57 58 59	Equivalent to 3-day regimen with TMP-SMX
Pefloxacin	800 mg	SD	Ia	B	Naber 1994	60	With pefloxacin, there was significantly more AE than with norfloxacin 5-day therapy. Pefloxacin should be given with food to lower the gastrointestinal AE
Pivmecillinam	200 mg bid	7 days	Ib	A	Nicolle 2000 Nicolle 2002 Menday 2002	31 32 33	Pooling bacteriological outcomes showed similar results with 7-day pivmecillinam 200 mg bid or 3-day norfloxacin 400 mg bid, but significantly lower incidence of candidal vaginitis with pivmecillinam than with norfloxacin
Pivmecilinam	400 mg bid	3 days	Ib	B	Nicolle 2000 Nicolle 2002 Menday 2002	31 32 33	Lower rate of bacterial eradication occurred with 3-day pivmecillinam 400 mg od than with 7-day therapy (200 mg bid)
Rufloxacin	400 mg	SD	Ib	B	Jardin 1995	23	With rufloxacin significantly more AE than with pefloxacin and norfloxacin
TMP	200 mg bid	5-7 days	Ib IIa	A	Warren 1999 Goettsch 2004	16 17	Can be considered as one standard empirical therapy, but only if the prevalence of TMP-resistant *E. coli* is less than (10%-)20%; 5- and 7-day courses were more effective than 3-day courses
TMP	200 mg bid	3 days	Ib	B	Gossius 1985	61	With 3-day therapy, significantly less AE occurred than with 10-day therapy
TMP-SMX	160/800 mg bid	3 days	Ia	A	Warren 1999	16	For empirical therapy only, if prevalence of resistant *E. coli* < (10%-)20% TMP; with 3-day therapy, there was a trend to increased recurrence rate, which was counterbalanced by a trend towards more AE with therapy of longer duration

*LE = level of evidence; GR = grade of recommendation; TMP = trimethoprim; SMX = sulphamethoxazole; qid = four times daily; tid = three times daily; bid = twice daily; od = once daily; SD = single dose; SR = sustained release; AE = adverse events; *not available in Europe.*

Considering only those studies of antimicrobials, which have no apparent disadvantages (see remarks in Table 2.2), the regimens in Table 2.3 can probably be recommended equally (see also the recommendations in Appendix 12.2). The recommendation to use nitrofurantoin has been rated as B, because of the rare, but serious, adverse events associated with its use. However, its efficacy is established when used according to the recommended regimens.

Table 2.3: Recommended antimicrobial regimens for the treatment of acute uncomplicated bacterial cystitis in adult premenopausal, non-pregnant women

Substance	Dosage	Duration
Cefpodoxime	100 mg bid	3 days
Ciprofloxacin*	250 mg bid	3 days
CiproXR*	500 mg od	3 days
Fosfomycin trometamol	3000 mg SD	1 day
Levofloxacin*	250 mg od	3 days
Nitrofurantoin	50-100 mg tid, 100 mg SR bid	5-7 days
Norfloxacin*	400 mg bid	3 days
Ofloxacin*	200 mg bid	3 days
Pivmecillinam	200 mg bid	7 days
Trimethoprim (TMP)*	200 mg bid	5-7 days
TMP-SMX*	160/800 mg bid	3 days

**Resistance rates of E.coli vary considerably within Europe. These substances are only recommended for empirical therapy when the resistance rate of E. coli is < (10%-)20%.*
CiproXR = ciprofloxacin sustained release; SMX = sulphamethoxazole; od = once daily; bid = twice daily; qid = four times daily; SD = single dose; SR = sustained release.

vii) Other treatment modalities
Urinary analgesics, such as phenazopyridine, 200 mg three times daily, can be administered to patients who have experienced severe dysuria for 1 or 2 days. Women with cystitis, including those with severe dysuria and urgency, usually show resolution or marked improvement of symptoms within 2-3 days of initiating therapy. This should be explained to the patient. Thus, the need for, and duration of, analgesic therapy in women with UTIs must be individualized.

Although it is generally recommended that patients with UTIs increase their fluid intake to promote micturition and the elimination of uropathogens, it remains unclear as to whether this is beneficial or detrimental to patients with UTI (2).

2.5.4 Post-treatment follow-up

Urinalysis (e.g using a dipstick method) is sufficient for routine follow-up. Routine post-treatment cultures in asymptomatic patients may not be indicated because the benefit of detecting and treating asymptomatic bacteriuria in healthy women has been demonstrated only in pregnancy and prior to urological instrumentation or surgery. 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 testing should be performed. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used and retreatment with a 7-day regimen using another agent should be considered (IVC).

2.6 Acute uncomplicated pyelonephritis in pre-menopausal, non-pregnant women

2.6.1 Diagnosis

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness, and may occur with or without cystitis symptoms. The presentation of an acute uncomplicated pyelonephritis usually varies from a mild to a moderate illness. A life-threatening condition with multi-organ system dysfunction, including sepsis syndrome with or without shock and renal failure, must be considered a complicated case.

Urinalysis is indicated to look for pyuria and haematuria. In contrast to cystitis, 80-95% of episodes of pyelonephritis are associated with > 10^5 cfu uropathogen/mL (62). For routine diagnosis, a breakpoint of 10^4 cfu/mL can be recommended (10,11). An evaluation of the upper urinary tract with ultrasound (63) should be performed to rule out urinary obstruction. Additional investigations, such as an unenhanced helical computed tomography (64) (to rule out urolithiasis), an excretory urogram or DMSA scan, according to the clinical situation should be considered if the patient remains febrile after 72 hours of treatment to rule out further

complicating factors, e.g. urolithiasis, renal or perinephric abscesses. Routine performance of an excretory urogram in patients with acute uncomplicated pyelonephritis has little value because most adults with uncomplicated acute pyelonephritis have a normal upper urinary tract.

2.6.2 Treatment

Of several hundred articles screened by the IDSA group (16), only five were prospective, randomized, controlled trials (8,64-68) and the following conclusions can be drawn for initial therapy from their analysis and the five studies (69-72) published thereafter.

1. TMP-SMX is preferred over ampicillin (IbA) (no controlled study used TMP alone).
2. Two weeks of therapy with TMP-SMX for acute uncomplicated pyelonephritis appears to be adequate for the majority of women (IbA). In some studies with various antibiotics, e.g. aminoglycosides (but none that were sufficiently powered), an even shorter duration of therapy of 5-7 days was recommended (IIIB).
3. In communities in which the resistance rate of *E. coli* to TMP is > 10%, a fluoroquinolone should be recommended as the drug of choice for empirical therapy. It was demonstrated that a 7-day regimen of ciprofloxacin, 500 mg twice daily, showed a significantly higher rate of bacterial eradication and a lower rate of adverse effects when compared with a 14-day therapy using TMP-SMX, 960 mg twice daily (69) (IbA). The higher efficacy seen with ciprofloxacin was mainly due to TMP-resistant *E. coli* strains. In clinical trials, the following fluoroquinolones were comparable to conventional ciprofloxacin 500 mg twice daily, ciprofloxacin extended release formulation (1000 mg once daily), gatifloxacin (400 mg once daily), levofloxacin (250 mg twice daily), and lomefloxacin (400 mg once daily) (70-72) (IbA).
4. For an aminopenicillin plus a BLI, as well as for most group two and group three oral cephalosporins, there are no sufficiently powered comparative studies versus a fluoroquinolone or TMP-SMX. In a prospectively randomized study, a 10-day therapy with cefpodoxime proxetil 200 mg twice daily showed equivalent clinical efficacy as that with ciprofloxacin 500 mg twice daily (73) (IbA).
5. In areas with a rate of *E. coli* resistance to fluoroquinolones > 10% and in situations in which fluoroquinolones are contraindicated (e.g. pregnancy, lactating women, adolescence), an aminopenicillin plus a BLI, or a group three oral cephalosporin is recommended, either for initial use, or if a patient has to be switched to an oral regimen (IIIB).

Based on this analysis, the UTI Working Group of the EAU Guidelines Office recommends in mild and moderate cases an oral fluoroquinolone for 7 days as first-line therapy. In situations where a fluoroquinolone is not indicated (see above), a group three oral cephalosporin, e.g. cefpodoxime proxetil, may be an alternative for empirical therapy (B). If a Gram-positive organism is seen on the initial Gram stain, an aminopenicillin plus a BLI is recommended (B). More severe cases of acute uncomplicated pyelonephritis should be admitted to hospital and, if the patient cannot take oral medication, treated parenterally with a fluoroquinolone, an aminopenicillin plus a BLI, a group three cephalosporin, or an aminoglycoside (B). With 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 weeks' course of therapy (B).

In Table 2.4, the oral antimicrobial treatment options of acute uncomplicated pyelonephritis in adult pre-menopausal non-pregnant women according to level of evidence and grade of recommendations as defined in the Introduction (Section 1) are summarized (see also the recommendations in Appendix 12.2).

Although approximately 12% of patients hospitalized with acute uncomplicated pyelonephritis have bacteraemia (74), it is common practice to obtain blood cultures only if the patient appears ill enough to warrant hospitalization. There is no evidence that bacteraemia has prognostic significance or warrants longer therapy in an otherwise healthy individual with pyelonephritis.

Table 2.4: Oral treatment options of acute uncomplicated pyelonephritis in adult pre-menopausal non-pregnant women according to level of evidence and grade of recommendation. (For parenteral therapy, see text.)

Substance	Dosage	Duration	LE	GR	Author, year	Ref	Remarks
Ciprofloxacin	500 mg bid	7 days	Ib	A	Talan 2000	69	a) Ciprofloxacin significantly more effective than cetriaxone/TMP-SMX and with trend towards less AE
CiproXR	1000 mg od	7-10 days	Ib	A	Talan 2004	70	b) Efficacy and tolerance of extended release ciprofloxacin (ciproXR) 1000 mg od equivalent with 10-day conventional ciprofloxacin
Cefpodoxime*	200 mg bid	10 days	Ib	B	Naber 2001	73	c) Clinically equivalent with ciprofloxacin 500 mg bid
Gatifloxacin	400 mg od	10 days	Ib	A	Naber 2004	71	d) Equivalent with ciprofloxacin 500 mg bid, not available in Europe
Levofloxacin	250 mg od	10 days	Ib	A	Richard 1998	72	e) Equivalent with ciprofloxacin 500 mg bid
Lomefloxacin	400 mg od	10 days	Ib	B	Richard 1998	72	f) Study statistically underpowered
TMP-SMX	160/800 mg bid	14 days	Ib	B	Stamm 1987 Talan 2004	68 70	g) Only if uropathogen is known to be susceptible to TMP

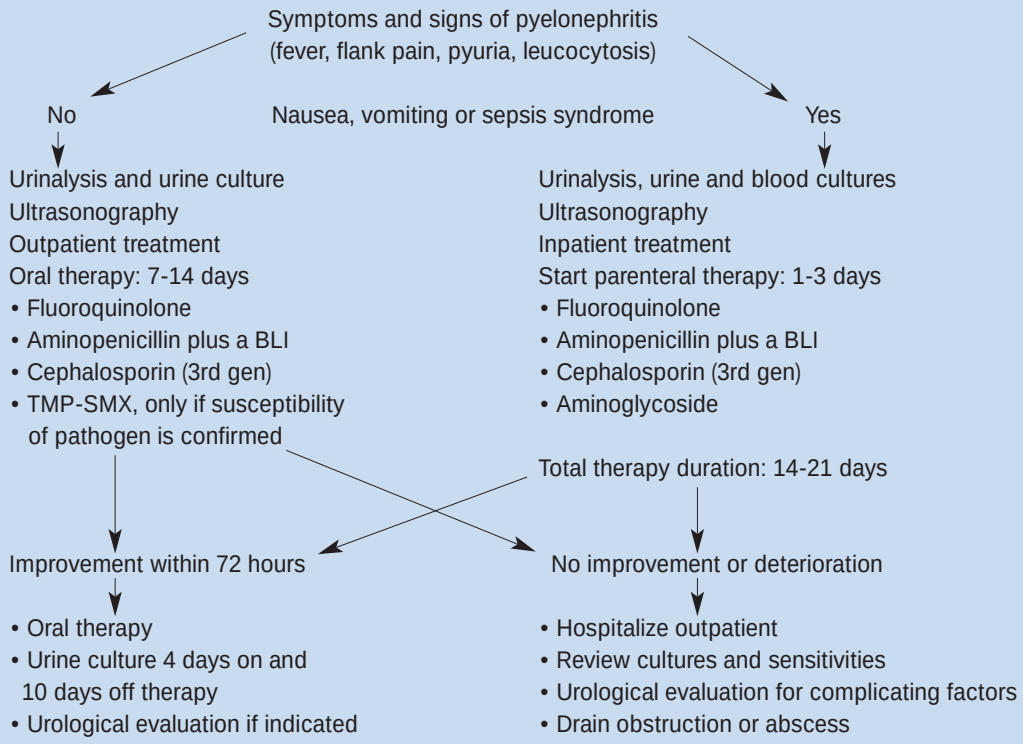
**Cefpodoxime proxetil.*

LE = level of evidence; GR = grade of recommendation; TMP = trimethoprim; SMX = sulphamethoxazole; tid = three times daily; bid = twice daily; od = once daily; AE = adverse events.

2.6.3 Post-treatment follow-up

Routine post-treatment cultures in an asymptomatic patient may not be indicated; routine urinalysis using a dipstick method is sufficient. In women whose pyelonephritis symptoms do not improve within 3 days, or that resolve and then recur within 2 weeks, a repeat urine culture, antimicrobial susceptibility testing and an appropriate investigation, such as renal ultrasound or scan, should be performed. In the patient with no urological abnormality, it should be assumed that the infecting organism is not susceptible to the agent originally used and retreatment with a 2-week regimen using another agent should be considered. For those patients who relapse with the same pathogen as the initially infecting strain, a 6-week regimen is usually curative. An overview 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.

2.7 Recurrent (uncomplicated) UTIs in women

2.7.1 Background

Recurrent urinary tract infection (RUTI) is defined in the literature by three episodes of UTI in the last 12 months or two episodes in the last 6 months. Risk factors for RUTI are genetic and behavioural (75) (IIa). Some studies estimate that 20-30% of women who have a UTI will have a RUTI (76). Women who are non-secretors of blood group substances have an increased occurrence of RUTI (77) (IIa). A secretor is defined as a person who secretes their blood type antigens into body fluids and secretions, such as saliva, etc. A non-secretor on the other hand puts little to none of their blood type antigens into these fluids. In the USA about 20% of the population are non-secretors. Women with RUTI have an increased frequency of urinary infection in first-degree female relatives (78) (IIa). In addition, *E. coli*, the most common uropathogen, adheres more readily to epithelial cells in women who experience RUTI (79,80) (IIb). Behavioural factors associated with RUTI include sexual activity, with a particularly high risk in those who use spermicides as a birth control method (81,82) (IIa). According to cohort and case control studies (4-6) (IIa), risk factors associated with RUTI in sexually active pre-menopausal women are frequency of sexual intercourse, spermicide use, age of first UTI (less than 15 years of age indicates a greater risk of RUTI) and history of UTI in the mother, suggesting that genetic factors and/or long-term environmental exposures might predispose to this condition. Following the menopause, risk factors strongly associated with RUTI are vesical prolapse, incontinence and post-voiding residual urine. Other risk factors such as blood group substance non-secretor status and a history of UTI before the menopause need to be confirmed by further research (83).

Recurrent UTIs result in significant discomfort for women and have a high impact on ambulatory health care costs as a result of outpatient visits, diagnostic tests and prescriptions. Different approaches have

been proposed for the prevention of RUTI, including non-pharmacological therapies, such as voiding after sexual intercourse or the ingestion of cranberry juice (84), and the use of antibiotics as preventive therapy given regularly or postcoital prophylaxis in sexually active women.

With respect to antibiotic prophylaxis, it is not known which antibiotic schedule is best or the optimal duration of prophylaxis, the incidence of adverse events, or the recurrence of infections after stopped prophylaxis or treatment compliance.

2.7.2 Prophylactic antimicrobial regimens

One effective approach for the management of recurrent uncomplicated UTI is the prevention of infection through the use of long-term, prophylactic antimicrobials taken on a regular basis at bedtime (85-87) (Ib) or postcoital (88) (Ib). In a Cochrane review (89) (Ia) every published randomized controlled trial from 1966 to April 2004 was analyzed in which antibiotics were used as a preventive strategy for recurrent UTIs and administered for at least 6 months. Nineteen out of 108 studies involving 1120 women were eligible for inclusion. In nine of these studies one antibiotic regimen was compared with placebo. In another seven studies different antibiotic regimens were compared concerning microbiological outcome, while in another three studies antibiotic regimens with non-antibiotic regimes were compared concerning microbiological outcome (Table 2.5) (90-107).

During active prophylaxis the rate of microbiological recurrence per patient-year was 0 to 0.9 per patient-year in the antibiotic group, which was significantly lower than 0.8 to 3.6 per patient-year in the placebo group. The relative risk of having one microbiological recurrence was 0.21 (95% CI 0.13-0.34), significantly favouring antibiotic prophylaxis. For clinical recurrences the relative risk was 0.15 (95% CI 0.08-0.28), significantly favouring antibiotic prophylaxis. The relative risk of having one microbiological recurrence after prophylaxis was 0.82 (95% CI 0.44-1.53). The relative risk for severe side effects was 1.58 (95% CI 0.47-5.28) and for other side effects the relative risk was 1.78 (95% CI 1.06-3.00), significantly favouring placebo. Side effects included vaginal and oral candidiasis and gastrointestinal symptoms.

Generally, the number of patients with microbiological recurrent UTIs decreased by eightfold as compared to the period of time before prophylaxis and compared to placebo by fivefold. The UTI episodes per patient-year was reduced in general by 95% during antimicrobial prophylaxis as compared to the period of time before prophylaxis. The initial duration of prophylactic therapy was usually 6 months or 1 year. However, for co-trimoxazole (TMP-SMX), continuous prophylaxis for as long as 2 (86) or 5 years (85) has remained efficacious. Prophylaxis does not appear to modify the natural history of a recurrent UTI. When discontinued, even after extended periods, approximately 60% of women will become re-infected within 3-4 months. Thus, prophylaxis did not appear to exert a long-term effect on the baseline infection rate (108) (III).

Table 2.5: Efficacy (reduction of microbiological recurrences) of antibiotics for preventing recurrent urinary tract infection in non-pregnant women (modified according 85) with a study period of at least 6 months

Substance	Dosage	n/N	Comparator	Dosage	n/N	Weight (%)	Relative Risk (95% CI)	Author, Year	Ref
Antibiotic vs Placebo									
Cinoxacin	250 mg/24h	1/23	Placebo		17/22	5.4	0.06 (0.01-0.39)	Martens 1995	91
Cinoxacin	500 mg/24h	8/21	Placebo		17/19	24.2	0.43 (0.24-0.75)	Martorana 1984	92
Cinoxacin	500 mg/24h	2/15	Placebo		4/13	7.9	0.43 (0.09-1.99)	Schaeffer 1982	93
Cinoxacin	500 mg/24h	1/20	Placebo		8/21	5.1	0.13 (0.02-0.96)	Scheckler 1982	94
Norfloxacin	200 mg/24h	0/11	Placebo		10/13	2.9	0.06 (0.00-0.85)	Nicolle 1989	95
Norfloxacin	200 mg/24h	4/18	Placebo		13/17	16.0	0.29 (0.12-0.72)	Rugendorff 1987	96
Nitrofurantoin	100 mg/24h	1/13	Placebo		5/6	5.5	0.09 (0.01-0.63)	Stamm 1980	97
Nitrofurantoin	50 mg/24h	3/25	Placebo		15/25	12.5	0.20 (0.07-0.61)	Bailey 1971	98
Cephalexin	125 mg/24h	1/20	Placebo		13/23	5.3	0.09 (0.01-0.62)	Gower 1975	99
TMP-SMX	40/200 mg/24h	1/13	Placebo		5/7	5.3	0.11 (0.02-0.75)	Stamm 1980	97
TMP-SMX	40/200 mg postcoital	2/16	Placebo		9/11	9.8	0.15 (0.04-0.58)	Stapleton 1990	90
Total		**24/195 (12.3%)**			**116/177 (65.5%)**		**0.21 (0.13-0.34)**		
Antibiotic vs Antibiotic									
Cefaclor	250 mg/24	8/49	Nitrofurantoin	50 mg24h	8/48	20.0	0.98 (0.40-2.40)	Brumfitt 1995	100
Norfloxacin	400 mg/24	2/26	Nitrofurantoin	100 mg/24h	0/26	7.2	5.00 (0.25-99.4)	Nunez 1990	101
Trimethoprim	100 mg/24h	16/38	Nitrofurantoin	100 mg/24h	4/34	19.2	3.58 (1.33-9.66)	Brumfitt 1985	102
TMP-SMX	40/200 mg/24h	1/13	Nitrofurantoin	100 mg/24h	1/13	8.5	1.00 (0.07-14,3)	Stamm 1980	97
Trimethoprim	100 mg/24h	1/12	Cinoxacin	500 mg/24h	2/14	10.3	0.58 (0.06-5.66)	Seppanen 1988	103
Pefloxacin	400 mg/weekly	17/185	Pefloxacin	400 mg/mon	52/176	22.6	0.31 (0.19-0.52)	Guibert 1995	104
Ciprofloxacin	125 mg postcoital	2/70	Ciprofloxacin	125 mg/24h	2/65	12.2	0.93 (0.13-6.40)	Melekos 1997	105
Total		**47/393 (12.0%)**			**69/376 (18.4%)**				
Antibiotics vs Non-antibiotics									
Nitrofurantoin	50 mg/12h	4/43	Meth. hippurate	1 g/12h	19/56		0.27 (0.10-0.75)	Brumfitt 1981	106
Trimethoprim	100 mg/24h	8/20	Povidone iodine	Topical	10/19		0.76 (0.38-1.51)	Brumfitt 1983	107
Trimethoprim	100 mg/24h	8/20	Meth. hippurate	1 g/12h	10/25		1.00 (0.49-2.05)	Brumfitt 1983	107

TMP-SMX = trimethoprim-sulphamethoxazole; Meth. hippurate = methanamine hippurate.

The recommendations for antimicrobial regimens for the prevention (prophylaxis) of recurrent uncomplicated UTI in pre-menopausal women are listed in Table 2.6. Trimethoprim, co-trimoxazole or nitrofurantoin can still be considered as the standard regimen. Fosfomycin trometamol (FT), 3g every 10 days for 6 months can be considered as an alternative as shown by a recent placebo (PL) controlled study in 302 evaluable non-pregnant females suffering from recurrent lower UTI (109) (Ib). The UTI episodes per patient-year (0.14 vs 2.97), the time to first infection recurrence (38 days vs 6 days), the percentage of patients with at least one episode of recurrent UTI (7.0% vs 75.0%), and the number of UTI episodes per patient during 6 months treatment (0.07 vs 1.44) and during the 6 months, follow-up, period (0.55 vs 1.54) were all statistically in favour of the FT-treated group. In cases of 'breakthrough' infection due to resistant pathogens, low doses of fluoroquinolones may also be used. No increased emergence of resistance was observed (101,105). During pregnancy, an oral first-generation cephalosporin is recommended.

An alternative prophylactic approach is post-intercourse prophylaxis for women in whom episodes of infection are associated with sexual intercourse (88,89,105) (IbA). Generally, for this approach, the same antimicrobials can be used in the same doses as though recommended for continuous prophylaxis. A patient-initiated treatment may also be suitable for management in well-informed, young women, in whom the rate of recurrent episodes is not too common (112). This is, however, strictly speaking, not prophylaxis but early treatment.

Table 2.6: Recommendations for antimicrobial prophylaxis of recurrent uncomplicated UTI in women (IA)

Agent[1]	**Dose**
Standard regimen:	
• Nitrofurantoin	50 mg/day (98)
• Nitrofurantoin macrocrystals	100 mg/day (101,106)
• Trimethoprim-sulphamethoxazole	40/200 mg/day (97) or three times weekly (110)
• Trimethoprim	100 mg/day (103)
• Fosfomycin trometamil	3 g/10 day (109)
'Breakthrough' infections:	
• Ciprofloxacin	125 mg/day (105)
• Norfloxacin	200-400 mg/day (101,111)
• Pefloxacin	800 mg/week (104)
During pregnancy:	
• Cephalexin	125 mg/day (99)
Cefaclor	250 mg/day (100)

[1] *Taken at bedtime.*

2.7.3 Alternative prophylactic methods

Alternative methods, such as the acidification of urine (113), cranberry juice (84), extract from uvae ursi and the vaginal application of lactobacilli (114,115), show variable effects. A meta-analysis of five, placebo-controlled, double-blind studies using oral immuno-active *E. coli* fractions (UroVaxom) resulted in a significant reduction of recurrent infections as compared with placebo (116) (Ia). In a recently published study (117) (Ib), a total of 453 patients were included in a placebo-controlled, double-blind study. Patients received either the immunotherapeutic OM-89 (UroVaxom) or a matching placebo. After receiving one capsule per day for 90 days, patients had 3 months without treatment, before being given one capsule on the first 10 days in the following 3 months. Patients were followed up for 12 months from the beginning of treatment. The mean rate of post-baseline UTI episodes was significantly lower in the active group than in the placebo group (0.84 vs 1.28; $p<0.003$), corresponding to a 34% reduction in patients treated with OM-89 as compared to placebo. In the OM-89 treated group, 93 patients (40.3%) had 185 post-baseline UTI episodes, compared to 276 UTI episodes in 122 patients (55.0%) in the placebo group ($p=0.001$). The safety profile of OM-89 was good and consistent with earlier reports. The most frequent adverse event was headache, followed by gastrointestinal events, amounting to respectively 17% and 15% in both groups (Ib).

Another method of immunoactive prophylaxis is intramuscular and intravaginal immunization with heat-killed uropathogenic bacteria. In one small study, 27 adult women with recurrent cystitis (subgroup analysis) were immunized by three intramuscular injections (Solco-Urovac) at biweekly intervals compared to a control group of 26 patients without immunization. Within 6 months, 16/27 (59%) of the immunized were statistically significantly free of recurrent cystitis compared with only 1/26 (4%) of the control patients (118) (Ib).

In a phase 2, double-blind, placebo-controlled trial using a vaginal vaccine, 54 women received either three doses of primary vaccination alone or, in addition, three booster immunizations or placebo. Women receiving six immunizations remained free of infections for a significantly longer period than those receiving placebo or primary immunization (119) (Ib).

Unfortunately, there are no studies comparing directly antimicrobial prophylaxis with immuno-active prophylaxis. However, from the reported results, it seems that the efficacy of antimicrobial prophylaxis is superior to immunization regimens presently available.

Water diuresis may be effective in some women with an uncomplicated UTI, but it often delays more effective management. The evidence is also too weak to recommend that women change their usual habits and menstrual practices or void after intercourse.

2.8 UTIs in pregnancy

Urinary tract infections are common during pregnancy. There is some debate about whether these infections can be classified as uncomplicated, even in cases where no further risk factors besides pregnancy can be found. Bearing this in mind, the three entities, asymptomatic bacteriuria, acute cystitis and acute pyelonephritis, will be discussed in this section with regard only to pregnancy and not to other risk factors.

The factors that predispose a woman to UTI in pregnancy appear to be related to the anatomical and physiological changes in the kidney and urinary tract that occur during pregnancy. The ureters become dilated above the pelvic brim and the bladder is displaced anteriorly and superiorly by the enlarging uterus. Renal blood flow and the glomerular filtration rate increase by about 30-40% during pregnancy and the kidneys become slightly enlarged and hyperaemic. Urine flow may be sluggish and the bladder may not empty completely.

2.8.1 Epidemiology

The prevalence of asymptomatic bacteriuria in American, European and Australian studies varies between 4% and 7% (120). Incidence relates to sexual activity and increases with increasing age and gravidity. It is also higher among patients from lower socio-economic groups. Symptomatic infection occurs in about 1-2% of pregnant women.

Most women acquire bacteriuria before pregnancy. At the first examination, the rates of bacteriuria in pregnant women are similar to those in non-pregnant women with similar risk factors. About 37-57% of bacteriuric schoolgirls develop UTIs during pregnancy. An additional 1% of infections occur during pregnancy (121) (III). In a study conducted in Sweden, the risk of acquiring bacteriuria increased with the duration of pregnancy, reaching a maximum between gestational weeks 9 and 17 (122) (III). Bacteriuria during pregnancy is associated with a significant increase in the number of low-birth-weight infants (≤ 2500 g), low gestational age (< 37 weeks), and neonatal mortality. Women with persistent infection despite treatment or with evidence of 'tissue invasion' are at a higher risk of delivering premature infants. It should, however, be mentioned that bacterial vaginosis is also an important independent risk factor for premature birth; hence, treatment is recommended.

2.8.2 Asymptomatic bacteriuria

Early studies by Kass (121) and others demonstrated that 20-40% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy. Treatment of the bacteriuria lowers this risk (123) (IIa). It is therefore generally recommended that pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated if results are positive (124) (IaA). Wadland and Plante (125) found screening to be cost effective when the prevalence of bacteriuria was > 2%. In socially stable populations with a low prevalence of asymptomatic bacteriuria, screening programmes may be not necessary (125) (IIIB). On the other hand, a sharp reduction in the annual incidence of pyelonephritis could be achieved following the introduction of a programme to screen and treat asymptomatic bacteriuria among pregnant women (123) (IIaB). To avoid unnecessary treatment, asymptomatic bacteriuria is defined as two consecutive positive cultures of the same species. The false-positive rate of a single MSU may be as high as 40% (IIb). Therefore, women with a positive urine culture should be asked to return within 1-2 weeks, at which time, after stressing the importance of a careful cleansing of the vulva before micturition, a second MSU or straight catheter urine specimen is obtained for culture (IIaB).

Treatment should be based on antibiotic sensitivity testing and usually involves a 5- to 7-day course of antibiotics (124) (IIIB); however, some authors recommend short-term therapy, as for acute cystitis (126) (IIaB). Follow-up cultures should be obtained 1-4 weeks after treatment and at least once more before delivery (IIIB). A Cochrane analysis of eight studies involving 400 patients was performed concerning the duration of treatment for asymptomatic bacteriuria during pregnancy (127). All the studies were comparisons of single-dose treatment with 4-7 days of treatment, though it should be noted that the trials were generally of poor quality. The analysis found no difference in 'no-cure' rates between single dose and short course (4-7 day)

treatment for asymptomatic bacteriuria in pregnant women (relative risk 1.13, 95% CI 0.82-1.54), as well as in recurrent asymptomatic bacteriuria (relative risk 1.08, 95% CI 0.70-1.66). However, these results showed significant heterogeneity. No differences were detected for preterm births and pyelonephritis, but the trials involved had a small sample size. Treatment of longer duration was associated with increased adverse events (relative risk 0.53, 95% CI 0.31-0.91). Overall, there was therefore not enough evidence to evaluate whether single dose or longer-duration doses were more effective in treating asymptomatic bacteriuria in pregnant women (C). Since a single dose costs less and is likely to increase patient compliance, this comparison should be explored in an adequately powered randomized controlled trial.

2.8.3 Acute cystitis during pregnancy

Most symptomatic UTIs in pregnant women present as acute cystitis, as occurs in non-pregnant women. Usually a 7-day treatment course is recommended, e.g. with pivmecillinam (128) (IbA). Short-term therapy is not as established in pregnant women as it is in non-pregnant women, but it is recommended by smaller studies and expert opinion (126) (IIaB). Fosfomycin trometamol (3 g single dose) or second- and third-generation oral cephalosporins (e.g. ceftibuten 400 mg once daily) could be considered candidates for effective short-term therapy (129) (IIaB). Otherwise conventional therapy with amoxycillin, cephalexin or nitrofurantoin is recommended (IVC).

Follow-up urine cultures should be obtained after therapy to demonstrate eradication of the bacteriuria. As in non-pregnant women, there is no advantage to be gained by using long-term prophylaxis except for recurrent infections. Low-dose cephalexin (125-250 mg) or nitrofurantoin (50 mg) at night are recommended for prophylaxis against re-infection if indicated, lasting up to and including the puerperium. Postcoital prophylaxis may be an alternative approach (130,131) (IIaB).

2.8.4 Acute pyelonephritis in pregnancy

Acute pyelonephritis tends to occur during the later stages of pregnancy, usually in the last trimester. A review by Gilstrap et al. (132) found acute pyelonephritis in 2% of 24,000 obstetric patients. The incidence is increased in the puerperium. Characteristically, the patient is acutely ill with high fever, leucocytosis and costovertebral angle pain. Bacteraemia is common, but mortality and complications are low when the patient is treated with effective therapy. The major causes of concern are the presence of underlying urological abnormalities and associated risks to the mother and fetus, such as toxaemia, hypertension, prematurity and perinatal mortality.

Currently, antimicrobial therapy is so effective that, even with bacteraemia, almost all patients with uncomplicated pyelonephritis do well and become afebrile within a few days. Recommended antibiotics include second- or third-generation cephalosporins, an aminopenicillin plus a BLI, or an aminoglycoside. During pregnancy, quinolones, tetracyclines and TMP should not be used during the first trimester, while sulphonamides should not be used in the last trimester (133,134). In cases of delayed defeverescence and upper tract dilatation, a ureteral stent may be indicated and antimicrobial prophylaxis until delivery and including the puerperium should be considered (C).

In a Cochrane analysis on treatments for symptomatic UTIs during pregnancy, eight studies were included recruiting a total of 905 pregnant women. In most of the comparisons, there were no significant differences between treatments with regard to cure rates, recurrent infection, incidence of preterm delivery and premature rupture of membranes, admission to the neonatal intensive care unit, need for change of antibiotic and incidence of prolonged pyrexia. Although antibiotic treatment is effective for the cure of UTIs (A), there are insufficient data to recommend any specific treatment regimen for symptomatic UTIs during pregnancy. Complications were very rare. Future studies should evaluate the most promising antibiotics, in terms of class, timing, dose, acceptibility, maternal and neonatal outcomes and costs (135).

2.9 UTIs in post-menopausal women

The normal vagina contains only low numbers of Gram-negative enteric bacteria because of competition from the resident microbial flora. Lactobacilli account for the low vaginal pH. They tend to be less abundant in post-menopausal women and after antimicrobial therapy. Oestrogens are presumed to exert a protective force against recurrent UTIs in post-menopausal women because they enhance the growth of lactobacilli and decrease vaginal pH (136) (IIb). Gram-negative enteric bacteria do not ordinarily colonize the vagina in post-menopausal women unless these women are prone to recurrent UTIs (137) (IIb). In post-menopausal women with recurrent UTIs, therapy with oral (138, 139) or intravaginal oestriol (136) reduced significantly the rate of recurrence (IbA). For other patients, an antimicrobial prophylactic regimen (see previously) should be recommended in addition to hormonal treatment.

In the case of an acute UTI, the antimicrobial treatment policy is similar to that in pre-menopausal women. Short-term therapy in post-menopausal women is not, however, as well documented as in younger women. Raz et al. (140) (Ib) published a study in post-menopausal women (mean age 65 years) with an

uncomplicated UTI in which ofloxacin, 200 mg once daily for 3 days, was significantly more effective in both short- and long-term follow-up than a 7-day course of cephalexin, 500 mg four times daily, even though all the uropathogens were susceptible to the two agents. In another double-blind study (46) (Ib), including a total of 183 post-menopausal women of at least 65 years of age with acute uncomplicated UTI, similar results were obtained with either a 3-day or a 7-day oral course of ciprofloxacin 250 mg two times daily (bacterial eradication 2 days after treatment 98% vs 93%, p=0.16), but the shorter course was better tolerated. The rate of bacterial eradication in this study was generally high and the rate of bacterial resistance to ciprofloxacin low. However, these results should not be extended to the frail elderly population with significant comorbidities, who frequently present with UTI caused by Gram-negative or resistant organisms.

In the case of RUTI, a urological or gynaecological evaluation should be performed in order to eliminate a tumour, obstructive problems, detrusor failure or a genital infection (IVC).

2.10 Acute uncomplicated UTIs in young men

2.10.1 Pathogenesis and risk factors

It has been conventional to consider all UTIs in men as complicated because most UTIs occurring in the newborn, infant or elderly male are associated with urological abnormalities, bladder outlet obstruction or instrumentation. A UTI in an otherwise healthy adult man between the ages of 15 and 50 years is very uncommon. In Norway, a rate of 6-8 UTIs per year per 10,000 men aged 21-50 years has been reported (141).

The large difference in the prevalence of UTIs between men and women is thought to be caused by a variety of factors, including the greater distance between the usual source of uropathogens (the anus and the urethral meatus); the drier environment surrounding the male urethra; the greater length of the male urethra; and the antibacterial activity of the prostatic fluid. It has become clear, however, that a small number of men aged 15-50 years suffer acute uncomplicated UTIs. The exact reasons for such infections are not clear, but risk factors associated with such infections include intercourse with an infected partner, anal intercourse and lack of circumcision (142); however, these factors are not always present. More than 90% of men with febrile UTI (fever > 38.0°C), with or without clinical symptoms of pyelonephritis, have a concomitant infection of the prostate, as measured by transient increases in serum PSA and prostate volume (143), irrespective of prostatic tenderness.

2.10.2 Diagnosis

The symptoms of uncomplicated UTIs in men are similar to those in women. Urethritis must be ruled out in sexually active men using a urethral Gram stain or a first-voided urine specimen wet mount to look for urethral leucocytosis. A urethral Gram stain demonstrating leucocytes and predominant Gram-negative rods suggests *E. coli* urethritis, which may precede or accompany a UTI. Dysuria is common to both UTI and urethritis.

The aetiological agents that cause uncomplicated UTIs in men are also similar to those in women. Krieger et al. (144) noted that 93% of 40 uncomplicated UTIs in men were caused by *E. coli*.

2.10.3 Treatment

Due to the infrequency with which UTIs occur in this group of men, data from controlled treatment studies are non-existent. Empirical use of the agents discussed previously for uncomplicated cystitis or pyelonephritis in women are recommended (IIIB). Nitrofurantoin should not be used in men with a UTI, since it does not achieve reliable tissue concentrations (IVC). For acute uncomplicated pyelonephritis, the use of a fluoroquinolone as initial empirical treatment is recommended in areas where the rate of *E. coli* resistance to fluoroquinolones is low (< 10%) (IIaB). Otherwise, alternative drugs have to be considered (see Table 2.4). Since in most men with febrile UTI or pyelonephritis, prostatic involvement also has to be considered, the goal of treatment is not only to sterilize the urine, but also to eradicate the prostatic infection. Thus, antimicrobials with good prostatic tissue and fluid penetration are preferable, e.g. fluoroquinolones (143) (IIbB).

Although it is possible that short-course treatment is effective in men with uncomplicated cystitis, there are no studies to support this practice. It is therefore recommended that such men receive a minimum of 7 days of therapy because of the relatively greater likelihood of an occult complicating factor in men compared with women (IIIB). Also, longer treatment may reduce the likelihood of persistent prostatic infection. There was, however, no statistically significant difference in outcome when men with febrile UTI were treated orally for 2 or 4 weeks with ciprofloxacin 500 mg twice daily, but the study did not have sufficient statistical power to show equivalence (145) (IIaB). Serum PSA should not be analyzed in conjunction with, or earlier than 6 months after, an episode of febrile UTI, unless prostate cancer is otherwise suspected (143) (IIbB).

The value of a urological evaluation in a man who has had a single uncomplicated UTI has not been determined. Urological evaluation should be carried out routinely in adolescents and in men with febrile UTI, pyelonephritis and recurrent infections, or whenever a complicating factor is present (IIIB).

2.11 Asymptomatic bacteriuria

Asymptomatic bacteriuria is common (146-150). Populations with structural or functional abnormalities of the genitourinary tract may have an exceedingly high prevalence of bacteriuria, but even healthy individuals frequently have positive urine cultures. Asymptomatic bacteriuria is seldom associated with adverse outcomes. Pregnant women (see section 2.8.2) and individuals undergoing traumatic genitourinary interventions are at risk for complications of bacteriuria and show benefit from screening and treatment programmes (124) (IbA). Although some experts (151) recommend screening for renal transplant recipients, the benefits for these patients are less clear; no recommendation can therefore be made (124).

For other populations, including most bacteriuric individuals, negative outcomes attributable to asymptomatic bacteriuria have not been described. Screening for or treatment of asymptomatic bacteriuria is not recommended for the following persons (124):

- pre-menopausal, non-pregnant women (IbA)
- diabetic women (IbA)
- older persons living in community (IIaB)
- elderly institutionalized subjects (IbA)
- persons with spinal cord injury (IIaB)
- catheterized patients while the catheter remains *in situ* (IaA).

In fact, treatment of bacteriuria may be associated with harmful outcomes, such as increased short-term frequency of symptomatic infection, adverse drug effects, and re-infection with organisms of increased antimicrobial resistance. Screening for asymptomatic bacteriuria and treatment is recommended only for selected groups where benefit has been shown (124):

- pregnant women (IbA)
- before transurethral resection of the prostate (IbA) and other traumatic urological interventions (IIaB).

Antimicrobial therapy should be initiated before the procedure (124) (IIaB). Short-term antimicrobial treatment of asymptomatic women with catheter-acquired bacteriuria that persists 48 hours after removal of the indwelling catheter may be considered (124,152) (IIaB).

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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 (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 (B). Surgical re-implantation or endoscopic treatment is reserved for the small number of children with breakthrough infection (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 (A). If the child is severely ill with vomiting and dehydration, hospital admission is required and parenteral antibiotics are given initially (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) (IIa). 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) (IIa).

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) (IIa). 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 UT	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 10^4 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 ≥ 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) (IIa).

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) (III). In contrast, the positive predictive value of significant Gram staining with pyuria is 85% (20) (IIb). 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 ≥ 10 WBC/mm^3 and ≥ 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) (IIa). 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) (IIa).

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) (IIa).

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) (IIa).

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.

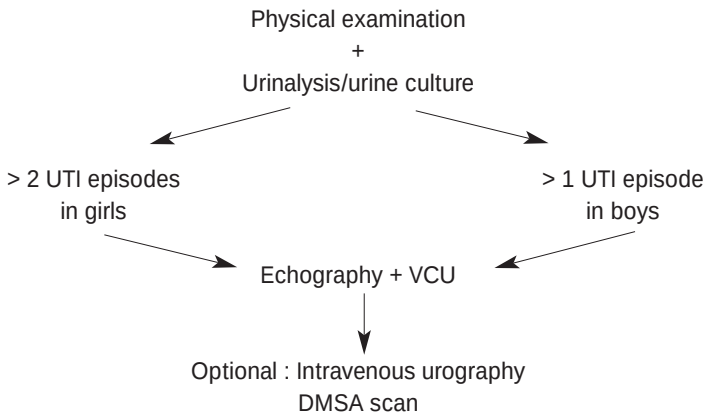
3.7.3.5 Urodynamic evaluation

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

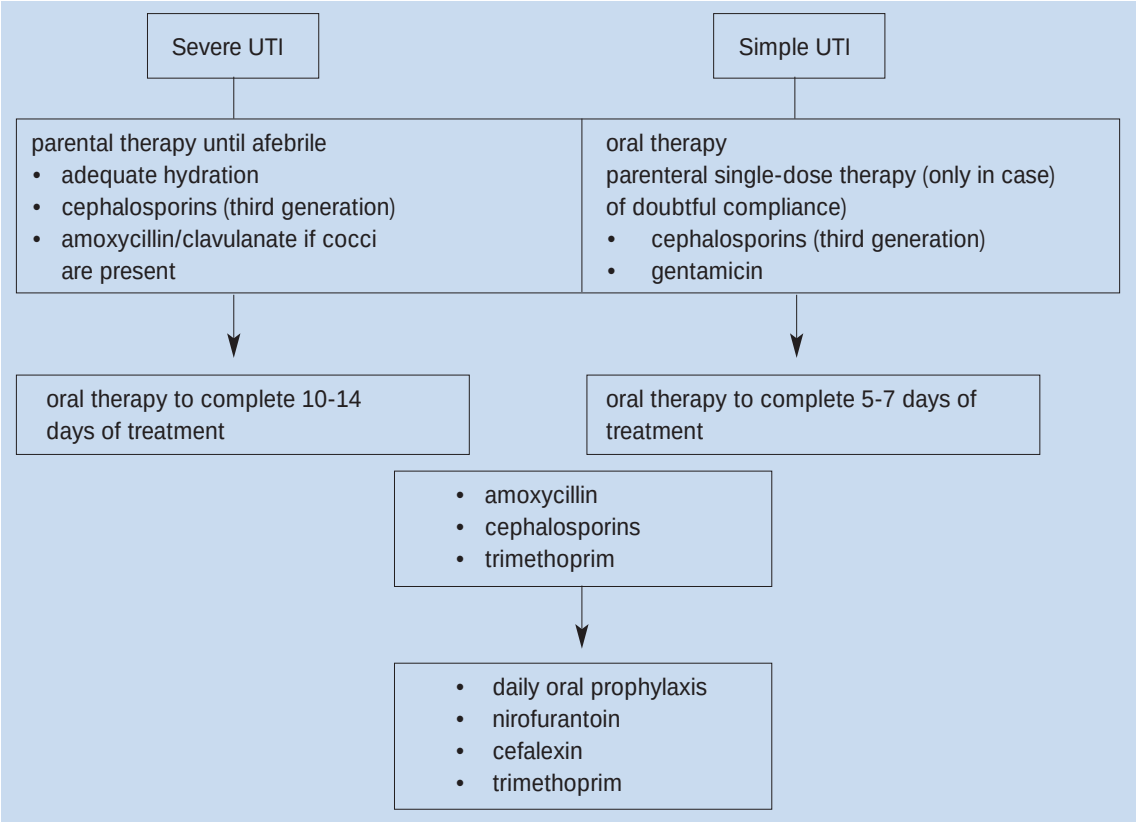
A severe UTI requires adequate parenteral fluid replacement and appropriate antimicrobial treatment, preferably with cephalosporins (third generation). If a Gram-positive UTI is suspected by Gram stain, it is useful to administer aminoglycosides in combination with ampicillin or amoxycillin/clavulanate (59) (IIa). 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) (Ib). A single parenteral dose may be used in cases of doubtful compliance and with a normal urinary tract (66) (IIa). 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) (IIa). 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 Acknowlegement

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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 (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 (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 (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 (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) (IIa). 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) (IIa).

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) (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) (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) (IIb).

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) (IIb). In particular, serum levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) are elevated (12,13) (IIb). Tissue damage is reflected by urinary secretion of tubular proteins and enzymes, such as α2-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) (IIb). 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) (IIb).

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) (IIb).

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) (IIb).

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) (IIa). 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) (IIa). These lesions were found to have persisted 3-6 months later at follow-up in 77% of patients (9) (III).

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 (III). 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) (IIa).

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 (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) (IIa).

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) (Ib), 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 (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) (III)

Tuberculosis and leprosy can cause renal damage through the development of amyloid and also of a form of proliferative glomerulonephritis (32,33). (IIb). 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) (IIb).

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) (III).

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) (IIb). Fluoroquinolones are generally the most effective (A).

After transplantation, overall graft and patient survival rates do not differ between ADPK and control groups (42) (IIa). 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) (III).

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) (IIb).

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) (IIa).

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) (III).

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 12.3. 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. aminoglycosides
•	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 doxycycline

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) (IbA)
•	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) (IIa). 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) (Ib). 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 (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) (III). 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 (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 (1bB).

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* (1bB), 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 (1bB).

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

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 (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.

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6. CATHETER-ASSOCIATED UTIs

6.1 Summary and recommendations

The urinary tract is the commonest source of nosocomial infection particularly when the bladder is catheterized (IIa). Most catheter-associated urinary tract infections are derived from the patient's own colonic flora (IIb).

The predominant risk factor for development of catheter-associated bacteriuria is the duration of catheterization (IIa), with 5% of patients colonized each day. Therefore the majority will become bacteriuric by the thirtieth day, a convenient dividing line between short and long-term catheterization (IIa).

Most episodes of short-term catheter-associated bacteriuria are asymptomatic and caused by a single organism (IIa). Further organisms tend to be acquired by patients catheterized for more than 30 days.

The clinician should be aware of two priorities: the catheter system should remain closed, and the duration of catheterization should be minimal (A).

Whilst the catheter is in place systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended (A). There are exceptions: (a) patients at risk of progression to severe infective complications, (b) patients undergoing urological surgery, (c) implantation of prostheses, (d) patients infected with bacterial strains known to cause bacteraemia (B), (e) specific symptomatic infection (e.g. pyelonephritis, epididymitis), (f) non-specific febrile illness presumed due to uropathogenic bacteraemia following exclusion of other causes of infection.

Definitive antibiotic therapy should be adjusted according to laboratory sensitivities of pathogens. Therefore, before any antibiotic therapy has started, a urine sample for culture has to be taken.

If the likelihood of bacteraemia is low, a short course of treatment is sufficient (5-7 days) (B). If systemic infection is suspected, a longer course will be required (B). Long-term prophylactic antibiotic treatment is virtually always contraindicated (A). Antibiotic irrigation is of no value (A).

Wherever possible, when antibiotics are given for symptomatic catheter related infection, urine should be cultured and the catheter changed. Similarly, when catheterization is finally discontinued, urine should always be cultured (A). Arguably, a single dose or short course of antibiotics should be given whenever a catheter is changed or removed (B).

Routine urine cultures in the asymptomatic catheterized patient are not recommended (C).

Carers should be constantly aware of the risk of cross-infection between catheterized patients and should observe protocols on hand washing and the use of disposable gloves (B).

Clinicians should always consider alternatives to indwelling urethral catheters, which are less prone to causing symptomatic infection (e.g. suprapubic catheters, condom drainage systems, intermittent catheterization) (A).

A minority of patients can be managed with the use of the non-return valve avoiding the closed drainage bag. Intuitively, such patients exchange the convenience of on-demand drainage and the possible benefit of intermittent expansion of the bladder with an increased risk of a significant infection.

Patients with urethral catheters in place for five years or more should be screened annually for bladder cancer (B).

6.2 Background

Forty per cent of nosocomial infections originate in the urinary tract. The majority of patients have chronic indwelling catheters (80%) (1-5) (III).

In the 1920s, Foley introduced the self-retaining catheter. However, initially it was used with open drainage, and bacteriuria was virtually universal by the end of the fourth day. With the introduction and development of plastics technology and the design of suitable receptacles, closed-catheter systems were introduced. Development of bacteriuria was delayed but still universal after 30 days (1,6,7) (IIa,III). A control trial comparing open with closed catheters was never performed and quite soon it became clear that there was little point in stating the obvious and closed systems became the standard. Interestingly, there has been a recent relaxation of the closed-system principle with the development of the so-called flip valve allowing a patient to void intermittently through an open catheter.

6.3 Risk of bacteriuria

An indwelling catheter bypasses normal urethral host defences, so allowing continuous access of organisms to the urinary tract. Multivariate analyses have emphasized that the duration of catheterization is the most important risk factor in the development of catheter-associated bacteriuria (8-12) (IIa,III). The duration of catheterization is influenced by the indication:

(a) routine abdominal surgery (1 to 7 days)
(b) measurement of urine output in the context of critical care (7-30 days)
(c) acute and chronic urinary retention (1 to more than 30 days)

(d) urinary incontinence (more than 30 days).

Other risk factors include the following (11,13-15) (IIa):

(a) colonization of the drainage bag, catheter and periurethral segment
(b) diabetes mellitus
(c) female patient
(d) renal function impairment
(e) poor quality of catheter care.

6.4 Pathogenesis

The urethral catheter can inhibit or bypass some defence mechanisms which would normally prevent or minimize bacteria-epithelial cell interactions, e.g. GAG layer, biofilm formation.

Bacteria can enter the urinary tract in catheterized patients through the following routes:

6.4.1 At the time of catheter insertion

This may be a consequence of inadequate cleansing of the introitus, distal urethra and perineum. There is unlikely to be any consequence in otherwise healthy individuals. It would be responsible for the bacteriuria seen in patients on intermittent clean catheterization, where very little attempt is made to cleanse the 'entry points' before introduction of the catheter. It is doubtful whether such cleansing is of any significant benefit, but introduction of organisms at the time of catheterization could be critical in hospitalized patients. Up to 20% of individuals will be colonized immediately after catheterization (9,11) (IIa,III).

6.4.2 After catheter insertion

Long-term catheterization will promote the development of a mucous sheath developing loosely between the catheter and urethral mucosa. This provides a favourable environment for bacterial invasion and perforation. Arguably, it is responsible for a greater proportion of bacteriuria in women (70-80%) than in men (20-30%) (13-15) (III).

In males the predominant route is through the lumen of the catheter and collecting system by retrograde spread, i.e. ascending infection against the flow of urine. The taps of the drainage bags commonly become contaminated and regular opening of these and the connecting points, which may become disconnected for the purposes of bladder washout or urine collection, will promote entry of bacteria into the system.

6.4.3 Biofilm infection

Biofilm is an accumulation of micro-organisms and their nucleic acid fragments within a mucopolysaccharide medium, which together form a structured community on a solid surface. Biofilms are ubiquitous. In the context of urological practice they can be demonstrated on catheters, drainage bags and other foreign bodies and prostheses (16). They can also be found within renal scars at sites of chronic infection (e.g. prostatitis, epididymitis) (IIb).

Biofilm is composed of three layers: (a) the linking film, attached to the surface tissue or biomaterial, (b) the base, and (c) the surface film adjacent to the lumen and into which planktonic organisms can be released. These organisms are frequently derived from subcellular fragments growing within the basal layer (16-19) (IIb). Organisms within the biofilm appear to be well protected from the mechanical flow of urine, other host defences and antibiotics. Conventional laboratory testing can of course firmly detect planktonic free-floating bacteria within the urine or occasionally in the tissue. However, bacterial fragments from within the substance of the biofilm will not grow on standard media (16,17,20-24) (IIa,III).

6.5 Methods of catheterization and risk of UTI

6.5.1 Single catheterization - 'in-out'

Bacteriuria develops in 1-5% of patients (7,13,14) (III). The risk is increased in females, patients with retention, peripartum catheterization, prostatic obstruction, diabetes mellitus, debilitation and the elderly (25) (III).

6.5.2 Short-term catheterization

This might be done to monitor patients under critical care or those who are unable to void or who are incontinent. Between 15% and 25% of patients admitted to hospital may be catheterized between 2 and 4 days during their stay (7,14) (III). Between 10% and 30% will develop bacteriuria (3,26,27) (IIa,III).

Most episodes of short-term catheter-associated bacteriuria are asymptomatic and are caused by single organisms. 15% may be polymicrobial (5) (III), reflecting the prevailing flora in hospital or community environments. Therefore the most common species are *E. coli*, *Pseudomonas aeruginosa, Klebsiella*

pneumoniae, Proteus mirabilis, Staphylococcus epidermidis, Enterococcus spp. and *Candida* spp. (7,13,14) (IIb). Most catheter-associated bacteriurias are accompanied by pyuria.

The incidence of bacteraemia is significantly high in patients with long-term catheters who undergo instrumentation for endoscopic surgery, e.g. TURP (28) (IIb).

Despite the high amount of bacteriuria in patients with long-term indwelling catheters, symptomatic manifestations occurring either through ascending infection or through bacteraemia are surprisingly unusual. Studies in a long-term facility identify UTIs as a source of less than 10% of febrile episodes (14) (III). Thus, if a significant febrile event develops in a catheterized patient, it is extremely important to rule out other sources.

Transient asymptomatic bacteraemia is common during initial catheter insertion or during exchanges in chronically catheterized patients (29) (III). Rather surprisingly, the risk of bacteraemia occurring during initial catheter insertion is similar, whether there is a pre-existing UTI (7%) or when the urine is sterile (8.2%) (30,31) (IIa). The relatively low incidence of febrile UTI and bacteraemia may be due to the fact that colonization is by less virulent organisms. For example, in a catheter-associated infection with *E. coli*, the *E. coli* micro-organisms may lack P fimbriation (32) (IIb).

The evidence for the presence of an indwelling catheter as a risk factor for serious morbidity or death is surprisingly equivocal. There seems little doubt that the death rate after TURP and similar operations is approximately doubled in catheterized patients and yet data from the National Infections Surveillance survey and from elsewhere indicate that catheter-associated infections have a low risk of mortality even in elderly patients (33-36) (IIa,III). Studies that concentrate on nosocomial catheter-associated bacteraemia indicate that contributable mortality varies between 9% and 13% (37,38). Other risk factors include the severity of comorbid disease in appropriate antibiotic therapy, presence of infection at another site, and possibly the presence of an unrecognized urological abnormality (39) (III).

6.5.3 Long-term catheterization

Bacteriuria with at least one strain is universal, while most patients are infected with two or more strains (40,41) (IIb). The commonest infecting organism is *E. coli*. Persistence is related to the presence of type 1 pilus, an adhesin for uroepithelium and Tamm-Horsfall protein. Another organism rarely found outside of the catheterized urinary tract is *Providencia stuartti* (40,42) (IIb,III). For this organism, the adhesins MR/K are more common (38,43) (IIb). Other associated flora include *Pseudomonas, Proteus, Morganella* and *Acinetobacter species*. Bacteriuria is polymicrobial in up to 95% of urine specimens (7,13,14,42) (IIb,III). One-quarter of organisms in catheter urine are not present in urine simultaneously obtained by suprapubic bladder puncture, suggesting that some organisms only colonize the catheter (44) (IIb).

It is self-evident that long-term catheterization can lead to long periods of obstruction of the lower urinary tract due to catheter blockage, urinary tract stones, epididymitis, prostatitis and scrotal abscess (7,13,14,45-48) (IIa,III). Nevertheless, over 30% of patients dying with long-term catheters in place, who were afebrile at the time of death, were shown to have autopsy findings of acute pyelonephritis (49-51) (III).

Up to 50% of patients undergoing catheterization for more than 28 days' experience recurrent encrustation and catheter blockage (45-48) (IIa). Intermittent urinary retention can lead to VUR and ascending complicated infection. Infecting organisms often include *P. mirabilis* on account of its properties as a potent producer of urease, which promotes the development of struvite stones by mechanisms which include hydrolysis of urea to ammonium (7,13,14,45-48) (IIb,III).

Bladder catheterization for more than 10 years as in patients with a spinal injury suggests that there is an increased risk of bladder cancer (52,53) (IIa).

6.6 Alternative methods of urine drainage

Prevention of catheter-associated infection may be accomplished by finding alternatives to indwelling catheterization and perhaps treatment of bacteriuria.

6.6.1 Intermittent catheterization

This has proved popular in the management of voiding dysfunction due to a wide variety of causes, including the neuropathic bladder. Bacteriuria is acquired at the rate of approximately 1-3% per catheterization. Therefore it is universal by the end of the third week (54-57) (III). Intuitively it would be expected that local periurethral infection, febrile episodes, stones and deterioration of renal function would all be much less common than for patients permanently catheterized, but there have been no well-designed comparative studies. Complications include the following: bleeding, urethral inflammation stricture, false passage, epididymitis, bladder stone, and hydronephrosis.

A randomized study showed no difference in symptomatic UTIs between clean and sterile intermittent catheterization, though obviously the former was associated with reduced costs (58) (1b). In patients with non-spinal cord injury, however, the incidence of UTI was less frequent with sterile than with non-sterile intermittent cathetierization (59) (Ib). The EAU guidelines recommend aseptic IC as the method of choice in patients with

neurogenic lower urinary tract dysfunction. Benefits from prophylactic antibiotics and antibacterial substances, such as methenamine and instillation of povidine-iodine and chlorhexidine preparations, have never been established.

6.6.2 Suprapubic catheterization

This is used principally in patients undergoing urological or gynaecological procedures. They offer several advantages over urethral catheterization, particularly in terms of patient comfort. Clamping of the suprapubic catheter can facilitate testing of voiding through the urethra. Suprapubic catheterization is associated with a lower incidence of bacteriuria and, of course, urethral strictures and pain (60-64) (III). Again, there has been no convincing randomized trial.

6.6.3 Condom catheters

This can be useful in male patients without outlet obstruction. However, condom drainage may be unsatisfactory in the confused or uncooperative patient or where there is obesity and/or a short penis. Skin maceration and ulceration can occur. Evidence suggests that condom catheters offer a substantially lower incidence of bacteriuria compared with long-term urethral catheterization (65,66) (III).

6.6.4 Urethral stents/prostheses

Surprisingly, there is little evidence for a significant increase in bacteriuria or clinical UTI with a variety of urethral inserts and stents. They are often inserted in the prostate for a variety of indications, including neurogenic bladder dysfunction, prevention of strictures and the treatment of urinary retention.

Bacteriuria, which is usually asymptomatic, occurs in 10-35% of patients (67-74) (III). Urethral inserts have also been used as occlusive devices in the treatment of genuine stress incontinence. Approximately 50% achieved satisfactory control (67) (III).

6.6.5 Urinary diversion

Occasionally, construction of a continent or non-continent reservoir using bowel segments is offered as an alternative to indwelling catheterization. The rate of bacteriuria is variable, but with some varieties of reconstruction, particularly incontinent urinary diversion through a conduit, it may be universal (75,76) (III).

6.7 Prevention of catheter-associated bacteriuria

6.7.1 Catheter care

The following recommendations will be very familiar (7,77,78) (III). An indwelling catheter should be introduced using antiseptic conditions. Urethral trauma should be minimized by the use of adequate lubricant and the smallest possible catheter size. Poor-quality evidence indicates that the use of sterile or clean technique or an antiseptic gel makes no difference with respect to risk of bacteriuria (79,80) (IIa). Closed drainage was thought to be mandatory.

However, there seems to be a resurgence of interest in the use of the flip valve as a replacement for the daytime catheter bag. Although the valves have not been formally studied, it is expected that risk of colonization of such a device will be assessable, although perhaps outweighed by the convenience of facilitating intermittent voiding. It is self-evident that adequate urine flow must be ensured and preferably sufficient fluids given orally to maintain an output of more than 100 mL/hour. Bacteraemia is not prevented by topical antiseptics or antibiotics applied to the catheter, urethra or meatus.

There is no consensus on the time before routine catheter changes are made. This may be dictated by the manufacturer's instructions and conditions for indemnity. Shorter periods may be necessary if there is catheter malfunction or leakage. Catheters should always be changed under high-dose broad-spectrum parenteral antibiotics, which are also given where there is febrile infection (7,15,25) (III). Once the catheter has been removed, a follow-up urine culture should be undertaken.

6.7.2 Additional methods of prevention

Materials scientists have varied the physical and chemical composition and coatings in the manufacture of catheters and stents. Clearly the object is to delay the onset of bacteriuria and to prevent bacterial adherence and growth.

The local host inflammatory response and tissue necrosis associated with catheter use are greatest with natural rubber, but less with latex and minimal with silicone (81) (IIa). Latex catheters are the least expensive but irritation and allergic reaction may occur (46) (IIa). Silicone catheters offer no advantage over latex, although they are more comfortable and therefore a better choice for long-term usage. Silicone is less subject to encrustation than latex. Teflon or even silicone-coated latex is still more prone to catheter encrustation (82-88) (IIa). Other strategies have included the incorporation of biocides or antibiotics into the

catheter material or development of materials with surface properties preventing adherence of bacterial cells. A thin layer of polymer matrix covering the biomaterial surface may assist the metered release of drugs into the urine. Unfortunately, whatever the agent, such specialist catheters seem to offer no advantage in terms of long-term prevention of bacteriuria (84-88) (IIa), but may possibly be effective during short-term catheter use, particularly in intensive care units (84-88) (IIa).

Silver oxide coating may delay bacteriuria in short-term use, but silver alloy-coated catheters seem to be more effective by precipitating membrane proteins of surface-associated bacteria and inhibiting colonization. Silver ions bound to murein are bacteriostatic, whereas at higher silver concentrations the silver ions may be bactericidal (89,90) (IIb). Phosphorylcholine and heparin coating may also inhibit encrustation and biofilm formation (46,91-94) (IIa).

Finally, there may be some application in the use of continuous electric current applied to the catheter surface (i.e. electromechanical dissociation). As yet, no device has been developed for clinical use.

6.8 Treatment

6.8.1 Treatment of asymptomatic bacteriuria

Asymptomatic bacteriuria should in general not be treated as it would only select complications of resistant organisms. Obviously there are occasional exceptions (7,25,95-97):

(a) treatment may be part of a plan to control nosocomial infection by a particularly virulent organism which is prevalent in a treatment unit
(b) patients who have a high risk of serious complications (granulocytopenia)
(c) patients undergoing urological surgery or implantation of prostheses
(d) patients with recurrent catheter obstruction and persistent infection with *Proteus* spp.
(e) patients infected with strains causing a high incidence of bacteraemia, e.g. *Serratia marcescens.*

Usually, after catheter removal, the urinary tract will clear bacteria spontaneously (97,98) (III). However, elderly females may need treatment, since bacteriuria in these patients may not resolve spontaneously (99) (IIa).

6.8.2 Treatment of symptomatic UTI

Parenteral antibiotics should be administered to catheterized patients who are febrile and ill, particularly if the blood culture is positive, though the results of culture may not become available in time to influence treatment decisions. Of course, other causes for pyrexia should be considered. Catheter removal should be considered as part of the treatment of symptomatic catheter-associated bacteriuria with the rationale that bacteria are sequestered within the biofilm coating the external and internal catheter surfaces (99-102) (IIb,III).

After the initial administration of empirical treatment, the choice of antibiotic may need to be adjusted based on culture results of the urine and the catheter itself. Therefore before any antibacterial therapy is initiated, a urine sample for culture has to be taken.

In general broad-spectrum antibiotics should be given. If the urine shows no Gram-positive cocci, an aminoglycoside can be used alone. As soon as the results of the urine culture are available the initial empirical treatment can be adjusted according to the sensitivities of the pathogens. Treatment for 10-14 days is usually required (99) (Ib).

When the blood culture is negative and/or symptoms are minor, patients can be treated with short courses of oral antibiotics (3-5 days). This will usually sterilize the urine without selecting more resistant bacteria (7,99) (IIa,III). Occasionally, culture may show candidal infection. This is usually asymptomatic and resolves without treatment. If the infection is complicated, systemic therapy with amphotericin or fluconazole may be indicated (103,104) (IIa).

Long-term antibiotic treatment is not effective because the catheter acts as a foreign body. Urine cannot be permanently sterilized (7,99-102) (IIa,III).

6.9 Prevention of cross-infection

Periurethral bacterial flora in the mucous sheath, surfaces of the catheter and drainage system, the reservoir of contaminated urine contained within it and the skin of the patient provide a source of infection to be readily transmitted on the hands of the medical and nursing staff (95-97,106) (IIb,III). This may be reduced by treating the catheterized urinary tract as an open wound, and therefore using gloves after hand washing in antiseptic solutions (100,105,106) (IIa,III). The addition of antimicrobial agents to the urine drainage bag or the use of oral methenamine, which theoretically results in the release of formaldehyde into the urine, should perhaps be revisited (7) (IV).

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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 (IaA). The drainage of any obstruction in the urinary tract is essential as first-line treatment (IbA).

Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists (IIaB).

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 (IIaB).

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: Temperature > 38°C or < 36°C Heart rate > 90 beats min Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (< 4.3kPa) 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-α (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 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 ≥ 25 or the presence of ≥ 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.

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8. URETHRITIS

8.1 Definition

Primary urethritis has to be differentiated from secondary urethritis, which may 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 (3).

8.2 Epidemiology

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

8.3 Pathogens

Pathogens include *N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium* and *T. vaginalis*. The frequency of the different species varies between patient populations (4-8). *Mycoplasma hominis* probably does not cause urethritis, while *Ureaplasma urealyticum* is an infrequent cause. In most cases, clinical evidence of *Mycoplasma* or *Ureaplasma* is due to an asymptomatic colonization 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*) causing a pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the genito-urinary tract to cause epididymitis in the male or cervicitis, endometritis and salpingitis in the female.

8.5 Clinical course

Purulent discharge and alguria 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 showing more than five leucocytes per high power field (x 1,000) and, eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis. A positive leucocyte esterase test or > 10 leucocytes per high power field (x 400) in the first voiding urine specimen are 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* can usually be identified microscopically.

8.7 Therapy

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

- Cefixime, 400 mg orally as a single dose
- Ceftriaxone, 125 mg intramuscularly (with local anaesthetic) as a single dose
- Ciprofloxacin, 500 mg orally as single dose
- Ofloxacin, 400 mg orally as single dose
- Levofloxacin, 250 mg orally as as single dose.

Please note that fluoroquinolones, such as ciprofloxacin, levofloxacin, and ofloxacin, are contraindicated in adolescents (<18 years) and pregnant women.

As gonorrhoeae is frequently accompanied by chlamydial infection, an antichlamydial active therapy should be added. The following treatments have been successfully applied in *C. trachomatis* infections.

As first choice of treatment:

- Azithromycin, 1 g orally as single dose
- Doxycycline, 100 mg orally twice daily for 7 days.

As second choice of treatment:

- Erythromycin base, 500 mg orally four times daily for 7 days
- Erythromycin ethylsuccinate, 800 mg orally four times daily for 7 days
- Ofloxacin, 300 mg orally twice daily for 7 days
- Levofloxacin, 500 mg orally once daily for 7 days.

Doxycycline and azithromycin are considered to be equally effective in the treatment of chlamydial infections. Erythromycin is less effective and causes more side effects. Since in pregnant women fluoroquinolones and doxycycline are contraindicated, besides erythromycin and azithromycin a regimen with amoxicillin 500 mg three times daily for seven 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 sexually transmitted diseases, the treatment of sexual partners is necessary.

8.8 Prevention

Patients with sexually transmitted urethritis should avoid unprotected sexual contact for the duration of the treatment and until symptoms have disappeared.

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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 (IIIB). In less severe cases, a fluoroquinolone may be given orally for 10 days (IIIB).

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 (IIIB).

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 8.3).

Other inflammatory markers include elevated pH, lactate dehydrogenase (LDH) and immunoglobulins (20). The cytokines, interleukin (IL)-1ß and tumour necrosis factor (TNF)-α, 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 Isolation of an aetiologically recognized organism from the prostatic fluid/urine
Chronic abacterial prostatitis	Significant prostatic inflammation 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 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) (IIbB), 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 (IIbB).

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) (IIIB).

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) (IIaB). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given (33,38) (IIbB).

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) (IbB). 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) (IbB). 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			
	• Favourable pharmacokinetics • Excellent penetration into the prostate • Good bioavailability • Equivalent oral and parenteral pharmacokinetics (depending on the substance) • Good activity against 'typical' and atypical pathogens and *Pseudomonas aeruginosa* • In general, good safety profile	Depending on the substance: • Drug interactions • Phototoxicity • Central nervous system adverse events	Recommend
Trimethoprim			
	• Good penetration into prostate • Oral and parenteral forms available • Relatively cheap • Monitoring unnecessary • Active against most relevant pathogens	• No activity against *Pseudomonas*, some enterococci and some Enterobacteriaceae	Consider
Tetracyclines			
	• Cheap • Oral and parenteral forms available • Good activity against *Chlamydia* and *Mycoplasma*	• No activity against *Ps. aeruginosa* • Unreliable activity against coagulase-negative staphylococci, *E.coli*, other Enterobacteriaceae, and enterococci • Contraindicated in renal and liver failure • Risk of skin sensitization	Reserve for special indications
Macrolides			
	• Reasonably active against Gram-positive bacteria • Active against Chlamydia • Good penetration into prostate • Relatively non-toxic	• Minimal supporting data from clinical trials • 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) (IbB). Pentosan polysulphate sodium may reduce symptoms and improve quality of life in patients with CPPS (42) (IIaB). Finasteride will provide some improvement for patients with category IIIA prostatitis (43) (IbB).

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) (IIaB). 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) (IbB). 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) (III). Acute epididymitis in young males is associated with sexual activity and infection of the consort (3) (III).

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) (III). The majority of cases of epididymitis are due to common urinary pathogens, which are also the most common cause of bacteriuria (2, 6) (III). 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) (III).

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) (III).

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) (IIa).

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 (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 (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 (C).

In case of *C. trachomatis* epididymitis, the sexual partner should also be treated (C). If uropathogens are found as causative agents, a thorough search for micturition disturbances should be carried out to prevent relapse (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. PERI-OPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

11.1 Summary

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

There is no evidence for any benefits of antibiotic prophylaxis in standard non-complicated endoscopic procedures and extracorporeal shockwave lithotripsy (ESWL), though it is recommended in complicated procedures and patients with identified risk factors.

For open surgery, the same rules as in abdominal surgery can be applied. No antibiotic prophylaxis is required for clean operations, while a single or 1-day dosage is recommended in clean-contaminated operations. Opening of the urinary tract should be considered as clean-contaminated surgery.

It is essential to categorize patients according to risk factors for infection. These include:

- history of genitourinary infection
- previous instrumentation
- assumed bacterial colonization
- prolonged hospital or institutional stay
- risk factors related to general health, e.g. diabetes mellitus, impaired immune system, malnutrition.

A single dose or a short course of antimicrobials can be given, either parenterally or orally. The administration route will depend on the type of intervention and patient characteristics. Oral administration requires drugs having good bioavailability. In a case of continuous urinary drainage, prolongation of peri-operative antibiotic prophylaxis is not recommended.

Many antibiotics are suitable for peri-operative antibacterial prophylaxis, e.g. second-generation cephalosporins, co-trimoxazole-sulphamethoxazole (TMP-SMZ), fluoroquinolones, aminopenicillins plus a beta-lactam inhibitor (BLI), and aminoglycosides. Broader-spectrum antibiotics should be used sparingly 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.

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 (1-5).

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 (6), the French Association of Urology (7) and the Swedish-Norwegian Consensus Group (8).

A recent Pan-European survey was carried out by the European Society for Infection in Urology, which is associated to the EAU 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) (9). The result 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 peri-operative antibacterial prophylaxis

Antibiotic prophylaxis and antibiotic therapy are two different issues. Antibiotic prophylaxis aims at preventing healthcare-associated infections resulting 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 (10). These definitions were also used in the recent Pan-European study on NAUTI (see above) (9). Revision of definitions and recommendations are on-going in some countries (11). Table 11.1 illustrates the different types of infectious complications encountered in urological surgery.

Table 11.1: Main types of healthcare associated infections encountered in urological practice

Site of infection	Minor	Major
Surgical wound	Superficial wound infection	Deep wound infection
		Wound rupture (abdominal dehiscence)
		Deep abdominal or surgical site abscess
Urinary tract	Asymptomatic bacteriuria (bacterial colonization)	Febrile genitourinary infection
		Pyelonephritis
		Renal abscess
Other urogenital sites	Epididymitis	Acute bacterial prostatitis
Other sites	Bacteraemia	Sepsis
		Pneumonia
		Septic embolism

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

The endpoints of peri-operative 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 11.1). 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 transurethral resection of the prostate (TURP) or other endourological procedures may disappear spontaneously and is usually of no clinical significance. Another question is whether peri-operative prophylaxis should also be concerned with the prevention of non-urological infections, e.g. endocarditis and post-operative pneumonia. Obviously, peri-operative 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 11.2) are underestimated in most trials. However, they are important in pre-operative assessment of the patient. They are related to: (a) general condition of the patient, (b) special risk factors, which are either endogenous (e.g. urinary tract stone, bacteriuria, impaired renal function), or exogenous (e.g. catheters, ureteral stents or prosthetic devices) procedures.

The traditional classification of surgical procedures according to Cruse and Foord (12) into clean, clean-contaminated, contaminated, and dirty operations applies to open surgery but not to endourological interventions. It is still controversial 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. The classification of transurethral surgery is also controversial, but considered by the members of the EAU Expert Group as clean-contaminated because the lower genitourinary tract is colonized by a microflora, even in the presence of sterile urine (5,13,14).

Table 11.2: Generally accepted risk factors for infectious complications

General risk factors	Special risk factors associated with an increased bacterial load
High age	Long pre-operative hospital stay or recent hospitalization
Deficient nutritional status	History of recurrent genitourinary infections
Impaired immune response	Surgery involving bowel segment
Diabetes mellitus	Colonization with micro-organisms
Smoking	Long-term drainage
Extreme weight	Urinary obstruction
Co-existing infection at a remote site	Urinary stone
Lack of control of risk factors	

The Pan-European study on NAUTI (9) identified the three most important risk factors for infectious complications as:

(a) an indwelling catheter
(b) previous urogenital infection

(c) long pre-operative 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 (5).

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 (14,15). It is essential to individualize the choice of antibiotic prophylaxis according to each patient's cumulative risk factors (16). Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection (17-19).

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 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 hours before but not later than 3 hours after the start of an intervention (20-22). For practical purposes, oral antibiotic prophylaxis should be given approximately 1 hour 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 (23). It is worth noting that a bloodstream infection can develop in less than an hour (20).

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 hours before intervention. Giving 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, this issue has not yet been adequately addressed and cannot be answered. In principle, the duration of peri-operative prophylaxis should be minimized, ideally to a single pre-operative antibiotic dose. Peri-operative prophylaxis should be prolonged only where there are significant risk factors (see Section 11.4) (C).

11.5.4 Choice of antibiotics

No clearcut recommendations can be given, as there are considerable variations in Europe regarding both bacterial spectra and susceptibility to different antibiotics. Antimicrobial resistance is usually higher in the Mediterranean countries compared with the Northern European countries; resistance is correlated with an up to four-fold difference in sales of antibiotics (24). 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, the contamination load, the target organ, and the role of local inflammation.

In general, many antibiotics are suitable for peri-operative antibacterial prophylaxis, e.g. second generation cephalosporins, TMP-SMZ, fluoroquinolones, aminopenicillins plus a BLI and aminoglycosides. Broader-spectrum antibiotics should be used sparingly and reserved for treatment. This applies also to the use of vancomycin.

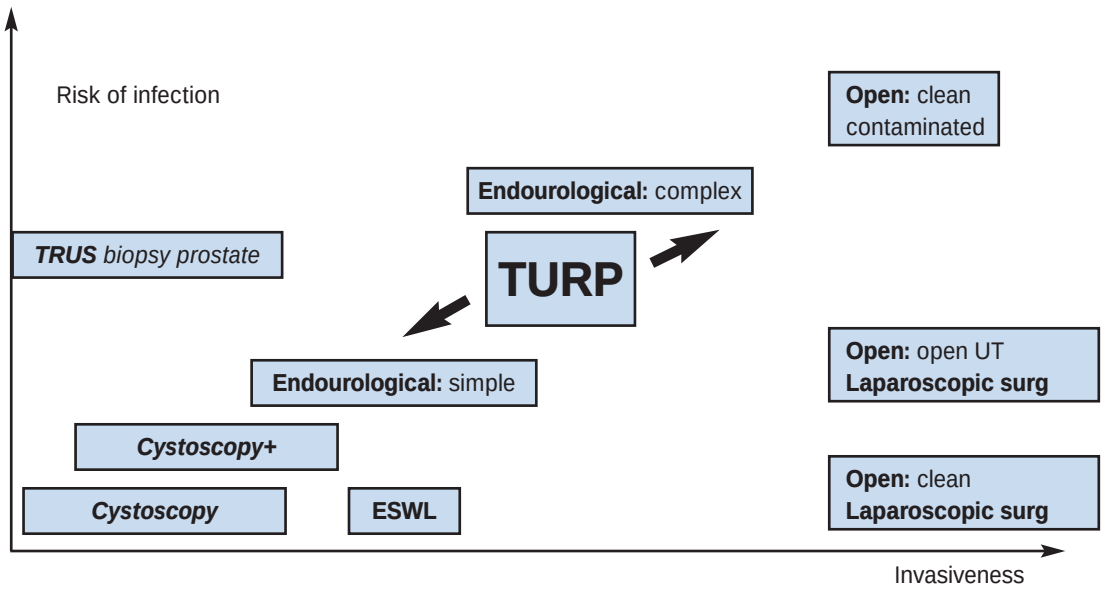
11.6 Prophylactic regimens in defined procedures

The list of major urological diagnostic and therapeutic procedures is given in Table 11.3 and the empirical relationship between the level of invasiveness and risk for infective complications is illustrated in Figure 11.1.

Table 11.3: 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 nephrone-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 is summarized in Table 11.4 and Appendix 12.4.

11.6.1. Diagnostic procedures

Antimicrobial prophylaxis in core biopsy of the prostate is generally recommended (25,26) (A). However, the choice of regimens remains debatable. Most regimens used are effective and recent studies suggest that one-day doses and even single doses are sufficient (27,28) (IbA).

No benefit of antibiotic prophylaxis has been reported for cystoscopy, urodynamic examinations and diagnostic simple ureteroscopy. However, bacteriuria, indwelling catheter and a history of genitourinary infection are risk factors that must be considered (29,30) (IbA).

11.6.2. Endo-urological treatment procedures

There is little evidence for benefit of antibiotic prophylaxis in transurethral resection of a bladder tumour (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 (IIIC).

Transurethral resection of the prostate is the best-studied urological intervention. A meta-analysis of 32 prospective, randomized and controlled studies, including more than 4,000 patients, showed a benefit of antibiotic prophylaxis with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively (31) (IaA). There is a difference between smaller resections in healthy patients and large resections in at-risk patients (Figure 11.1).

There are few studies defining the risk of infection following ureteroscopy. No clearcut evidence exists. It is reasonable, however, to distinguish between 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 the surgeon's experience) also need to be considered in the choice of regimen (5,32-34) (IIbB).

ESWL is one of the most commonly performed procedures in urology. No standard prophylaxis is recommended. However, prophylaxis must be considered in cases of internal stent and treatment due to the increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, infectious stones) (35) (IbA).

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 surgery. However, it seems reasonable to manage laparoscopic surgical procedures in the same manner as the corresponding open procedures (IVC).

11.6.4. Open urological operations without bowel segment, with or without opening of the urinary tract

No standard antibiotic prophylaxis is recommended in clean operations. In a case of opening of the urinary tract, a single peri-operative parenteral dose is recommended. This is particularly true for open enucleation of prostatic adenoma for which there is a very high risk of post-operative infection (36) (IIbB).

11.6.5. Open urological operations with bowel segment

Antibiotic prophylaxis is recommended as for clean-contaminated operations in general surgery. Single-dose or one-day dosage is recommended, although prolonged operation and other morbidity risk factors may support the use of a prolonged regimen, which should be less than 72 hours. The choice of antibiotic should focus on both aerobic and anaerobic pathogens. Evidence is based on colorectal surgery (IaA), but the experience is limited as for specific urological interventions (IIIB).

11.6.6. Post-operative drainage of the urinary tract

When continuous urinary drainage is left in place after surgery, the prolongation of peri-operative antibacterial prophylaxis is not recommended unless a complicated infection requiring treatment is suspected. Asymptomatic bacteriuria (bacterial colonization) is only to be treated prior to surgery or after removal of the drainage tube (IIIB).

11.6.7. Implant 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 (37-39) (IIaB).

Table 11.4: recommendations for antibiotic prophylaxis in standard urological surgery

Procedure	Pathogens (expected)	Prophylaxis	Antibiotics	Remarks
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes?	All patients	Fluoroquinolones TMP ± SMX Metronidazole?	Short course (<72h)
Cystoscopy Urodynamic examination	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd generation TMP ± SMX	Consider only in risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd generation TMP ± SMX	Consider in risk patients
Endourological surgery and ESWL				
ESWL	Enterobacteriaceae Enterococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI[a]	In patients with stent or nephrostomy tube Consider in risk patients
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI Fluoroquinolones	In patients with stent or nephrostomy tube Consider in risk patients
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI Fluoroquinolones	Short course Length to be determined Intravenous suggested
TUR of the prostate	Enterobacteriaceae Enterococci	All patients (see Section 10.6.2)	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI	Low-risk patients and small-size prostate require no prophylaxis
TUR of bladder tumour	Enterobacteriaceae Enterococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI	Consider in risk patients and large necrotic tumours
Open urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter- associated uropathogens	No		Consider in high-risk patients Short post-operative catheter treatment
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	Cephalosporin 2nd or 3rd generation TMP + SMX Aminopenicillin/BLI	Single peri-operative course
Clean-contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	Cephalosporin 2nd or 3rd generation Metronidazole	As for colonic surgery
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients	Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)	
Laparoscopic procedures				As for open surgery

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

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12. APPENDICES

12.1 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 $\geq 10^3$ 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 $\geq 10^4$ 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 $\geq 10^5$ cfu/mL* in women $\geq 10^4$ cfu/mL* in men, or in straight catheter urine in women
4	Asymptomatic bacteriuria	No urinary symptoms	$\geq$ 10 WBC/mm^3 $\geq 10^5$ cfu/mL* in two consecutive MSU cultures $\geq$ 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.*

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12.2 Recommendations for antimicrobial therapy in urology

Diagnosis	Most frequent pathogen/species	Initial, empirical antimicrobial therapy	Therapy duration
Cystitis	• *E. coli*	• Trimethoprim-sulphamethoxazole°	3 days
acute,	• *Klebsiella*	• Fluoroquinolone*	(1-)3 days
uncomplicated	• *Proteus*	• Fosfomycin trometamol	1 day
	• *Staphylococci*	• Pivmecillinam	(3-)7 days
		• Nitrofurantoin	(5-)7 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).

12.3 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 Zoster: 800mg tds	Simplex: 200mg bd Zoster: 800mg bd	Give post HD
Amikacin	5-6mg/kg 12h	3-4mg/kg 24h HD: 5mg/kg post HD and monitor levels	2mg/kg 24-48h	Give post HD 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. Consider using liposomal/lipid complex amphotericin. Daily monitoring of renal function (GFR) essential.			
Ampicillin IV	normal	250-500mg 6h	250mg 6h (500mg 6h)	Give post HD
Benzylpenicillin	normal	75%	20-50% Max. 3.6g/day (1.2g.qds)	Give post HD 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 Max 2g/day	
Cefuroxime IV	normal	750mg-1.5g 12h	750mg 24h (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 (1.2g 12h)	1.2 stat then 50% 24h (1.2g stat then 600mg 12h)	Give post HD
Co-Amoxiclav po (Augmentin)	normal	375mg-625mg 12h (375mg 8h)	375mg 12h (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 Max. 1.5g/day (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 ONCE DAILY	**GFR 10-40ml/min** 3mg/kg stat (max 300mg) Check pre-dose levels 18-24 hours after first dose. Redose only when level < 1mg/L.		**GFR < 10ml/min** 2mg/kg (max 200mg) redose according to levels	BOTH METHODS Give post HD Monitor blood levels:
2) Gentamicin CONVENTIONAL	80mg 12h	80mg 24h	80mg 48h HD: 1-2 mg/kg Post HD: redoes According to levels	Once daily: pre only 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 Check pre-dose level before 3rd dose	1g 48h Check pre-dose level before 2nd dose	1g stat (or 15mg.kg, up to max 2 g). Recheck level after 4-5 days. 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

12.4 Recommendations for peri-operative antibacterial prophylaxis in urology

Procedure	Pathogens (expected)	Prophylaxis	Antibiotics	Remarks
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes?	All patients	Fluoroquinolones TMP ± SMX Metronidazole?	Short course (<72h)
Cystoscopy Urodynamic examination	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd generation TMP ± SMX	Consider only in risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd generation TMP ± SMX	Consider in risk patients
Endourological surgery and ESWL				
ESWL	Enterobacteriaceae Enterococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI[a]	In patients with stent or nephrostomy tube Consider in risk patients
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI Fluoroquinolones	In patients with stent or nephrostomy tube Consider in risk patients
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI Fluoroquinolones	Short course Length to be determined Intravenous suggested
TUR of the prostate	Enterobacteriaceae Enterococci	All patients (see Section 9.6.2)	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI	Low-risk patients and small-size prostate require no prophylaxis
TUR of bladder tumour	Enterobacteriaceae Enterococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI	Consider in risk patients and large necrotic tumours
Open urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter- associated uropathogens	No		Consider in high-risk patients Short post-operative catheter treatment
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	Cephalosporin 2nd or 3rd generation TMP + SMX Aminopenicillin/BLI	Single peri-operative course
Clean-contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	Cephalosporin 2nd or 3rd generation Metronidazole	As for colonic surgery
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients	Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)	
Laparoscopic procedures				As for open surgery

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

12.5 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 = _____

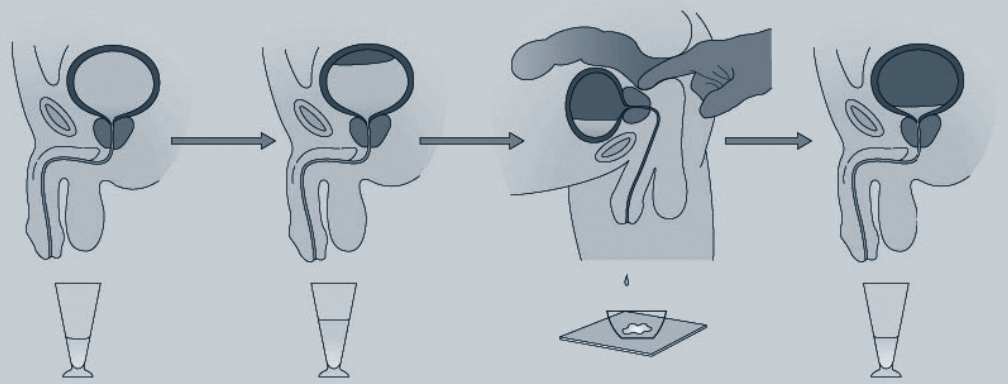
Urinary Symptoms:
Total of items 5 and 6 = _____

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

12.6 Meares & Stamey Localization technique

MEARES AND STAMEY LOCALIZATION TECHNIQUE

1. Approximately 30 minutes before taking the specimen, the patient should drink 400ml of liquid (two glasses). The test starts when the patient wants to void
2. The lids of four sterile specimen containers, which are marked VB_1, VB_2, EPS and VB_3, should be removed. Place the uncovered specimen containers on a flat surface and maintain sterility
3. Hands are washed
4. Expose the penis and retract the foreskin so that the glans is exposed. The foreskin should be retracted throughout
5. Cleanse the glans with a soap solution, remove the soap with sterile gauze or cotton and dry the glans
6. Urinate 10–15ml into the first container marked VB_1
7. Urinate 100–200ml into the toilet bowl or vessel and without interrupting the urine stream, urinate 10–15ml into the second container marked VB_2
8. The patient bends forward and holds the sterile specimen container (EPS) to catch the prostate secretion
9. The physician massages the prostate until several drops of prostate secretion (EPS) are obtained
10. If no EPS can be collected during massage, a drop may be present at the orifice of the urethra and this drop should be taken with a 10µl calibrated loop and cultured
11. Immediately after prostatic massage, the patient urinates 10–15ml of urine into the container marked VB_3.



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from

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12.7 Antibacterial agents

Table 12.7.1 Antibacterial agents according to groups and agents used in urology

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.

12.7.1 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.

12.7.1.1 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.

12.7.1.2 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.

12.7.1.3 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.

12.7.2 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 12.6.2).

12.7.2.1 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).

12.7.2.2 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.

12.7.2.3 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.

12.7.2.4 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.

12.7.2.5 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.

12.7.2.6 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 12.7.2: Classification of parenteral cephalosporins (2)

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

12.7.3 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 3).

Table 12.7.3: Classification of oral cephalosporins (1)

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

12.7.3.1 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.

12.7.3.2 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.

12.7.3.3 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.

12.7.4 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.

12.7.5 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 and meropenem 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.

12.7.6 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 12.6.4).

Table 12.7.4: 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.*

12.7.6.1 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.

12.7.6.2 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.

12.7.6.3 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%.

12.7.7 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.

12.7.8 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.

12.7.9 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.

12.7.10 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*.

12.7.11 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.*

12.7.12 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.

12.7.13 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.

12.7.14 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.

12.7.15 REFERENCES

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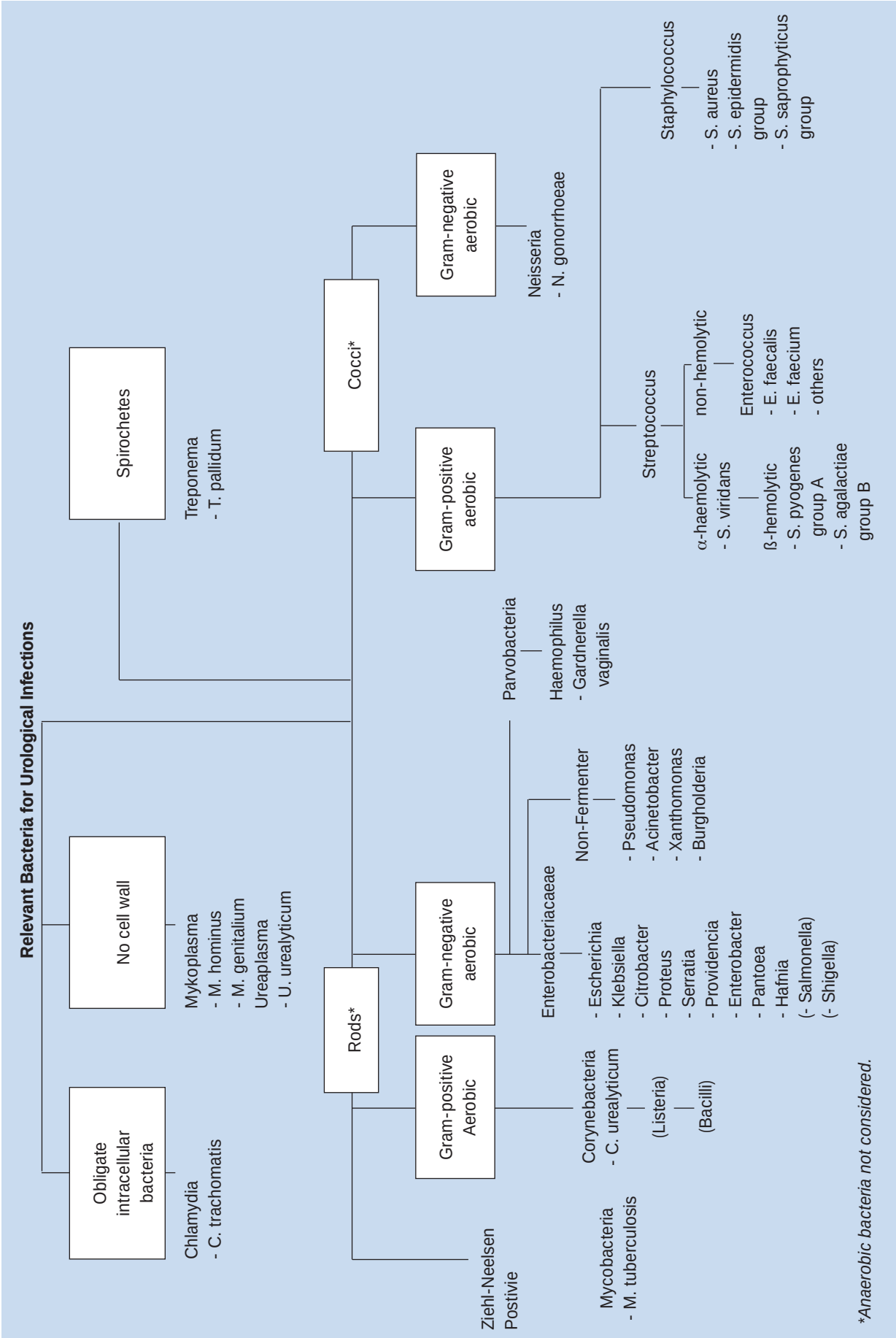
12.8 Relevant bacteria for urological infections



13. 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
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
RUTIs	recurrent UTIs
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*