



European Association of Urology

**GUIDELINES
ON
URINARY AND
MALE GENITAL
TRACT
INFECTIONS**

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1. INTRODUCTION

Micro-organisms reach the urinary tract by the way of the ascending, haematogenous, or lymphatic routes. There is clinical and experimental evidence that the ascent of micro-organisms within the urethra is the most common pathway leading to a urinary tract infection (UTI), especially for organisms of enteric origin (i.e. *Escherichia coli* and other Enterobacteriaceae). This is 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 a UTI in almost 100% of cases within 3-4 days. The use of a closed drainage system delays the onset of infection. This finding provides evidence that catheterized patients become infected via the ascending route. It is thought that bacteria migrate within the mucopurulent space between the urethra and catheter, and that this leads to the development of bacteriuria within about 4 weeks. This is despite the fact that the urine in the bag may be sterile (due to the addition of antibacterial agents) and that retrograde flow from the bag into the catheter may be prevented.

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 that 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. Different types of pili of *E. coli* represent such virulence factors.

Some questions remain. For example, what number of bacteria is considered relevant for the diagnosis of a UTI? According to Rubin and Stamm et al. (1,2), the following bacteriuria is considered to be relevant (see Appendix 1):

- $\geq 10^3$ colony-forming units (cfu) of uropathogen/mL of a mid-stream sample of urine (MSU) in acute uncomplicated cystitis in a woman
- $\geq 10^4$ 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 ≥ 24 hours apart show bacteriuria of $\geq 10^5$ cfu uropathogen/mL.

It is obvious that methods of urine collection and culturing, and the quality of laboratory investigations may vary. Therefore, two levels of standard must be used for the management of patients. A basic standard level is necessary for routine assessment; a higher standard level is required for scientific assessment. In research, the need for a precise definition of sampling methods, 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: clinical symptoms; the results of selected laboratory tests (blood, urine or expressed prostatic secretion [EPS]); and evidence of the presence of microbes by culturing or other specific tests. Most of these investigations can today be performed in any laboratory.

Occasionally, histological investigation will indicate the presence of inflammation (e.g. in prostatic chips or prostate biopsies). 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. However, histological findings usually contribute very little to the treatment decision.

1.1 Classification

Infections can be classified according to their location within the urogenital tract, such as pyelonephritis, ureteritis (mainly a histological or roentgenological diagnosis), cystitis, prostatitis, prostatovesiculitis, urethritis, funiculitis, 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 predominating 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) (1) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (2), are summarized in Appendix 1.

1.2 REFERENCES

Recommended reading

Naber KG.

Experience with the new guidelines on evaluation of new anti-infective drugs for the treatment of urinary tract infections. *Int J Antimicrob Agents* 1999; 11: 189-196.

1. **Rubin RH, Shapiro ED, Andriol VT, Davies RJ, Stamm WE.**
Evaluation of new anti-infective drugs for the treatment of UTI. *Clin Infect Dis* 1992; 15 (Suppl 1): S216-S227.
2. **Rubin RH, Shapiro ED, Andriol VT, Davies RJ, Stamm WE, with modifications by a European Working Party (Norrby SR).**
General guidelines for the evaluation of new anti-infective drugs for the treatment of UTI. Taufkirchen, Germany: The European Society of Clinical Microbiology and Infectious Diseases, 1993; 294-310.

2. UNCOMPLICATED UTI'S IN ADULTS

2.1 SUMMARY

Definition

Acute, uncomplicated UTIs in adults include episodes of acute cystitis and acute pyelonephritis in otherwise healthy individuals (mostly women who have no risk factors, i.e. no structural or functional abnormalities within the urinary tract or no underlying disease known to increase the risks of acquiring infection or of failing therapy).

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 over 5% of cases. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* spp. or enterococci, are isolated.

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

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

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 is generally less effective than the same antibiotic used for a longer duration. However, most suitable antimicrobials given for 3 days are as effective when given for longer durations. Longer treatment usually shows a higher rate of adverse events.

Trimethoprim (TMP) or TMP-sulphamethoxazole (SMX) can be recommended as first-line drugs for empirical therapy in communities with rates of uropathogen resistance to TMP of < 10-20%. Otherwise, fluoroquinolones are recommended as first-line drugs for empirical therapy. Fosfomycin trometamol, pivmecillinam and nitrofurantoin are alternative oral drugs, especially in situations in which fluoroquinolones are not indicated.

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 that resolve and then recur within 2 weeks, urine culture and antimicrobial susceptibility testing should be performed.

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

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

An evaluation of the upper urinary tract with ultrasound and probably plain X-ray should be performed to rule out urinary obstruction or renal stone disease. Additional investigations, such as an excretory urogram, computed tomography (CT) 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. renal or perinephric abscesses.

As first-line therapy in mild cases, an oral fluoroquinolone for 7 days is recommended. If a Gram-positive organism is seen on the initial Gram stain, an aminopenicillin plus a β -lactamase inhibitor (BLI) could be recommended. More severe cases of acute uncomplicated pyelonephritis should be admitted to hospital and treated parenterally. 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. In areas with increased resistance rate of *E. coli* against fluoroquinolones and in situations in which fluoroquinolones are contra-indicated (e.g. pregnancy, lactating women, adolescence), a second- or third-generation oral cephalosporin is recommended.

Routine post-treatment cultures in an asymptomatic patient may not be indicated; urinalysis including a

dipstick method is sufficient as routine. In women whose pyelonephritis symptoms resolve but then recur within 2 weeks, a repeat urine culture, antimicrobial susceptibility testing, and an appropriate investigation should be performed to rule out abnormalities within the urinary tract.

Recurrent (uncomplicated) UTIs in women

Recurrent UTIs 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
- post-intercourse prophylaxis for women in whom episodes of infection are associated with sexual intercourse

Prophylactic alternative methods are not yet as effective as antimicrobial prophylaxis.

UTIs in pregnancy

UTIs 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.

Most symptomatic UTIs in pregnant women present as acute cystitis. Short-term therapy is not as established in pregnant women as it is 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. Post-intercourse prophylaxis may be an alternative approach.

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

UTIs in post-menopausal women

In the case of an acute UTI, the antimicrobial treatment policy in post-menopausal women is similar to that in pre-menopausal women. Short-term therapy in post-menopausal women is, however, not as well documented as that in younger women. In the case of a recurrent UTI, a urological or gynaecological evaluation should be performed in order to eliminate a tumour, obstructive problems or a genital infection.

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

Acute uncomplicated UTIs in young men

Only a small number of 15-50-year-old men suffer from acute uncomplicated UTI. Such men should receive, at a minimum, a 7-day antibiotic regimen. Urological evaluation should be carried out routinely in adolescents and men with pyelonephritis, recurrent infections, or whenever a complicating factor is suspected.

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 none of the factors that are known to increase the risks of complications or of treatment failure. 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 (1).

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. 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 1).

Table 1: Factors that suggest a potential complicated UTI (modified according to ref 2)

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 serve only as guidelines 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. Recurrent UTIs are common among young, 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 diagnosis of, and therapeutic approaches for, such UTIs.

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 over 5% of cases. Occasionally, other Enterobacteriaceae, such as *P. mirabilis* and *Klebsiella* spp., or enterococci, are isolated from such patients. In as many as 10-15% of symptomatic patients, bacteriuria cannot be detected using routine methods.

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

Acute cystitis is associated with considerable morbidity. On average, each episode of this type of UTI in young 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 (3).

2.5.1 Diagnosis

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

- 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.

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 woman has had a new sex partner in the past few weeks or if her sex 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.

A 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 of voided MSU, based on studies of women with acute pyelonephritis and asymptomatic bacteriuria that were carried out four decades ago (4). 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 of $< 10^5$ cfu/mL (5,6). For practical purposes, colony counts of $\geq 10^3$ cfu/mL should be used for the diagnosis of acute uncomplicated cystitis (7,8).

The determination of colony counts by 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 the polymerase chain reaction or ligase chain reaction tests).

2.5.2 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.

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, therefore no general recommendations are suitable throughout Europe.

Short courses of antimicrobials are highly effective in the treatment of acute uncomplicated cystitis in pre-menopausal women (9). 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, one must also consider the potential added expense associated with treatment failures or recurrences arising from short-course therapy. One must also consider the potential psychological aspects of single-dose therapy, such that symptoms may not subside for 2 or 3 days during which time the patient may have misgivings 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 reviewed systematically the English medical literature up to 1999. They consequently developed guidelines for the antimicrobial treatment of acute uncomplicated bacterial cystitis and pyelonephritis in women. The recommendations were classified by strength and by quality of evidence. These guidelines were reviewed by several infectious disease specialists and urologists worldwide and were endorsed by the American Urological Association (AUA) and the ESCMID. Since these guidelines were derived recently and used the best available evidence-based medicine, the Health Care Office (HCO) UTI Working Group of the EAU is now using their data (10).

Of the several thousand titles and abstracts screened, only 75 studies met the preset inclusion and exclusion criteria; 32 studies were double-blinded. In these studies, the following antimicrobials were considered: TMP, TMP-SMX, TMP-sulphadiazin, quinolones (ciprofloxacin, fleroxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, pipemidic acid, rufloxacin), nitrofurantoin, β -lactams (amoxicillin, ampicillin-like compounds, cefadroxil, pivmecillinam, ritipenem axetil) and fosfomycin trometamol.

The following conclusions can be drawn:

- In otherwise healthy adult non-pregnant women with acute uncomplicated cystitis, single-dose therapy is generally less effective than the same antibiotic used for a longer duration. However, the most suitable (see below) antimicrobials 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.

- 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. TMP alone was equivalent to TMP-SMX with regard to eradication and adverse effects. Considering possible rare but serious adverse effects caused by sulphonamides, TMP alone may be considered the preferred drug over TMP-SMX. TMP or TMP-SMX can be recommended as first-line drugs for empirical therapy only in communities with rates of uropathogen resistance to TMP of < 10-20%, because there is a close correlation between susceptibility and the eradication of *E. coli* on one hand and resistance and persistence of the uropathogen on the other (11). 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 and ciprofloxacin (12), which had the lowest risk.
- The fluoroquinolones (ciprofloxacin, fleroxacin, norfloxacin and ofloxacin) are equivalent to TMP-SMX when given as a 3-day regimen. Pefloxacin and rufloxacin (13-16), 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. 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 of > 10-20%. In some countries, however, the resistance of *E. coli* to fluoroquinolones has already increased to > 10%. In this situation, alternative oral drugs should be considered for empirical therapy (see section). With any of these agents, one should expect > 90% eradication of the bacteriuria.
- β -lactams as a group are less effective than the aforementioned drugs. 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 analysis. Only one study of adequate size compared a β -lactam antimicrobial (pivmecillinam) for 3 days with treatment for a longer duration (17): 3 days of therapy was 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. Pooling bacteriological outcomes showed that 7 days of pivmecillinam, 200 mg twice daily, and 3 days of norfloxacin, 400 mg twice daily, have similar results (18).
- Fosfomycin trometamol used as single-dose therapy may be an interesting alternative. However, large trials are necessary to demonstrate its equivalence with standard agents, e.g. TMP, TMP-SMX or one of the fluoroquinolones administered as 3-day regimen.
- Nitrofurantoin needs further study and cannot yet be considered a suitable drug for short-term therapy of acute uncomplicated cystitis. A 7-day course is recommended if used for this indication.
- Although not examined in controlled trials, cystitis caused by *S. saprophyticus* may respond better to longer treatment durations, e.g. 7 days.

The antibacterial treatment options are summarized in Appendix 2.

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 a UTI 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 a UTI.

2.5.3 Post-treatment follow-up

Urinalysis including 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.

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 to look for pyuria and haematuria is indicated. In contrast to cystitis, 80-95% of the episodes of pyelonephritis are associated with $> 10^5$ cfu of uropathogen/mL (19). For routine diagnosis, a breakpoint of 10^4 cfu/mL can be recommended (7,8). An evaluation of the upper urinary tract with ultrasound (20) and probably plain X-ray should be performed to rule out urinary obstruction or renal stone disease. Additional investigations, such as an excretory urogram, CT or DMSA scans, should be considered if the patient remains febrile after 72 hours of treatment to rule out further complicating factors, e.g. renal or perinephric abscesses. Routine performance of an excretory urogram in patients with acute uncomplicated pyelonephritis has little value because up to 75% of adults with uncomplicated acute pyelonephritis have a normal upper urinary tract.

2.6.2 Treatment

Of several hundred articles screened by the IDSA group (10), only five were prospective, randomized, controlled trials (5,21-24) and the following conclusions were drawn from their analysis and one study (25) published thereafter.

1. TMP-SMX is preferred over ampicillin (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. 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.
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 (25). The higher efficacy seen with ciprofloxacin was mainly due to TMP-resistant *E. coli* strains.
4. For an aminopenicillin plus a BLI, as well as for second- or third-generation oral cephalosporins, sufficiently powered comparative studies versus a fluoroquinolone or TMP-SMX are missing.
5. In areas with a rate of *E. coli* resistance to fluoroquinolones of $> 10\%$ and in situations in which fluoroquinolones are contra-indicated (e.g. pregnancy, lactating women, adolescence), an aminopenicillin plus a BLI, or a second- or third-generation oral cephalosporin is recommended, either for initial use, or if a patient has to be switched to an oral regimen.

Based on this analysis, the HCO UTI Working Group recommends an oral fluoroquinolone for 7 days as first-line therapy, except in situations where a fluoroquinolone is not indicated (see above). If a Gram-positive organism is seen on the initial Gram stain, an aminopenicillin plus a BLI is recommended. 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 two or three cephalosporin, or an aminoglycoside. 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 week course of therapy.

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

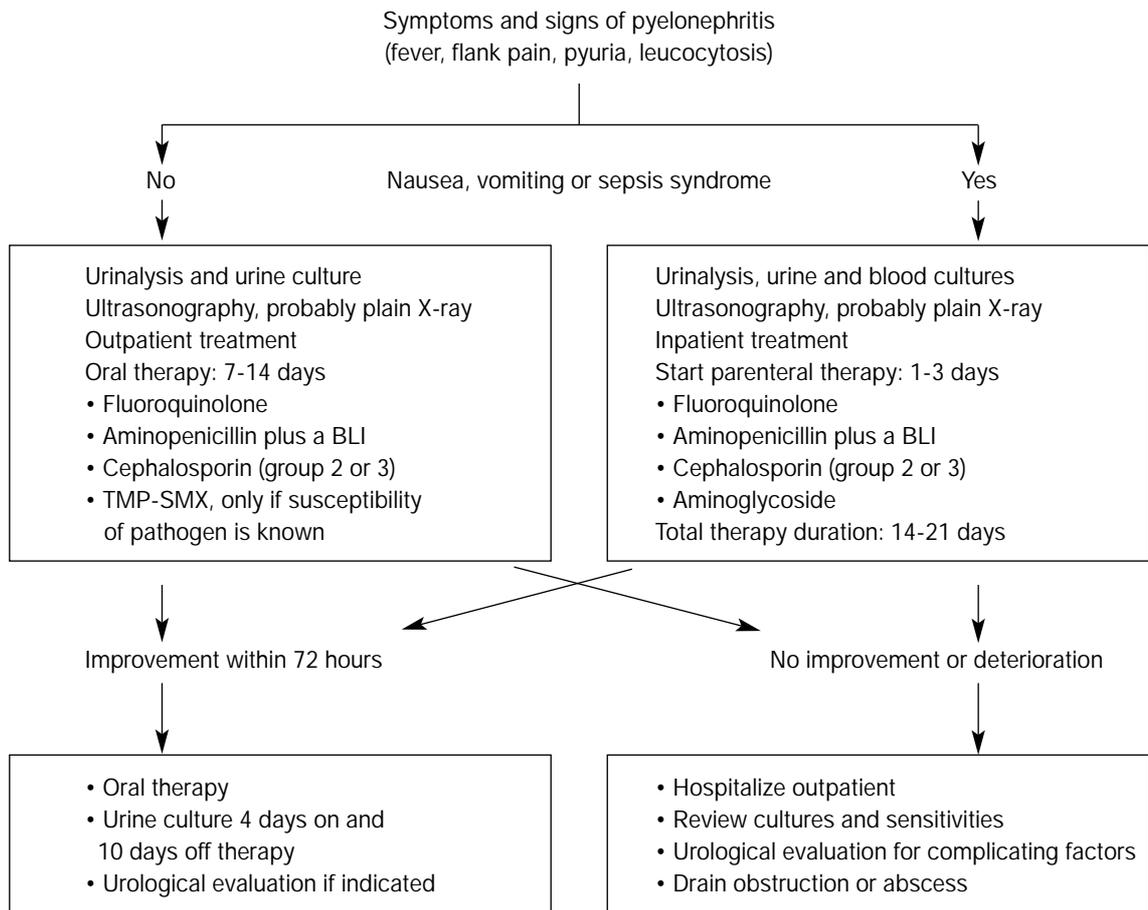
The antibacterial treatment options are summarized in Appendix 2.

2.6.3 Post-treatment follow-up

Routine post-treatment cultures in an asymptomatic patient may not be indicated; urinalysis including a dipstick method is sufficient as routine. 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 CT scan, should be performed. In the patient with no urological abnormality, one should assume 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 1.

Figure 1: Clinical management of acute pyelonephritis (modified according to ref 26)



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

2.7 Recurrent (uncomplicated) UTIs in women

2.7.1 Background

Between 10% and 20% of women experience a recurrent uncomplicated UTI (27). Risk factors for recurrent urinary infection are both genetic and behavioural. Women who are non-secretors of blood group substances have an increased occurrence of recurrent urinary infection (28). Women with recurrent infection have an increased frequency of urinary infection in first-degree female relatives (29). In addition, *E. coli*, the most common uropathogen, adheres more readily to epithelial cells in women who experience recurrent infection (30,31). Behavioural factors associated with recurrent urinary infection include sexual activity, with a particularly high risk in those who use spermicides as a birth control method (2,3,32,33).

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, low-dose prophylactic antimicrobials taken at bedtime (34). A summary of different regimens is shown in Table 2.

Table 2: Antimicrobial regimens of documented prophylactic efficacy for the prevention of an acute uncomplicated urinary infection in women

Agent	Dose
Standard regimen ¹ :	
• Trimethoprim-sulphamethoxazole	40/200 mg/day or three times/week
• Trimethoprim	100 mg/day
• Nitrofurantoin	50 mg/day
• Nitrofurantoin macrocrystals	100 mg/day
Others:	
• Cephalexin	125 or 250 mg/day
• Norfloxacin	200 mg/day
• Ciprofloxacin	125 mg/day

¹ Taken at bedtime.

Generally, the occurrence of infections is decreased by 95% by the use of prophylaxis. The initial duration of prophylactic therapy is usually 6 months or 1 year. However, for co-trimoxazole (TMP-SMX), continuous prophylaxis for as long as 2 (35) or 5 years (36) 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.

An alternative prophylactic approach is post-intercourse prophylaxis for women in whom episodes of infection are associated with sexual intercourse (37-39).

2.7.3 Alternative prophylactic methods

Alternative methods, such as the acidification of urine, cranberry juice (40), extract from *uvae ursi* and the vaginal application of lactobacilli (41,42), show variable effects. Reports on immunostimulating extracts of *E. coli* showed a reduced frequency of recurrent infections (43) and a decrease in the degree of bacteriuria in paraplegic patients (44).

Water diuresis may be effective in some women with an uncomplicated UTI, but it often delays more effective management with antimicrobial drugs until the patient's condition deteriorates. The evidence is also too weak to recommend that women change their bodily habits and menstrual practices or void after intercourse (45).

2.8 UTIs in pregnancy

UTIs 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 a 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% (46). 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 school-girls develop UTIs during pregnancy. An additional 1% of infections occur during pregnancy (47). 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 (48). Bacteriuria during pregnancy is associated with a significant increase in the number of low-birth-weight infants ($\leq 2,500$ g), low gestational age (< 37 weeks), and neonatal mortality. Women with persistent infection despite treatment or 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 (47) and others demonstrated that 20-40% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy. Treatment of the bacteriuria lowers this risk (49). It is still debatable whether screening (e.g. after the first 3-month period) for asymptomatic bacteriuria in pregnant women is warranted. Wadland and Planten (50) 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 (46). 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 (49). 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%. 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.

Treatment should be based on antibiotic sensitivity testing and usually involves a 7-day course of antibiotics; however, some authors recommend short-term therapy, as for acute cystitis (51). Follow-up cultures should be obtained 1-4 weeks after treatment and at least once more before delivery.

2.8.3 *Acute cystitis during pregnancy*

Most symptomatic UTIs in pregnant women present as acute cystitis, as is found in their non-pregnant counterparts. Short-term therapy, however, is not as established in pregnant women as it is in non-pregnant women. Second- and third-generation oral cephalosporins, pivmecillinam or fosfomycin trometamol could be considered candidates for effective short-term therapy. Some smaller studies and expert opinion support this approach (51). Otherwise conventional therapy with amoxicillin, cephalexin or nitrofurantoin is recommended.

Follow-up urine cultures should be obtained after therapy to demonstrate eradication of the bacteriuria. There is no advantage to be gained by using long-term prophylaxis except for recurrent infections, as in non-pregnant women. 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. Post-intercourse prophylaxis may be an alternative approach (52,53).

2.8.4 *Acute pyelonephritis in pregnancy*

Acute pyelonephritis tends to occur during the later stages of pregnancy, usually in the last trimester. Gilstrap et al. (54) found acute pyelonephritis in 2% of 24,000 obstetric patients reviewed. 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, such as toxæmia, 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. Second- or third-generation cephalosporins, an aminopenicillin plus a BLI, or an aminoglycoside may be recommended antibiotics. Quinolones, tetracyclines and TMP in the first trimester, and sulphonamides in the last trimester, should not be used during pregnancy. In cases of delayed defervescence and upper tract dilatation, a ureteral stent may be indicated and antimicrobial prophylaxis until delivery and including the puerperium should be considered.

2.9 UTIs in post-menopausal women

The vagina ordinarily 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 (55). Gram-negative enteric bacteria do not ordinarily colonize the vagina in post-menopausal women unless these women are prone to recurrent UTIs (56). In post-menopausal women with recurrent UTIs, therapy with oral (57,58) or intravaginal oestriol (55) was able to reduce significantly the rate of recurrence. For other patients, an antimicrobial prophylactic regimen (see previously) should be recommended in addition to hormonal treatment.

In 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. (59) 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 the case of a recurrent UTI, a urological or gynaecological evaluation should be performed in order to eliminate a tumour, obstructive problems or a genital infection.

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 of those that occur in the new-born, the infant or the elderly 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 (60).

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 15-50-year-old men 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 (61); however, these factors are not always present.

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 a UTI and urethritis.

The aetiological agents that cause uncomplicated UTIs in men are also similar to those in women. Krieger et al. (62) 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. Nitrofurantoin should not be used in men with a UTI, since it does not achieve reliable tissue concentrations. For acute uncomplicated pyelonephritis, the use of a fluoroquinolone as initial empirical oral treatment is recommended in areas where the rate of *E. coli* resistance to fluoroquinolones is low (< 10%). Otherwise, alternative drugs have to be considered (see section).

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 recommended, therefore, 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. Also, longer treatment may reduce the likelihood of persistent prostatic infection.

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 pyelonephritis and recurrent infections, or whenever a complicating factor is present.

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3. UTI'S IN CHILDREN

3.1 SUMMARY

The clinical presentation of a UTI in infants and young children can be very atypical. Investigation should be undertaken after two episodes of a UTI in girls and one in boys. The objective is to rule out the unusual occurrence of obstruction, vesico-ureteric reflux (VUR) and a neuropathic spinal disorder. Phimosis, labial adhesions and constipation may also be relevant.

Ultrasonography of the renal tract is the imaging investigation of first choice, supplemented by voiding cysto-urethrography (VCU) in infants and very young children. Later on in childhood, the VCU is replaced by indirect radionuclide cystography.

Chronic pyelonephritic renal scarring develops very early in life due to the combination of a UTI, intra-renal reflux and VUR. It sometimes arises in utero due to dysplasia. New scars very rarely develop after the age of 2 years. It is unlikely that very early identification and treatment of reflux can significantly alter the incidence of reflux nephropathy and therefore screening for asymptomatic bacteriuria in infants is of little benefit.

VUR is treated with long-term prophylactic antibiotics and surgical re-implantation is reserved for the small number of children with break-through infection.

The principles for the treatment of a UTI in children are slightly different from those for adults. Short courses are not generally accepted and therefore treatment is continued for 7-10 days. If the child is severely ill with vomiting and dehydration, hospital admission will be required and parenteral antibiotics given for at least the first 2 days. Tetracyclines and fluoroquinolones should not be given because of their effects on teeth and cartilage.

3.2 Background

UTIs represent the most common bacterial infections in children < 2 years of age (1). 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 will eventually lead to hypertension, proteinuria, renal damage and end-stage renal disease in up to 24% of children, requiring chronic dialysis treatment, and will contribute to chronic renal failure in significant number of adults (2).

It has been suggested that 5% of school-girls and up to 0.5% of school-boys undergo at least one episode of a UTI during their school life. The risk of a UTI during the first decade of life is 1% for male infants and 3% for female infants. The incidence is different for children < 3 months of age, where it is more common in males. By 6 months of age, the estimated ratio is 10:1 for females:males. The incidence of asymptomatic bacteriuria is 0.7-3.4% in new-borns, 0.7-1.3% in infants < 3 months of age and between 0.2% and 0.8% in pre-school boys and girls, respectively. The incidence of symptomatic bacteriuria is 0.14% in new-borns, with a further increase to 0.7% in boys and 2.8% in girls aged < 6 months. The overall recurrence rate for the new-born period has been reported to be 25% (3,4).

3.3 Aetiology

The most common pathogens are Gram-negative mainly enteric organisms. Of these, *E. coli* is responsible for 90% of the episodes of UTIs (5). Gram-positive organisms (particularly *Enterococcus* and *Staphylococcus* spp.) 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 Streptococcus are relatively common in the new-born. There is an increasing trend to the isolation of *S. saprophyticus* in UTIs in children, although the role of this organism is still debatable (6).

3.4 Pathogenesis

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). Phimosis can also predispose to a UTI, but to what extent is still controversial (8-10). The mechanism is obvious: 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 (3), which adhere to the inner layer of the preputial skin and to uro-epithelial cells (11). These are particularly likely to ascend, ultimately to the renal parenchyma. Most other urinary pathogens ascend via the lumen or perivesical and ureteric lymphatics.

Infection in neonates may exceptionally reach the renal parenchyma by haematogenous spread. 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). Such dysfunction can also be a manifestation of child abuse. Pelvic neuropathy is generally related to spina bifida and it can cause infection, particularly where there is obstruction from sphincter dyssynergia secondary to VUR. Residual urine can also accumulate as a result of a lower motor neuron lesion (3).

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, intra-renal 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 compounding factor is that many so-called scars are, in fact, dysplastic renal tissue that developed in utero.

3.5 Signs and symptoms

The symptoms are non-specific, though there is a direct relationship with the age of the child.

3.5.1 New-borns

The usual pattern presents with poor feeding, impairment of normal development, irritability, asymptomatic bacteriuria (1%) or septic shock.

3.5.2 Children < 6 months of age

There is a slight predominance of gastrointestinal signs, such as vomiting, diarrhoea, poor feeding, ill appearance or abdominal distension. In 5-10% of cases, the occult course of a febrile syndrome of unknown origin is a UTI. Jaundice is also a relatively frequent sign due to liver toxicity or the haemolytic effect of some *E. coli* strains. Other signs referable to the urinary tract, such as intermittent voiding dysfunction or poor urinary stream, may be vague.

3.5.3 Pre-school children (2-6 years of age)

Symptoms are more specific and related to the urinary tract. Fever, frequent voiding, dysuria, suprapubic and abdominal pain, or incontinence are the usual findings.

3.5.4 School-children and adolescents

It is feasible to distinguish between a lower UTI (cystitis) and an upper UTI (pyelonephritis) because patients are able to describe their symptoms and relate them to a certain anatomical location.

3.5.5 Severity of a UTI

From a practical point of view, severe and simple forms of UTIs should be distinguished, because the severity of symptoms to some extent dictates the degree of urgency with which investigation and treatment are undertaken (Figure 2).

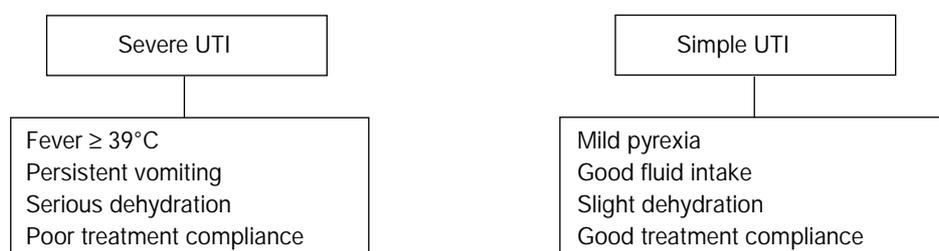
3.5.6 Severe UTIs

We consider a UTI severe when a child presents with fever of $\geq 39^{\circ}\text{C}$, ill sensation, persistent vomiting, and moderate or severe dehydration. When a low level of compliance is expected, such a child should be handled as one would a child with a severe UTI.

3.5.7 Simple UTIs

A child with a simple UTI may have only mild pyrexia, but is able to take fluids and oral medication. This child is only slightly or not dehydrated and has a good expected level of compliance.

Figure 2: Clinical classification of urinary tract infections (UTIs) in children



3.5.8 Epididymo-orchitis

Epididymo-orchitis is extremely unusual, and scrotal pain and inflammation in pre-pubertal boys is usually due to torsion.

3.6 Diagnosis

3.6.1 Physical examination

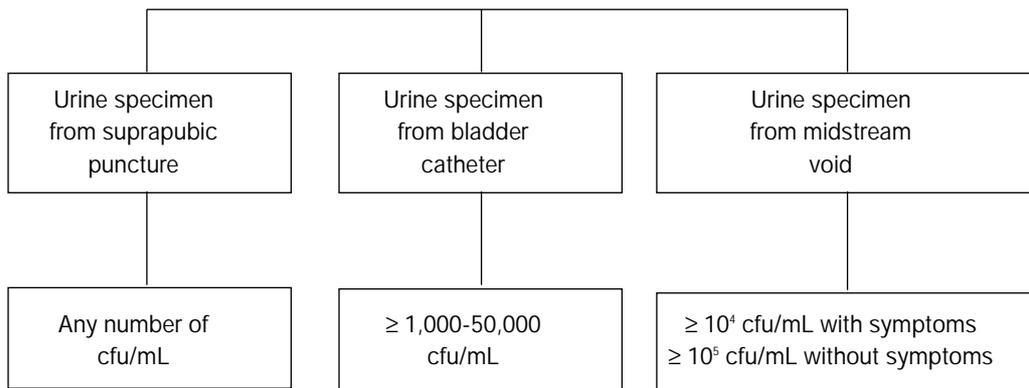
It is mandatory to rule out the presence of phimosis, labial adhesion or signs of pyelonephritis or epididymo-orchitis. The absence of fever does not exclude the presence of an infective process.

3.6.2 Laboratory tests

Urine culture: specimens are sometimes difficult to obtain and different methods are used. In children < 2 years of age, urinary specimens may be collected by attachment of a plastic bag to the genitalia, bladder catheterization or suprapubic aspiration. In older children, a mid-stream void may be a suitable specimen. When the urinary specimen is directly obtained from the collecting bag only a negative urinary culture is considered to be a valid result. Conversely, the most reliable specimen is obtained by suprapubic aspiration, since any organisms found are considered to be significant bacteriuria (with the exception of ≤ 300 cfu/mL coagulase-negative *Staphylococcus* spp.). The laboratory must be instructed to also look for 'low count' bacteriuria. In case of catheterization, a count of $\geq 1,000$ -50,000 cfu/mL is necessary in order to consider the bacteriuria significant. Alternatively, counts of $\geq 10,000$ cfu/mL in a mid-stream void in symptomatic children or $\geq 100,000$ cfu/mL on two different days in asymptomatic children are required in order to consider the bacteriuria significant.

However, there is growing agreement that the presence of 5,000-10,000 cfu pathogen/mL in two different specimens from a symptomatic child should be considered significant bacteriuria (5) (Figure 3).

Figure 3: Microbiological criteria of urinary tract infection in children



It is also necessary to bear in mind that the final concentration of bacteria in urine is directly related to the method of specimen collection, the diuresis and the method of storing and transporting the specimen after collection (13).

Urinalysis: Microscopic examination of the urinary sediment provides useful information on the presence of leucocytes and uropathogens. Moreover, the combination of a nitrite test with a test for leucocyte esterase on a single dipstick is helpful.

Bacteriuria without pyuria may be found in cases of bacterial contamination, when collecting a specimen before the onset of an inflammatory reaction or bacterial colonization - a clinical syndrome known as asymptomatic bacteriuria. 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 should make the diagnosis of a UTI questionable. Asymptomatic bacteriuria with a concomitant septic focus responsible for the febrile syndrome has to be considered instead.

Bacteriuria without pyuria is found in 0.5% of specimens, a prevalence that corresponds to the estimated rate of asymptomatic bacteriuria (14,15). Thus, the absence or presence of pyuria on its own may not be considered a reliable parameter by which to diagnose or exclude a UTI. Other factors can influence the result of the test, such as the degree of hydration, the method of specimen collection, the mode of centrifugation, the volume in which the sediment is resuspended and the subjective interpretation of the results (16). For all of these reasons, screening for UTIs in new-borns and children < 6 months of age, including urinary microscopy for white blood cells (WBC) or bacteria and a nitrite test, has a minimal predictive value (17-19). Conversely, the positive predictive value of a significant Gram staining with pyuria is 85% (14).

Combining both diagnostic procedures, in febrile children the findings of ≥ 10 WBC/mm³ and $\geq 50,000$

cfu/mL in a specimen collected by catheterization are significant for a UTI and discriminate between infection and contamination (14,17). According to Landau et al. (20), pyuria in children with a febrile attack is indicative of acute pyelonephritis.

Urinary N-acetyl- β -glucosaminidase, a marker of tubular damage, is increased in a febrile UTI and may become a reliable diagnostic test for UTIs (21), although it is also elevated in VUR. The clinical use of urinary concentrations of interleukin (IL)-6 in UTIs (22) is still at the research stage.

C-reactive protein (CRP): Although non-specific in febrile children with bacteriuria, CRP seems to be useful in distinguishing between acute pyelonephritis and asymptomatic bacteriuria co-incident with a non-urological problem. It is considered significant at a concentration > 20 μ g/mL.

3.6.3 *Imaging of the urinary tract*

The 'gold standard' imaging technique would be cost-effective, painless, safe, with minimal or nil radiation, and an ability to detect any significant structural anomaly. Current techniques do not as yet fulfill all such requirements. The most important imaging procedures are discussed below.

Ultrasonography: This has become very popular in children because of its safety, speed, lack of ionizing radiation and high accuracy in identifying the anatomy and size of the renal parenchyma and collecting system. It is subjective and therefore operator-dependent, and gives no information on renal function. However, scars can be identified, although not so well as with DMSA scanning (23-25). It has been shown to be as sensitive as excretory urography in detecting significant renal anomalies (26).

Radionuclide studies: Technetium (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 showing areas of hypo-activity or lack of function. A UTI interferes with the uptake of this radiotracer by the proximal renal tubular cells, allowing the adequate imaging of areas of focal defect in the renal parenchyma. Therefore, a radionuclide scan showing a decrease in the uptake of the radiotracer with a star-shaped defect in the renal parenchyma would indicate an acute episode of pyelonephritis; the same decrease, but with a focal lack of renal cortex visualization, would indicate the presence of a chronic lesion (27-29).

Tc-99m DMSA is useful in identifying reflux nephropathy presenting either as focal scarring or as a smooth uniform loss of renal substance (30,31). Rushton et al. (32) stated that only children who show a decreased uptake of the radiotracer are at serious risk of significant renal scarring regardless of the existence of VUR. For that reason, it would be sensible, in such cases, to begin antimicrobial prophylaxis. Ransley and Risdon (33) reported that Tc-99m DMSA showed a specificity of 100% and sensitivity of 80%. Other studies have found that a minimal parenchymal defect, when characterized by a slight area of hypo-activity, can be resolved with antimicrobial therapy in 100% of cases (34,35). Long-lasting defects are unavoidably associated with renal scarring. In fact, 40% of such renal scars occurring as a consequence of pyelonephritis will be irreversible (36).

Radionuclide scans also provide a method of early diagnosis: in the first week of an acute episode of pyelonephritis, 50-85% of children will show positive findings. Furthermore, such scans are considered more sensitive than excretory urography and ultrasonography in the detection of renal scars (37-40). It has therefore been proposed that radionuclide scans could substitute for echography as a first-line diagnostic approach in children with a UTI (41).

Cysto-urethrography: There are basically two types of cysto-urethrography.

- Conventional VCU is the most widely used radiological exploration for the study of the lower urinary tract and especially of VUR. It is considered mandatory in the evaluation of UTIs in children < 1 year of age. Its main drawbacks are the risk of infection, the need for retrograde filling of the bladder and the possible deleterious effect of radiation on children (42). In recent years, tailored low-dose fluoroscopic VCU has been used for the evaluation of VUR in girls in order to minimize radiological exposure (43).
- Radionuclide cystography (indirect) is performed by prolonging the period of scanning after the injection of Tc-99m DTPA/MAG-3 as part of dynamic renography. It represents an attractive alternative to conventional cystography, especially when following patients with reflux, because of its lower dose of radiation. Drawbacks are a poor image resolution and a difficulty in detecting lower urinary tract abnormalities (44).

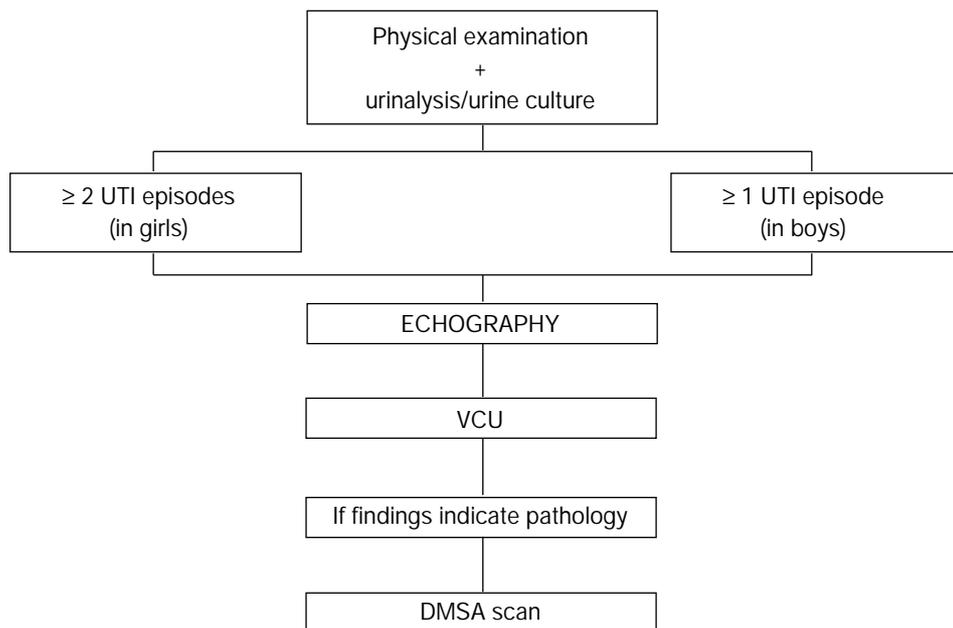
Excretory urography: This remains a valuable tool in the evaluation of the urinary tract in children, but its use in UTIs is debatable unless such preliminary explorations as VCU or radionuclide scans reveal the existence of VUR. The major disadvantages in infants are the risks of side effects from the contrast media and radiation exposure (45).

CT scan: Despite its established role in the diagnosis of upper urinary tract lesions, the use of CT scans in the follow-up of UTIs in children is very limited, for the same reasons as for excretory urograms (46).

3.7 Schedule of investigation

A schedule of investigation of a UTI in a child is shown in Figure 4.

Figure 4: Schedule of investigation of a urinary tract infection (UTI) in a child



VCU = voiding cysto-urethrography; DMSA = dimercaptosuccinic acid.

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. Therefore, after a maximum of two UTI episodes in a girl and one such episode in a boy, investigations should be undertaken, but not in case of asymptomatic bacteriuria (47-50). In the infant, ultrasound and direct VCU should be carried out. Later on (> 5 years of age), VCU is replaced by indirect radionuclide cystography. DMSA scanning should be undertaken after demonstration of VUR. The need for DTPA/MAG-3 scanning is determined by the ultrasound findings, particularly if there is suspicion of an obstructive lesion.

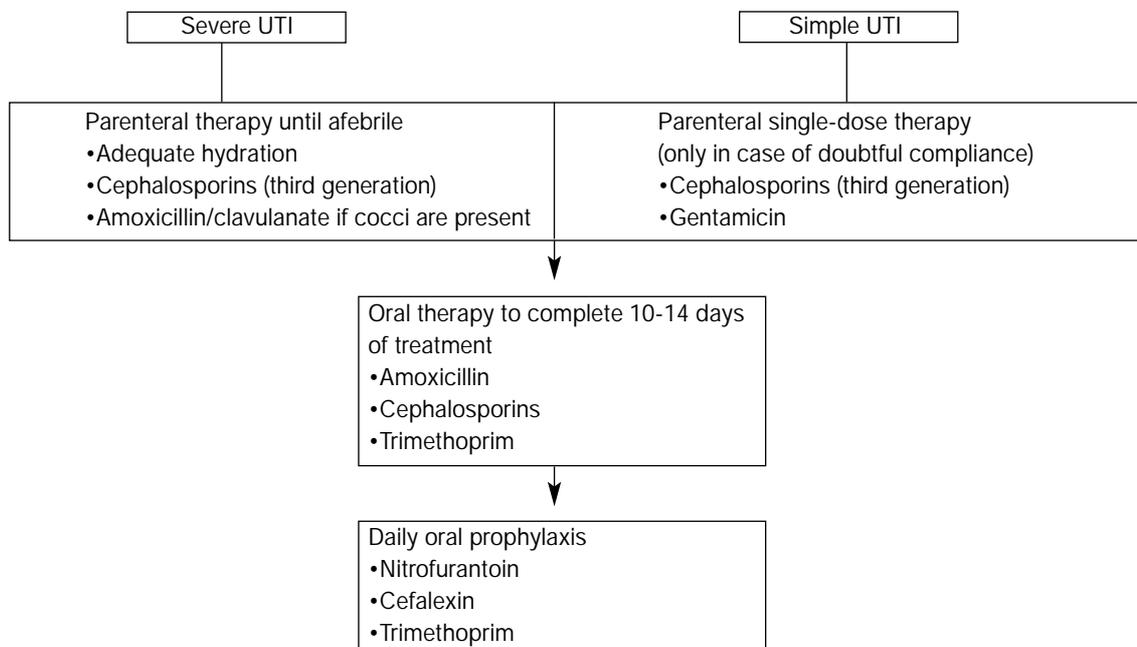
3.8 Treatment

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

An overview of the treatment of febrile UTIs in children is given in Figure 5.

Figure 5: Treatment of febrile urinary tract infection in (UTI) children



3.8.1 Severe UTIs

A severe UTI requires adequate parenteral fluid reposition and appropriate antimicrobial treatment, preferably with cephalosporins. If a Gram-positive UTI is suspected, it is useful to administer aminoglycosides, ampicillin or amoxicillin/clavulanate (51). In case of an allergy to cephalosporins, aztreonam or gentamicin may be used. When aminoglycosides are necessary, serum levels should be monitored. If cocci are found in the urine culture, ampicillin or amoxicillin/clavulanate represents the treatment of choice.

In new-borns, the surveillance of antimicrobial serum concentrations and subsequent dosage adjustment to compensate for renal function deficit is mandatory. Chloramphenicol, sulphonamides, tetracyclines, rifampicin, amphotericin B and quinolones should be avoided. The use of ceftriaxone must also be avoided due to its unwanted side effect of jaundice.

A wide variety of antimicrobials can be used in older children, with the exception of tetracyclines (because of teeth staining) and fluorinated quinolones (because of cartilage toxicity) (52). For a safety period of 24-36 hours, parenteral therapy should be administered. After the child is doing well, is afebrile and is able to take fluids, he/she may be given an oral agent to complete the 10-14 days of treatment. The preferred oral antimicrobials are: amoxicillin, cephalixin, cefixime or TMP. Outpatient treatment provides some advantages, such as less psychological impact on the child and more comfort for the whole family. It is less expensive, well tolerated and eventually prevents opportunistic infections (14). In children < 3 years of age who have difficulty taking oral medications, parenteral treatment for 7-10 days seems advisable.

Although debatable, a daily antimicrobial prophylaxis after the acute episode at least for 6 months seems a sensible policy. The most effective antimicrobial agents are: nitrofurantoin, TMP, cephalixin and cefaclor (53).

3.8.2 Simple UTIs

This is considered a low-risk infection in children and thus a single parenteral dose of a cephalosporin, such as ceftriaxone and, in case of allergy, aztreonam, will be adequate. This is then followed by TMP, cephalixin or amoxicillin to complete 10-14 days of treatment. Once treatment is completed, antimicrobial prophylaxis at least for 6 months should be started. In case of poor response, complications or positive blood cultures, the child must be admitted to hospital and parenteral treatment started (54).

The dosing of the antimicrobial agents mentioned are outlined in table 3.

Table 3 Dosing of antimicrobial agents in children. Adapted from ref. 55.

Antimicrobial agent	Application	Age	Total dosage per day	Doses per day
Ampicillin	i.v.	3-12 months	100-300 mg/kg BW	3
Ampicillin	i.v.	1-12 years	60-150 (-300) mg/kg BW	3
Amoxicillin	p.o.	3-12 months	50-100 mg/kg BW	2-3
Amoxicillin	p.o.	1-12 years	50-100 mg/kg BW	2-3
Amoxicillin/claculanate	i.v.	3-12 months	60-100 mg/kg BW	3
Amoxicillin/claculanate	i.v.	1-12 years	60-100 mg/kg BW	3
Amoxicillin/claculanate	p.o.	3-12 months	37.5-75 mg/kg BW	2-3
Amoxicillin/claculanate	p.o.	1-12 years	37.5-75 mg/kg BW	2-3
Cephalexin	p.o.	3-12 months	50-100 mg/kg BW	3
Cephalexin	p.o.	1-12 years	50-100 mg/kg BW	3
- for prophylaxis	p.o.	1-12 years	10 mg/kg BW	1-2
Cefaclor	p.o.	3-12 months	50-100 mg/kg BW	3
Cefaclor	p.o.	1-12 years	50-100 mg/kg BW	3
- for prophylaxis	p.o.	1-12 years	10 mg/kg BW	1-2
Cefixime	p.o.	3-12 months	8-12 mg/kg BW	1-2
Cefixime	p.o.	1-12 years	8-12 mg/kg BW	1-2
Cetriaxone	i.v.	3-12 months	50-100 mg/kg BW	1
Cetriaxone	i.v.	1-12 years	50-100 mg/kg BW	1
Aztreonam	i.v.	3-12 months	(50)-100 mg/kg BW	3
Aztreonam	i.v.	1-12 years	(50)-100 mg/kg BW	3
Gentamicin	i.v.	3-12 months	5-7.5 mg/kg BW	1-3
Gentamicin	i.v.	1-12 years	5 mg/kg BW	1-3
Trimethoprim	p.o.	1-12 years	6 mg/kg BW	2
- for prophylaxis	p.o.	1-12 years	1-2 mg/kg BW	1
Nitrofurantoin	p.o.	1-12 years	3-5 mg/kg BW	2
-for prophylaxis	p.o.	1-12 years	1 mg/kg BW	1-2

BW = body weight

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

4.1 SUMMARY

What are the acute effects of a UTI on the kidney and do the lesions become chronic?

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. In diabetes mellitus, occasionally overwhelming infection can predispose to pyogenic infection with intra-renal perinephric abscess formation and, very rarely, a specific form of infective interstitial nephritis. Papillary necrosis is a common consequence of pyelonephritis in diabetics.

Arguably, diabetic patients are susceptible to the rapid progression of parenchymal infection, and the clearance of asymptomatic bacteriuria should be attempted and then re-infection prevented with long-term antibiotics.

Does chronic renal disease progress more quickly as a result of infection and do particular renal diseases predispose to a UTI?

There are several factors of general potential importance predisposing to infection in uraemia, including loss of several urinary defence mechanisms and a degree of immunosuppression. Typically adult polycystic kidney disease (APCKD), gross VUR and end-stage obstructive uropathy will harbour infective foci or promote ascending infection, but not invariably so. Clearly, a severe UTI with accompanying bacteraemia can hasten the 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.

VUR and a UTI in end-stage chronic renal failure

Bilateral nephro-ureterectomy should only be carried out as a last resort.

Obstruction and a 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.

APCKD

Acute pyelonephritis, infected cysts (presenting as recurrent bacteraemia or 'local sepsis') should be treated with high-dose systemic fluoroquinolones. A long course should be given and followed by prophylaxis. Bilateral nephrectomy is used as a last resort.

Calculi and UTI

For patients without renal impairment (i.e. stone clearance), where possible minimize antibiotic treatment if the calculus cannot be removed. Nephrectomy is a last resort, but even residual renal function may be of vital importance.

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

There is a tendency for certain antibiotics to be removed at dialysis.

Are immunosuppressed patients prone to UTIs? Are UTIs a significant cause of graft failure?

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

4.2 Background

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

particularly in the immunosuppressed patient.

This section can be subdivided into four questions:

1. What are the acute effects of a 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 a UTI?
3. What problems arise with antibiotic therapy in patients with renal insufficiency and after renal transplantation?
4. Are immunosuppressed patients prone to UTIs particularly in the context of renal transplantation? Are UTIs a significant cause of graft failure?

4.3 What are the acute effects of a UTI on the kidney and do the lesions become chronic? Can they be prevented?

Some authors regard acute pyelonephritis as 'complicated' because it may cause renal scarring in a previously normal kidney (1,2). 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).

The effects of VUR and intra-renal 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 elements, although in almost all cases 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 the preservation of renal tissue in reflux nephropathy in the older child and adult, even if the reflux has not already been successfully treated (6). However, further discussion of reflux nephropathy is beyond the scope of this section.

Obstruction occurring through a voiding disorder or supraventrically causes renal tubular dysfunction and ultimately renal damage, mainly through the process of apoptosis. Infection enhances the process of parenchymal loss and, in extreme cases, pyonephrosis, perinephric abscess and widespread systemic sepsis will develop. It is virtually impossible to eradicate infection in the long term when obstruction is present (7). As a detailed discussion of obstructive nephropathy is not the subject of discussion in this chapter, it is suffice to say that a kidney that is permanently damaged from any cause will have less reserve to withstand the effects of reflux, obstruction and infection. In any circumstance, the combination of obstruction and infection is a surgical emergency and both must be relieved without delay.

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

The acute effects of a UTI on the normal kidney are complex. They are worth reviewing as they may provide a lead in deciding how chronic changes can occur. *E. coli* is the most common Gram-negative organism isolated from the majority of patients with acute pyelonephritis. The proportion is lower in adults than in children (69% vs 80%) (9). Virulent organisms will 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 in susceptible individuals (e.g. those with diabetes mellitus, immunosuppression) (10).

Bacterial infection in the urinary tract can induce fever, elevate acute-phase reactants (e.g. CRP and the erythrocyte sedimentation rate), and elicit immunoglobulin (Ig) A and cytokine responses (11). In particular, serum IL-2 and IL-6 levels are elevated (12,13). Tissue damage is reflected by the urinary secretion of tubular proteins and enzymes, e.g. α - and β -micro- and macroglobulin, and N-acetyl glucosaminidase. In functional terms, there may be a loss of concentrating power, which can persist in the long term (14,15). The findings that there is a serological immune response and that bacteria become coated with antibodies to various antigenic components of the organism are regarded as evidence of an immune response and therefore of exposure to organisms that are potentially damaging to the renal parenchyma (16).

There are many identifiable factors relating to the virulence of the bacterial cell and to its ability to adhere to the mucosa as a preliminary to invasion. For example, Type 1 pili or fimbriae will combine with mannose receptors on the uromucoid of the protective mucopolysaccharide layer on the uro-epithelial cells lining the urinary tract. Type 2 or P fimbriae bind to glycolipids of the blood group substances that are secreted by the host urothelium. In practical terms, Enterobacteriaceae that are pathogenic to the kidney appear to express P or Type 2 fimbriae, at least in children: 90% of children with acute pyelonephritis express these organisms compared with a much smaller proportion of those who have had cystitis or asymptomatic bacteriuria (17). Teleologically, bacterial adhesion may be of variable benefit to the organism, as its attachment may render it easier for host defence mechanisms to localize and abolish it.

Paradoxically, reduced adhesiveness can facilitate silent penetration into the renal parenchyma. In a study from the Netherlands, of a group of 160 patients who had recently suffered an acute UTI and had

developed reduced concentrating power, a significant proportion (40%) did not have a febrile illness (15). 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.

The possible development of scarring as a result of a UTI in the absence of reflux, obstruction or calculi is controversial. It is agreed that a dramatic reduction in renal perfusion and excretion can occur acutely, and so-called lobar nephronia can be demonstrated with the newer methods of imaging, such as CT or DMSA scanning, but not with standard intravenous urography. In one such study, it was shown that 55% of patients with no pre-existing lesions had acute parenchymal lesions during the episode of acute pyelonephritis (2). These persisted 3-6 months later in 77% of patients (9). Alwall (18) described 29 women followed for 20-30 years with evidence of increasing renal damage and chronic pyelonephritis on biopsy. This early study used cruder diagnostic techniques that might not have identified pre-existing disease. Therefore, such patients may have had renal damage at the start and 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. Here 37 of 81 patients had one or more perfusion defects, the majority of which resolved within 3 months. Where they persisted, intravenous urography was performed and invariably showed evidence of reflux or obstructive nephropathy, which must have predated the acute infective episode (19).

To summarize, small parenchymal scars, demonstrated by modern imaging, may develop as a result of acute non-obstructive pyelonephritis. However, patients with such scars do not develop chronic renal failure and their scar is a very different lesion from that seen in reflux nephropathy. This is in line with clinical experience. In acute pyelonephritis, intravenous urography or DMSA scanning during an acute urinary infection can be very alarming and dramatic, but in practical terms the changes mostly resolve. The severity of the symptoms in an episode of acute pyelonephritis and the very small risk of permanent damage occurring should not influence the clinician to provide excessive antibiotic treatment.

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

- Diabetes mellitus
- Tuberculosis.

4.3.1 *Diabetes mellitus*

Diabetes increases the risk of acute pyelonephritis from infection by Enterobacteriaceae originating in the lower urogenital tract, though *Klebsiella* spp. are particularly common (25% compared with 12% in non-diabetics). Asymptomatic bacteriuria is common in female diabetics (though not in males) and, if left untreated, may lead to renal function impairment (20). The mechanism involved is not well understood and, as for uncomplicated acute pyelonephritis, dubious. Other subtle factors may be present: there may be underlying diabetic nephropathy (21) and autonomic neuropathy causing voiding dysfunction. Impaired host resistance is said to predispose to the persistence of nephropathogenic organisms and the development of renal complications, though specific evidence is lacking. Glycosuria inhibits phagocytosis and perhaps cellular immunity and encourages bacterial adherence. However, poor glycaemic control does not increase the risk of bacteriuria (22).

Diabetic patients are also prone to an under-reported and probably unusual form of infective interstitial nephritis (23), characterized histologically by acute pyogenic infiltrate with micro-abscesses and the development of acute renal failure. The origin of the organisms may be haematogenous. Even in the absence of obstruction, acute parenchymal infection may progress insidiously to form an intra-renal abscess, which ruptures leading to a perinephric collection and a psoas abscess. This necrotizing infection, sometimes by gas-forming organisms, has a high mortality rate. 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 a cause of the nephropathy. There is general agreement that diabetic patients represent a class of individuals who are particularly susceptible to rapid progression of renal parenchymal infection and therefore clearance of asymptomatic bacteriuria should be attempted. Antibiotic prophylaxis may be required, particularly if there is papillary necrosis, but, as yet, such recommendations are made on a basis of good sense rather than evidence from prospective randomized studies.

4.3.2 *Tuberculosis*

Tuberculosis can cause both acute and chronic renal damage through bilateral renal infiltration. Rarely, this can lead to end-stage renal failure. However, a more subtle form of interstitial granulomatous disease can occur that is sufficient to cause renal failure in the absence of fibrosis, calcification or obstruction (24,25).

Tuberculosis and leprosy can cause renal damage through the development of amyloid glomerulonephritis and also a form of proliferative glomerulonephritis (26,27). Although the modern trend in the treatment of urogenital tuberculosis is to shorten the duration, in the presence of renal parenchymal disease, more prolonged treatment is required.

4.4 Does chronic renal disease progress more quickly as a result of infection and do particular renal diseases predispose to a UTI?

4.4.1 *Chronic renal disease and UTIs*

There are good reasons why all uraemic patients should be prone to UTIs and why UTIs 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 (28). Uraemic patients are also mildly immunosuppressed and the formation of protective uro-epithelial mucus may be inhibited (29-31). And yet, with few exceptions, there is little evidence for a causal relationship between pre-existing chronic renal disease and a persisting UTI (7). The results of removing a scarred or hydronephrotic kidney in the hope of curing infection are often disappointing.

There are some exceptions. A UTI is a prominent complication of APCKD in which a symptomatic UTI is the presenting feature in 23-42% of patients (usually female) (32). 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 (33). The efficacy of antibiotic treatment may depend on whether the 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 for acute pyelonephritis and require active transport, are often ineffective (34). Fluoroquinolones are generally the most effective, but occasionally, the only solution (particularly after transplantation) is bilateral nephrectomy. Polycystic disease is not to be confused with acquired renal cystic disease of the end-stage kidney, which has no predisposition to a UTI.

The issue of whether urological complications, including UTIs, affect the progression of renal failure in polycystic disease or in any other renal pathology is controversial. A severe symptomatic UTI may indicate an adverse prognosis particularly in males with APCKD. Nephrolithiasis, particularly from infective struvite stones, obstructive uropathy and gross reflux, clearly do promote infection although not invariably. Whether vigorous treatment of asymptomatic bacteriuria or even a mild clinical UTI will make any difference to the progression of renal disease is doubtful (35).

4.4.2 *UTIs in renal transplantation*

A UTI is common after renal transplantation. Bacteriuria is present in 35-80% of patients, although the risk has been reduced by improvements in donation surgery, lowering the dose of immunosuppression and the use of prophylactic antibiotics (36). Early factors predisposing to a UTI include infection in the donor kidney. After the kidney is removed from its storage box the effluent from the renal vein and the surrounding fluid in the sterile plastic bags containing the excized kidney should be cultured, as organisms are likely to be introduced during the donation process. Bladder catheters and ureteric stents promote the loss of the glycosaminoglycan layer from the uro-epithelium, as well as providing a source of organisms within the mucus biofilm covering the foreign body. Infection in the native kidneys may worsen considerably with maximum immunosuppression. This problem is most troublesome with papillary necrosis, particularly in diabetes mellitus (37), massive infective VUR, polycystic disease and with infective calculi. Also of concern are the increasing number of children with congenital uropathies, often in association with neuropathic bladder dysfunction and the sinister combination of infravesical 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.

In the first 3 months, a 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 urine infection through bacterial colonization of dead tissue. This often occurs with commensal or fastidious organisms. The infection may be impossible to eradicate until the kidney or at least the dead segment is removed.

There are several potential mechanisms by which a severe UTI can cause graft failure. Early on there was a suggestion that reflux into the graft could lead to pyelonephritis and parenchymal scarring. 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 other mechanisms, such as the direct effect of cytokines, growth factors (e.g. tumour necrosis factor [TNF]) and free radicals as part of the inflammation cascade (36). A UTI can also re-activate cytomegalovirus infection, which can lead to acute transplant rejection. Sometimes it can be very difficult to distinguish rejection from infection (38).

4.5 What problems arise with antibiotic therapy in patients with renal insufficiency and after renal transplantation?

4.5.1 Antibiotic therapy in renal failure/transplantation

Much of the detailed information on antibiotic prescribing in renal failure is summarized in Tables 4-8. 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 between immunosuppressive agents and antibiotics.

Table 4: Use of antibiotics for a urinary tract infection with renal impairment

<ul style="list-style-type: none"> • Most antibiotics have a wide therapeutic index; no adjustment of dose until glomerular filtration rate is < 20 mL/min • Drugs removed by dialysis should be administered after a dialysis treatment • Combination of loop diuretics, e.g. furosemide, and cephalosporins is nephrotoxic • Nitrofurantoin and tetracyclines are contra-indicated, but not doxycycline • Dose of aminoglycosides needs to be adjusted
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Table 5: Dialysis of antibiotics

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

* Peritoneal dialysis: drugs cleared

Table 6: Treatment of tuberculosis in renal failure

<ul style="list-style-type: none"> • Rifampicin and isonicotinic acid hydrazide not cleared by dialysis: give pyridoxine • Ethambutol not dialysed: reduce dose if glomerular filtration rate < 30 mL/min • Avoid rifampicin with cyclosporin

Table 7: Recommendations for the prevention and treatment of a urinary tract infection in renal transplantation

<ol style="list-style-type: none"> 1. Treat infection in recipient before transplantation 2. Culture donor tissue sample and perfusate 3. Peri-operative antibiotic prophylaxis 4. 6-month low-dose TMP-SMX (co-trimoxazole) 5. Empirical treatment of overt infection

TMP-SMX = trimethoprim-sulphamethoxazole

Table 8: A urinary tract infection in renal transplantation

Therapy	Similar to non-transplant patients, but continue for 10-14 days
Prophylaxis	Donor and recipient
Choice of antibiotic	Fluoroquinolone, TMP-SMX
Interactions with cyclosporin A	Rifampicin, erythromycin, aminoglycosides, TMP-SMX, amphotericin B

TMP-SMX = trimethoprim-sulphamethoxazole.

4.5.2 Treatment of a UTI in renal transplant recipients

The treatment of a symptomatic UTI in transplant patients is similar to that in non-transplant patients, although the benefit of 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; fluoroquinolones seem to be particularly effective.

In most units, the combination of TMP and SMX is effective in preventing a UTI (39). It will also prevent *Pneumocystis carinii* pneumonia and infection with other rare fastidious organisms. Low-dose antibiotic prophylaxis with co-trimoxazole has been recommended for 6 months after transplantation. This covers the high-risk period when infection will be more likely to be symptomatic and associated with acute graft impairment. At a low dose, adverse interactions with cyclosporin A will not occur, although in the higher dose advocated by some units, synergistic nephrotoxicity with TMP is possible. A number of other drug interactions need to be considered (e.g. gentamicin, TMP-SMX and amphotericin B promote cyclosporin A toxicity; rifampicin induces cytochrome p450 synthetase and erythromycin inhibits hepatic cyclosporin A metabolism).

4.5.3 Fungal infection

Candida can occur in any immunosuppressed patient, but is more common in diabetic patients, 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 stent is usually necessary.

In any patient 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.

The significance of asymptomatic bacteriuria after renal transplantation is still unresolved. It is probably wise to investigate such patients for a structural abnormality and to treat it if it is persistent.

4.6 Are immunosuppressed patients prone to UTIs, particularly in the context of renal transplantation? Are UTIs a significant cause of graft failure?

4.6.1 Immunosuppression

The place of immunosuppression per se in the development of a UTI is unresolved (40). Patients with end-stage renal failure are generally not particularly susceptible to the usual Gram-negative urinary pathogens, although they may acquire unusual and granulomatous infections. They do have evidence of reduced cellular and humoral immunity. However, the situation is a little clearer in male patients with human immunodeficiency virus and acquired immunodeficiency syndrome, in whom there is a close relationship between CD4 counts and the risk of bacteriuria, particularly in patients whose counts are < 200 cells/mL (41). About 40% of patients with bacteriuria will be asymptomatic. In these patients, *Pneumocystis carinii* pneumonia prophylaxis of the type used in transplant patients may not reduce the rate of bacteriuria, perhaps due to the previous development of resistant organisms. Also, in these patients, virus and fungal infections are relatively common.

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5. COMPLICATED UTI'S DUE TO UROLOGICAL DISORDERS

5.1 SUMMARY

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 that interferes with host defence mechanisms, which increases 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 predominant and *E. coli* is the most common pathogen, but 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 supporting 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 fluoroquinolone with mainly renal excretion, an aminopenicillin plus a BLI, a group 2 or 3a cephalosporin or, in the case of parenteral therapy, an aminoglycoside, are recommended alternatives.

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*, 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.

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

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.

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 9.

Table 9: 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 whatever the cause, e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumour
- VUR or other functional abnormalities
- Urinary tract modifications, such as ileal loop or pouch
- Chemical or radiation injuries of the uro-epithelium
- Peri- and post-operative UTI
- Renal insufficiency and transplantation, diabetes mellitus and immunodeficiency

A complicated UTI can arise in a heterogeneous group of patients. But neither patient age nor gender by itself is 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 at least into 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 up 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 of the lower urinary tract (LUTS), are not only caused by UTIs but also by other urological disorders, such as benign prostatic hyperplasia (BPH), transurethral resection of the prostate (TURP), etc.

Apart from urological abnormalities, concomitant medical conditions, such as diabetes mellitus (10%) and renal failure, which can be related to the urological abnormalities (5), are often present in a complicated UTI. These are discussed in more detail in Chapter 4.

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 microorganism are required. The requirement for pyuria is ≥ 10 WBC per high-power field (x 400) in the resuspended sediment of a centrifuged aliquot of urine or per mm³ 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 microorganisms with a higher prevalence of resistance against antimicrobials, and higher rates of treatment failure if the underlying abnormality cannot be corrected. The presence of a resistant strain on its own, however, is not enough to define a complicated UTI; a urinary abnormality (anatomical or functional) or the presence of an underlying disease predisposing to a UTI is also necessary.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than with an uncomplicated UTI and the bacteria are more likely to be antibiotic resistant (especially in a treatment-related complicated UTI), than those isolated in an uncomplicated UTI. *E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas*, *Serratia* spp. and enterococci are the usual strains found in cultures. Enterobacteriaceae predominate (60-75%) (6-8) and *E. coli* is the most common pathogen, particularly if this is the 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. 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 *Staphylococcus* spp. 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 and 82% of the patients were 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 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); biofilm has to be considered. Antimicrobial therapy may only be effective in the early stages of this infection (15).

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, supporting 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 needs knowledge of the spectrum of possible pathogens and local antibiotic resistance patterns, and 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 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 properly 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 infecting 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 infecting 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.

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 single-dose therapy of uncomplicated cystitis (17). The aminopenicillins, ampicillin or amoxicillin, are no longer sufficiently active against *E. coli*. In case of the 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 which 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.

Patients can generally be treated as outpatients. In more severe cases (e.g. hospitalized patients), antibiotics have to be given parenterally and a combination of an aminoglycoside with a β -lactam antibiotic 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 infecting 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 Appendix 2.

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 (18). Long-term antimicrobial therapy should be considered if complete removal of the stone can not be achieved (19).

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 (20,21). In short-term catheterization, antibiotics may delay the onset of bacteriuria, but do not reduce complications (22).

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 (23), even in case 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 specific group of patients.

Antimicrobial treatment options are summarized in Table 10.

Table 10: Antimicrobial treatment options for empirical therapy

<p>Recommended for initial empirical treatment</p> <ul style="list-style-type: none">• Fluoroquinolones• Aminopenicillin plus a BLI• Cephalosporin (group 2 or 3a)• Aminoglycoside <p>Recommended for empirical treatment in case of initial failure or for severe cases</p> <ul style="list-style-type: none">• Fluoroquinolone (if not used for initial therapy)• Ureidopenicillin (piperacillin) plus a BLI• Cephalosporin (group 3b)• Carbapenem• Combination therapy:<ul style="list-style-type: none">- Aminoglycoside + β-lactam antibiotic- Aminoglycoside + fluoroquinolone <p>Not recommended for empirical treatment</p> <ul style="list-style-type: none">• Aminopenicillins, e.g. amoxicillin, ampicillin• Trimethoprim-sulphamethoxazole (only if susceptibility of pathogen is known)• Fosfomycin trometamol

5.4.7 Follow-up after treatment

The greater likelihood of the resistance of micro-organisms involved in complicated UTIs is another feature of these infectious diseases. This is not a priori related to the urinary abnormality, but 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 5-9 days after the completion of therapy and also 4-6 weeks later.

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6. SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

6.1 SUMMARY

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a complicated UTI. Systemic inflammatory response (fever or hypothermia, tachycardia, tachypnoea, hypotension, oliguria, leucocyturia or leucopenia) is recognized as the first event in a cascade to multi-organ failure.

Urosepsis treatment calls for the combination of adequate life-supporting care, appropriate antibiotic therapy, adjunctive measures (e.g. sympathomimetic amines, corticosteroids, anticoagulation, granulocyte-colony stimulating factor [G-CSF] or granulocyte-macrophage-colony stimulating factor [GM-CSF], naloxone), and the optimal management of urinary tract disorders.

Urologists are recommended to treat patients in collaboration with intensive care specialists.

Much 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 techniques in order to avoid cross-infection.

6.2 Background

A UTI can manifest itself as bacteriuria, bacteraemia, septicaemia or sepsis syndrome, depending on its localized or systemic extension. Sepsis syndrome is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, hypotension, oliguria, leucocyturia or leucopenia).

Sepsis syndrome is a severe situation with a reported mortality rate ranging from 20% to 60% (1-7). In urology, sepsis syndrome depends upon the host response. Those more likely to develop the condition 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 conditions, 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 a 'systemic inflammatory response syndrome' (SIRS) may be present without septicaemia (7).

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.

6.3 Definition and clinical manifestation of sepsis syndrome in urology

The clinical evidence of a UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leucocyturia. The following definitions apply:

- Sepsis syndrome is a systemic response to severe infection
- Severe sepsis is sepsis associated with organ dysfunction
- Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation
- Refractory septic shock depends on response to therapy

Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic dysfunction. These characteristics have been developed into a set of clinical and laboratory criteria (Table 1).

Table 11: Clinical diagnostic criteria of sepsis and septic shock

Disorder	Definition
Infection	<ul style="list-style-type: none"> • Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response
Bacteraemia	<ul style="list-style-type: none"> • Bacteria present in blood as confirmed by culture; may be transient
Septicaemia	<ul style="list-style-type: none"> • Same as bacteraemia, but implies greater severity • Clinical evidence of infection plus evidence of a systemic response to infection. This systemic response is manifested by two or more of the following conditions: <ul style="list-style-type: none"> - Temperature > 38°C or < 36°C - Heart rate > 90 beats per minute - Respiratory rate > 20 breaths/min or PaCO₂ < 32 mmHg (< 4.3 kPa) - WBC > 12,000 cells/mm³, < 4,000 cells/mm³ or 10% immature (band) forms
Sepsis syndrome	<ul style="list-style-type: none"> • Infection plus evidence of altered organ perfusion with at least one of the following: hypoxaemia; elevated lactate; oliguria; altered mentation
Hypotension	<ul style="list-style-type: none"> • A systolic blood pressure of < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other cause of hypotension
Severe sepsis	<ul style="list-style-type: none"> • 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 on mental status
Septic shock	<ul style="list-style-type: none"> • Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities, which 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	<ul style="list-style-type: none"> • Septic shock that lasts > 1 hour and does not respond to fluid administration or pharmacological intervention
Systemic inflammatory response syndrome	<ul style="list-style-type: none"> • Response to a wide variety of clinical insults, which can be infectious, as in sepsis, but can be non-infectious in aetiology (e.g. burns, pancreatitis)

PaCO₂ = partial pressure of carbon dioxide in alveolar gas; WBC = white blood cells.

6.4 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 bacteraemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis (ABP), and is facilitated by obstruction. Some micro-organisms are more aggressive, such as methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa* and *Serratia* spp. Most commonly, the condition develops in compromised patients (e.g. those with diabetics or the immunosuppressed) with typical signs of generalized sepsis associated with local signs of infection. In such cases, the search for bacteria can be unsuccessful. A fatal outcome is described in 30-60% of all patients.

6.4.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis syndrome and 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. TNF- α , IL-1, IL-6 and IL-8 are cytokines that are often associated with sepsis. During infection and inflammation, the host produces cytokines with predominantly pro-inflammatory properties, as well as counter-inflammatory cytokines, such as IL-10 and IL-4 (5).

6.4.2 *Procalcitonin is a potential marker of sepsis*

Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally, procalcitonin is produced in the C cells of the thyroid gland and, 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 systemic inflammatory response 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.

6.5 Prevention

Septic shock is the most frequent cause of death for hospitalized patients with nosocomial infection (20-60%) (8). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for the combination of adequate life-supporting care and appropriate antibiotic therapy (9). In such a situation, urologists are recommended to collaborate with intensive care specialists for the best management of the patient.

6.5.1 *Preventative measures of proven or probable efficacy (10-13)*

The most effective methods used to prevent urosepsis are the same as are used to prevent nosocomial infection:

- Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
- Correct use of antimicrobial agents both in prophylaxis and in treatment of established infections to avoid selection of resistant strains. Antibiotic agents are chosen according to the predominant bacteria 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 catheter, as soon as the patient's condition allows. Nosocomial UTIs are promoted by bladder catheterization as well as ureteral stenting (14). 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: the routine use of protective, disposable gloves, frequent hand disinfection and respect of infectious disease control measures to prevent cross-infections.

6.5.2 *Appropriate peri-operative antimicrobial prophylaxis (6)*

For appropriate peri-operative antimicrobial prophylaxis, see Chapter 9. The potential side effects of antibiotics must be considered prior to their administration in a prophylactic regimen.

6.5.3 *Preventative measures of debatable efficacy (1)*

- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.
- Use of urinary catheters coated with antibiotics or silver nitrate.

6.5.4 *Ineffective or counterproductive measures (1)*

- Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase the risk of infection with resistant bacteria (2).
- 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 (2). Its use is reserved for immunosuppressed patients.

6.6 Treatment of underlying disease

The drainage of any obstruction in the urinary tract and the removal of foreign bodies, such as urinary catheters or stones, may by themselves cause resolution of symptoms and lead to recovery.

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 2.

6.6.1 Adjunctive measures (7)

- 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.
- Sympathomimetic amines have been widely used to treat the haemodynamic complications of shock. Alternative agents, such as isoproterenol, dopamine and dobutamine, have mainly replaced noradrenaline.
- Corticosteroids are thought to be beneficial as adjunctive therapy in Gram-negative infections, particularly those complicated by shock.
- Anticoagulation, particularly heparinization, to treat septicaemic states associated with disseminated intravascular coagulation is logical.
- Granulocyte transfusions were once popular for the treatment of infections in neutropenic subjects. Use of recombinant colony-stimulating factors, such as G-CSF and GM-CSF, has mainly replaced WBC transfusions.
- Naloxone, an antagonist of opiates and β -endorphins, has been shown to reverse the course of endotoxic and hypovolaemic shock.

6.7 Conclusion

Sepsis syndrome in urology remains a severe situation with a mortality rate as high as 20-60%. Early recognition of the symptoms may decrease mortality by timely treatment of the urinary tract disorder, e.g. obstruction, lithiasis. Adequate measures to ensure life-support and appropriate antibiotic treatment are the best approaches to improving patient survival. Prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections, using antibiotic prophylaxis and therapy in a logical and well-accepted manner.

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7. URETHRITIS

7.1 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 primary urethritis will be discussed in this Chapter (2).

7.2 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 on one side and the frequency of *N. gonorrhoeae* and *C. trachomatis* on the other. Infection is spread by sexual contact.

7.3 Pathogens

Pathogens include *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma genitalium* and *T. vaginalis*. The frequency of the different species varies between patient populations (3-7). *Mycoplasma hominis* probably does not cause urethritis, while *Ureaplasma urealyticum* is an infrequent cause. In most cases, the clinical evidence of *Mycoplasma* or *Ureaplasma* represents an asymptomatic colonization of the urogenital tract.

7.4 Route of infection and pathogenesis

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae*, *C. trachomatis*) and thus cause a pyogenic infection. Originating from urethritis, chlamydiae and gonococci can spread further and can cause epididymitis in the male or cervicitis, endometritis and salpingitis in the female.

7.5 Clinical course

Purulent discharge and alguria are symptoms of urethritis, but many infections of the urethra are asymptomatic.

7.6 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 where 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.

7.7 Therapy

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

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

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

First choice:

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

Second choice:

- Erythromycin, 500 mg orally four times daily for 7 days
- Ofloxacin, 200 mg orally twice 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. 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 four times daily orally for 7 days). As in other STD, the treatment of sexual partners is necessary.

7.8 Prevention

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

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8. PROSTATITIS, EPIDIDYMITIS AND ORCHITIS

8.1 SUMMARY

Prostatitis is a disease entity that is diagnosed by symptoms, the microscopy of expressed prostatic secretion (EPS), and the culture of EPS and segmented urine samples. According to the duration of symptoms, prostatitis is described as either acute or, where symptoms are present for at least 3 months, chronic. We recommend the classification of prostatitis suggested by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)/National Institutes of Health (NIH), in which bacterial prostatitis (acute and chronic) is distinguished from chronic pelvic pain syndrome (CPPS).

Acute bacterial prostatitis (ABP) can be a serious infection and parenteral administration of high doses of bactericidal antibiotics, such as aminoglycosides and a penicillin derivative or a third-generation cephalosporin, are required until defeverescence and the normalization of infection parameters. In less severe cases, a fluoroquinolone may be given orally for 10 days.

In chronic bacterial prostatitis (CBP) and CPPS, a fluoroquinolone or TMP should be given orally for 2 weeks after the initial diagnosis. The patient should then be re-assessed and antibiotics continued only if pre-treatment cultures were positive or if the patient reports a positive effect of the treatment in terms of pain relief. A total treatment period of 4-6 weeks is then recommended.

Inflammatory processes of the testis (orchitis) and epididymis (epididymitis) have to be classified as acute or chronic processes according to the onset and clinical course. The majority of cases of epididymitis are due to common urinary pathogens. Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection. Orchitis of the child and mumps-orchitis are of haematogenous origin. Epididymo-orchitis is also seen in systemic infections, such as tuberculosis, lues, brucellosis and cryptococcus disease. Antimicrobials should be selected on the empirical basis that in young, sexually active men *C. trachomatis* is usually the causative agent, and that in older men with BPH or other micturition disturbances, the most common uropathogens are involved.

Prior to antimicrobial therapy, a urethral swab and MSU should be obtained for microbiological investigation. Fluoroquinolones, preferably those with good activity against *C. trachomatis* (e.g. ofloxacin, 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 the aetiological agent, treatment could also be continued with doxycycline, 200 mg/day, for a total treatment period of at least 2 weeks. Macrolides may also be considered. For cases of *C. trachomatis* epididymitis, the sexual partner should also be treated.

8.2 Prostatitis

8.2.1 Background

What was previously denoted 'prostatitis', is today more frequently referred to as 'prostatitis syndrome'. This disease entity is diagnosed and classified by symptoms, microscopy and the culture of EPS and segmented urine samples, according to Meares and Stamey (1). The term 'syndrome' indicates that, in most cases, the aetiology is unknown and the diagnostic criteria are weak. A causative pathogen is detected in only 5-10% of cases (2). For the remaining patients, treatment is given on an empirical basis, and numerous medical and physical forms of treatment have been reported. In recent years, a new classification has been introduced, and hence a better systematization of treatment options may be of benefit for these patients (3,4). This section deals with documented or suspected bacterial infections of the prostate.

8.2.2 Classification systems

The purpose of the four-glass technique, described by Meares and Stamey (1), was to localize the infection to the urethra, the prostate or the bladder. Ten years later, Drach et al. (5) suggested a classification of prostatitis based on the work of Meares and Stamey. In this classification, various types of prostatitis are differentiated according to the findings of WBC or positive cultures in EPS and segmented urine samples (VB1 - first-voided urine; VB2 - mid-stream urine; VB3 - urine following prostatic massage). This has been the most widely used classification of prostatitis for almost three decades (Table 12). The latest World Health Organization (WHO) classification of diseases (International Classification of Diseases, 10th version) is based on this classification (6).

Table 12: Classification of prostatitis according to Drach et al. (5)

<p>Acute bacterial prostatitis</p> <ul style="list-style-type: none">• Clinically significant infection of the prostate with acute symptoms <p>Chronic bacterial prostatitis</p> <ul style="list-style-type: none">• Significant inflammation of the prostate• Isolation of an aetiologically recognized organism from the prostatic fluid/urine <p>Chronic abacterial prostatitis</p> <ul style="list-style-type: none">• Significant prostatic inflammation• Failure to isolate an organism from the prostatic fluid/urine, or the isolation of an organism the aetiological significance of which is debatable <p>Prostatodynia</p> <ul style="list-style-type: none">• No significant prostatic inflammation• Failure to isolate an organism from the prostatic fluid/urine
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In 1995, the NIDDK of the NIH, 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). This workshop recommended a new classification of the prostatitis syndrome, which was later accepted by the International Prostatitis Collaborative Network. The terms abacterial prostatitis and prostatodynia were changed to CPPS with or without inflammation, respectively. A new type, asymptomatic prostatitis (e.g. histological prostatitis), was added (Table 13). This classification provides a better logical base for treatment options.

Table 13: Classification of prostatitis according to the NIDDK/NIH (4)

<ol style="list-style-type: none">I. Acute bacterial prostatitis (ABP)II. Chronic bacterial prostatitis (CBP)III. Chronic pelvic pain syndrome (CPPS)<ol style="list-style-type: none">A. Inflammatory CPPS: WBC in semen/EPS/voided bladder urine-3 (VB3)B. Non-inflammatory CPPS: No WBC in semen/EPS/VB3IV. Asymptomatic inflammatory prostatitis (histological prostatitis)

EPS = expressed prostatic secretion; WBC = white blood cells.

8.2.3 Diagnosis

Clinical history and symptoms: According to the duration of symptoms, the prostatitis syndrome is described as either acute or, where symptoms are present for at least 3 months, chronic (4). The predominant symptoms are pain at various locations and LUTS (7-9). Zermann et al. (7) reported the following sites of pain in men with prostatitis:

- Prostate/perineum: 46%
- Scrotum and/or testes: 39%
- Penis: 6%
- Urinary bladder: 6%
- Lower back: 2%

The following LUTS were reported by Alexander and Trissel (9):

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

CBP is the most frequent cause of recurrent UTIs in the male (10). Several prostatitis symptom questionnaires have been developed for the quantification of symptoms (11-13). The NIH chronic prostatitis symptom index has been validated (13), but so far reports about its benefit in clinical studies are still awaited. Symptoms appear to be the strongest classification parameter in the prostatitis syndrome (11).

Clinical findings: The prostate may be swollen and painful on digital rectal examination in acute prostatitis, a condition in which prostatic massage is contra-indicated. The physical examination should also consider other urogenital and non-urogenital diseases (see differential diagnosis) and include an evaluation of the musculature of the pelvic floor.

Investigation of urine cultures and EPS: The most important investigations in the evaluation of the prostatitis patient are the quantitative segmental bacteriological localization cultures and microscopy of EPS, as described by Meares and Stamey (1). The Enterobacteriaceae, in particular *E. coli*, are the predominant pathogens (Table 13). The significance of intracellular bacteria such as *C. trachomatis* is uncertain. In patients with an immune deficiency or human immunodeficiency virus infection, prostatitis may be caused by fastidious pathogens such as *M. tuberculosis*, *Candida* spp. and rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis* and *Histoplasma capsulatum* (14).

Table 14: The most common pathogens in prostatitis. Adapted from Weidner et al. (2)

<p>Aetiologically recognized pathogens</p> <p><i>Escherichia coli</i> <i>Klebsiella</i> spp. <i>Proteus mirabilis</i> <i>Enterococcus faecalis</i> <i>Pseudomonas aeruginosa</i></p> <p>Organisms of debatable significance</p> <p>Staphylococci Chlamydia trachomatis Ureaplasma urealyticum Mycoplasma hominis</p>

Histology: In an increasing number of cases, prostatitis is diagnosed from biopsies taken for suspected prostate cancer. There is, however, no correlation between clinical symptoms and histological findings.

Other tests: The main parameter for diagnosing inflammation in the male urogenital tract is increased leucocytes in the prostatic fluid and prostate, as well as elevated pH, lactate dehydrogenase and immunoglobulins. Possible supporting parameters are complement C3, coeruleplasmin or polymorphonuclear leucocyte-elastase in the ejaculate, none of which are part of routine diagnostic evaluation (15).

Transrectal ultrasound may reveal intraprostatic abscesses, calculi in the prostate and dilatations in the seminal vesicles, but is not a determining classification parameter in prostatitis (16). Transrectal ultrasound is mainly used to measure prostate size and to guide the needle in prostate biopsies to rule out prostate cancer.

Additional investigations: The examination of EPS cannot be replaced by examination of ejaculate. It is difficult to differentiate spermatozoa and leucocytes in ejaculate (17), and the detection rate in positive cultures is significantly reduced (18). Prostate biopsies for the culture of intracellular bacteria should be reserved for selected cases or research purposes. Video urodynamics and advanced urodynamic examination with measurement of urethral closing pressure may be indicated in patients with CPPS in whom no infective agent can be found (7,19). The measurement of cytokines and biofilms in EPS is of research interest only (8,20). PSA values may be elevated in both symptomatic and asymptomatic prostatitis, but the measurement of free and total PSA adds no practical diagnostic information in prostatitis (21).

Differential diagnosis: Various urogenital and non-urogenital disorders can mimic symptoms found in patients with 'prostatitis syndrome', e.g. urethral stricture, bladder cancer, interstitial cystitis, prostate cancer, ureteral calculus, chronic epididymitis, anorectal disorders, pelvic floor myalgia and hernia inguinalis. Careful individualized investigations are necessary.

Order of diagnostic steps: The order of the diagnostic evaluation of a patient with symptoms consistent with a prostatitis syndrome depends on previous examinations, the established routine in different hospitals and countries, as well as on the distance from the patient's home to the urologist. A recommended order is presented in Table 15.

Table 15: Urological work-up of patients with prostatitis syndrome

<p>Clinical history Physical examination Urinalysis and urine culture (mid-stream urine) Rule out venereal diseases Micturition chart, uroflowmetry and residual urine Four-glass test according to Meares and Stamey (1), including microscopy and culture Antibacterial therapy in patients with proven or suspected infection In case of no improvement (after 2 weeks) further evaluation is necessary, e.g. video urodynamics</p>

8.2.4 Treatment

Antibacterial therapy: Antibiotics are recommended in ABP and in CBP, and as empirical therapy in inflammatory CPPS. ABP can be a serious infection with fever, intense local pain and general symptoms. Parenteral administration of high doses of bactericidal antibiotics, such as aminoglycosides, a broad-spectrum penicillin derivative or a third-generation cephalosporin, are required until defeverescence and the normalization of infection parameters. In less severe cases, a fluoroquinolone may be given orally for 10 days (3).

The recommended antibiotics in CBP and chronic inflammatory CPPS and their advantages and disadvantages are listed in Table 16 (22).

Table 16: Antibiotics in chronic bacterial prostatitis (adapted from Bjerklund Johansen *et al.* [22])

Antibiotic	Advantages	Disadvantages	Recommendation
Fluoroquinolones	<ul style="list-style-type: none"> • 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 <i>Pseudomonas aeruginosa</i> • In general, good safety profile 	Depending on the substance: <ul style="list-style-type: none"> • Drug interactions • Phototoxicity • Central nervous system adverse events 	Recommend
Trimethoprim	<ul style="list-style-type: none"> • Good penetration into prostate • Oral and parenteral forms available • Relatively cheap • Monitoring unnecessary • Active against most relevant pathogens 	<ul style="list-style-type: none"> • No activity against <i>Pseudomonas</i>, some enterococci and some Enterobacteriaceae 	Consider
Tetracyclines	<ul style="list-style-type: none"> • Cheap • Oral and parenteral forms available • Good activity against <i>Chlamydia</i> and <i>Mycoplasma</i> 	<ul style="list-style-type: none"> • No activity against <i>P. aeruginosa</i> • Unreliable activity against coagulase-negative Staphylococci, <i>Escherichia coli</i>, other Enterobacteriaceae, and enterococci • Contra-indicated in renal and liver failure • Risk of skin sensitization 	Reserve for special indications
Macrolides	<ul style="list-style-type: none"> • Reasonably activity against Gram-positive bacteria • Active against <i>Chlamydia</i> • Good penetration into prostate • Relatively non-toxic 	<ul style="list-style-type: none"> • Little supporting clinical trials' data • Unreliable activity against Gram-negative bacteria 	Reserve for special indications

Aminoglycosides are not recommended in CBP, although they have good activity against Gram-negative bacteria. They exist in parenteral formulation only, have dose-related toxicity and need monitoring if given in more than two or three doses, and have inadequate activity against Gram-positive bacteria. The oral β -lactams are not recommended because of poor penetration into the prostate, and there is unreliable sensitivity to this antibiotic; they are contra-indicated in patients with an allergy to them. Co-trimoxazole is not recommended mainly because there are no advantages over TMP alone and there is also a risk of serious adverse events (22).

The duration of antibiotic treatment is based on experience and expert opinion and is supported by many clinical studies (23). In CBP and in inflammatory CPPS, antibiotics should be given for 2 weeks after the initial diagnosis. Then the patient should be re-assessed and antibiotics only continued if pre-treatment cultures were positive or if the patient reports a positive effect of the treatment on pain relief. A total treatment period of 4-6 weeks is recommended. Relatively high doses are needed and oral therapy is preferred (22). The reason for the administration of antibiotics in chronic inflammatory prostatitis is that there may be a bacterial infection even though bacteria are not detected by available methods (23). Furthermore, many clinical studies report the good effect of antibiotics in inflammatory CPPS/abacterial prostatitis (24,25).

If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given (22,25).

Antibiotic and α -blocker combinations: Urodynamic studies have shown increased urethral closing pressure in patients with chronic prostatitis (7). A combination treatment of α -blockers and antibiotics is reported to have a higher cure rate than antibiotics alone in inflammatory CPPS (26). This is a treatment option favoured by many urologists.

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 (27,28).

Surgery: In ABP, some patients require bladder drainage, preferably with a suprapubic catheter. A positive effect of TURP has been observed by some authors in patients with CBP and severe discomfort (29). Even radical prostatovesiculectomies have been carried out to relieve the pain, the results of which are dubious (30). In general, surgery should be avoided in the treatment of prostatitis patients except for the drainage of prostatic abscesses.

Other treatments: Microwave energy delivered from Prostatron 2.0 has an in vitro bactericidal effect on laboratory cultured *E. coli* and Enterobacter (31) and, in controlled studies, transurethral microwave thermotherapy in patients with inflammatory CPPS showed better results than a sham procedure (32). However, transurethral microwave thermotherapy is still considered an experimental treatment option in patients in whom an infection is suspected.

A number of other medical and physical treatment modalities have been suggested in non-inflammatory CPPS. As there is no evidence of infection in this condition, this topic lies beyond the scope of this section and is discussed elsewhere (11,12).

8.3 Epididymitis and orchitis

8.3.1 Epidemiology

Definition and nomenclature: Epididymitis, inflammation of the epididymis, causes pain and swelling which is almost always unilateral and relatively acute in onset (33). 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 (34). 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 (35).

Incidence and prevalence: There are no new precise 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 (34). Acute epididymitis in young males is associated with sexual activity and infection of the consort (36).

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 (37). A primary chronic orchitis is the granulomatous disease, a rare condition with uncertain aetiology reported in about 100 cases in the literature (38).

8.3.2 Morbidity

Complications in epididymo-orchitis include abscess formation, testicular infarction, testicular atrophy, development of chronic epididymal induration and infertility (34).

Epididymitis caused by sexually transmitted organisms occurs mainly in sexually active males aged < 35 years (34,39). The majority of cases of epididymitis are due to common urinary pathogens, which are also the most common cause of bacteriuria (34,39). Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection.

8.3.3 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 (35,38). Orchitis of the child and mumps-orchitis are of haematogenous origin (35). Epididymo-orchitis is also seen in systemic infections such as tuberculosis, lues, brucellosis and cryptococcus disease.

8.3.4 Clinical features

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-gonorrhoeic urethritis. *C. trachomatis* will be isolated in approximately two-thirds of these patients (34,39).

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 (40). 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 (36).

8.3.5 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.

8.3.6 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 (41).

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.

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.

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.

In case of *C. trachomatis* epididymitis, the sexual partner should also be treated. If uropathogens are found as causative agents, a thorough search for micturition disturbances should be carried out to prevent relapse. 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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9. PERI-OPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

9.1 SUMMARY

The main aim of antimicrobial prophylaxis in urology is to prevent symptomatic/febrile genito-urinary infections, such as acute pyelonephritis, prostatitis, epididymitis and urosepsis, as well as serious wound infections.

The need for prophylaxis depends on the type of intervention and the individual risk for each individual patient. General antibiotic prophylaxis is not required in open operations without bowel segments. The same is true for reconstructive operations in the genital area, with the exception of long or secondary interventions, or implant surgery. For diagnostic interventions, peri-operative antibacterial prophylaxis is generally recommended only in transrectal prostate biopsy with a thick needle. Prophylaxis should always be considered in patients who have an increased risk of infection, and especially before a transurethral resection of the prostate (TURP) if there is a history of a UTI.

Generally, a single full dose of a suitable antibiotic, preferably administered parenterally (alternatively with oral drugs with excellent bioavailability, e.g. fluoroquinolones), is appropriate for prophylaxis. Only in the case of a prolonged intervention (> 3 hours) may additional doses be required, the size and timing of which are dictated by the pharmacokinetics of the antibiotic. Antibiotic prophylaxis should not be continued for > 24 hours. When continuous urinary drainage, e.g. indwelling catheter, stent, nephrostomy, etc., is left in place after an operation, prolongation of peri-operative antibacterial prophylaxis is contra-indicated.

Many antibiotics meet the criteria for use in prophylaxis (Appendix 4), e.g. second-generation cephalosporins, fluoroquinolones and aminopenicillins plus a BLI. Aminoglycosides should be reserved for high-risk patients and those who are allergic to β -lactams. Broad-spectrum antibiotics, such as third-generation cephalosporins, acylaminopenicillins plus a BLI, or carbapenems, should be used only sparingly, e.g. if the site of the operation is contaminated with multi-resistant nosocomial bacteria. This applies also to the use of vancomycin.

9.2 Introduction

Almost 50 years after its introduction, peri-operative prophylaxis is still controversial. Whereas a clear benefit has been established for certain surgical operations (e.g. elective colonic surgery), there is no general consensus on the use of antibacterial prophylaxis in urology. The traditional classification of surgical procedures according to Cruse and Foord (1) into clean, clean-contaminated, contaminated and dirty does not adequately describe the risk of infection in endo-urology. The overall risk is influenced by the patient's condition, the surgical procedure and environmental factors. However, the significance of each factor has not yet been quantified (2).

At present, most studies are poorly designed or lack statistical power. The differentiation between therapy and prophylaxis is not clear. Evaluation of risk factors is unsatisfactory and the terms bacteriuria and infection are used uncritically. In addition, many of these studies lack knowledge of pharmacokinetics and pharmacodynamics, bacterial pathogenicity and the role of nosocomial infections (3,4). Thus, it is not surprising that the literature is inconclusive with regard to prophylaxis, showing negative as well as positive results for every kind of urological intervention.

A recent survey of 320 German urologists revealed controversial opinions about peri-operative antibiotic prophylaxis (5). It was administered in only 51% of procedures involving the urinary tract and 9% of the responding urologists did not even use prophylaxis when opening the intestine. There was little agreement on the choice of antibiotics (35.3% used co-trimoxazole, 26.6% cephalosporins and 8.7% fluoroquinolones) and the duration of prophylaxis (only 10% used a single pre-operative dosing regimen). There are also variations between countries (6-8). Consequently, guidelines for the indication of peri-operative prophylaxis in urology are certainly necessary to improve the quality of patient care.

Presented are practical recommendations covering patients with normal and increased susceptibility, as well as different types of surgical procedures. These recommendations are based on clinical studies, expert opinion and professional consensus. They also consider the recommendations of societies, such as the Paul Ehrlich Society for Chemotherapy (9), the Working Group "Infectiology" of the German Society for Urology (10), Association Française d'Urologie (11) and the Swedish-Norwegian Consensus Group (12).

9.3 Goals of peri-operative antibacterial prophylaxis

The aim of peri-operative prophylaxis is to limit infection related to intervention. However, it can never compensate for poor operative technique. Antibiotic prophylaxis is only one component of infection prevention

management and should be integrated into the local antibiotic policy. Other important factors should not be neglected (e.g. short hospital stay, catheter care, use of closed drainage systems) and the education of the health care team is of paramount importance (13-15).

The endpoints of peri-operative prophylaxis in urology are debatable. It is generally agreed that its main aim is to prevent symptomatic/febrile genito-urinary infections, such as acute pyelonephritis, prostatitis, epididymitis and urosepsis, as well as serious wound infections. This might be extended to include post-operative asymptomatic bacteriuria or even a small wound infection, which could easily be treated on an outpatient basis. In some circumstances, these might assume greater significance, e.g. in implant surgery where either can cause the patient to risk loss of the implant. On the contrary, asymptomatic bacteriuria after TURP may disappear spontaneously and is usually of no significance. Another question is: should peri-operative prophylaxis also be concerned with the prevention of non-urological infections, e.g. endocarditis and post-operative pneumonia? It is considered that peri-operative antibacterial prophylaxis in urology has to go beyond the traditional aim of prophylaxis, which is the prevention of wound infections (3,16).

With transurethral resection of the prostate (TURP), several controlled studies have shown that the rate of post-operative bacteriuria can be reduced by peri-operative prophylaxis. And yet this does not necessarily translate into a reduction of symptomatic UTIs or the prevention of febrile episodes (17-22). Moreover, since the rate of septic complications is generally < 1%, a prospective study will require large numbers of patients to be recruited to reach statistical power. Until now, most of our knowledge on the prevention of urosepsis has come from retrospective studies and is therefore deficient (23).

It is generally agreed that the incidence of post-operative septic complications has fallen over the past 10-15 years, and this may have more to do with improved asepsis and advanced technology than with antibiotic prophylaxis.

9.4 Indications for peri-operative antibacterial prophylaxis

The need for prophylaxis depends on the type of intervention and the individual risk for each individual patient. Risk factors, such as chronic debility, metabolic dysfunction (e.g. diabetes mellitus), immunosuppression, poor surgical condition, re-operation and special risk factors (e.g. artificial cardiac valves) have to be considered (Table 17). A review of factors of importance for the prevention of surgical site infections was recently published (24).

Table 17: General factors increasing the risk of post-operative infection following urological intervention due to the patient's condition and/or increased bacterial load

Risk factors due to:	
Patient's Condition	Increased Bacterial Load
<ul style="list-style-type: none"> • Reduced general condition, e.g. debility • Metabolic dysfunction, e.g. diabetes mellitus • Immunosuppression • Re-operation • Special risk, e.g. artificial cardiac valve 	<ul style="list-style-type: none"> • Surgery using bowel segments • Transrectal biopsy of the prostate • Long-term urinary drainage • Urinary obstruction

Increased exposure to endogenous bacteria can be expected in procedures that include bowel segments and transrectal biopsy of the prostate with a thick needle. Furthermore, bacterial contamination of the urinary tract is often associated with long-term drainage (catheter, etc.) or with obstruction. Even short-term hospitalization may lead to colonization with multi-resistant strains, which may require a change in antibiotic policy.

In the absence of risk factors and with sterile urine, prophylaxis may not be necessary. However, if the anticipated risk changes during the operation (e.g. accidental perforation of the intestine or the infected urinary tract), intra-operative administration of antibiotics should be considered. In the pre-operative work-up of the patient, any infection, especially of the urinary tract, should be identified. If there is an infection present and the intervention cannot be delayed, antibiotic therapy should be given on an empirical basis before surgery and continued afterwards, preferably according to sensitivity testing, when it becomes available.

From a microbiological viewpoint, any peri-operative antibiotic prophylaxis represents a compromise. It has to be balanced between a reduction in bacterial load on one hand and an increased risk of adverse events and the selection of resistant strains on the other hand.

9.5 Timing and duration of peri-operative antibacterial prophylaxis

Basic studies have shown that wound infections are usually prevented by the administration of an antibiotic before contamination takes place (16,25,26). High blood levels are needed at the start of the surgical procedure

and, therefore, timing and dosing are important factors (27). In clinical practice, the best time for administration is 30-60 minutes prior to the start of an operation, i.e. when anaesthesia is initiated, if the antibiotic is given intravenously. If intra-operative complications occur, the antibiotic should be given immediately. This approach has been particularly effective in emergency general surgery (28).

Clinical studies have shown a significant increase in post-operative infections if a single prophylactic dose of antibiotic is given > 1 hour before the start of the operation (25). Any antibiotic given after wound closure will not alter the rate of wound infection. There are, however, no studies demonstrating such a correlation in endoscopic procedures.

Generally, a single full dose of a suitable antibiotic is as effective as multiple dosing. Only in the case of prolonged intervention (> 3 hours) is an additional dose required, the size and timing of which are dictated by the pharmacokinetics of the antibiotic. Antibiotic prophylaxis should not be continued for > 24 hours (13,29-31). The administration of antibiotics for > 1 day is not considered to be prophylaxis, but therapy. This may become necessary if the focus of infection cannot be eliminated by the operation or in case of severe contamination.

9.6 Choice of antibiotics

A suitable antibiotic should be highly effective, well tolerated and cheap. Its antibacterial spectrum should include the expected range of normal flora and pathogens usually found at the site of operation and on the surrounding skin and mucous membranes. In patients with prolonged pre-operative hospitalization, account should be taken of the local nosocomial bacterial spectrum and its resistance pattern (Table 18).

Table 18: Most common pathogens causing nosocomial urinary tract and wound infections

<i>Escherichia coli</i> <i>Proteus mirabilis</i> <i>Enterococci</i> <i>Pseudomonas spp.</i> <i>Staphylococci spp.</i> <i>Candida spp.</i>
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Many antibiotics meet these criteria and can be used, e.g. second-generation cephalosporins, fluoroquinolones and aminopenicillins combined with a BLI. Aminoglycosides should be reserved for high-risk patients and those who are allergic to β -lactams. Broad-spectrum antibiotics, such as a third-generation cephalosporin, an acylaminopenicillin plus a BLI, or a carbapenem, should be used only sparingly, e.g. if the site of operation is contaminated with multi-resistant nosocomial bacteria. Usually their administration should be restricted to the treatment of severe infections (13,29,30). This applies also to the routine use of vancomycin in prophylaxis, e.g. patients on dialysis or with suspected infections caused by venous catheters, because such policy may select vancomycin-resistant enterococci and staphylococci.

The choice of antibiotic also depends on its pharmacokinetic properties, and dosage should secure effective tissue levels during the operation. Depending on the half-life of the antibiotic and the duration of the intervention, an additional dose may be indicated. For urological indications it is advisable to choose a drug with high urinary concentrations. The recommendation to change the antibiotic regimens in the hospital from time to time to counteract selection and thus resistance seems reasonable, but has still to be investigated. It also seems reasonable not to use the same antibiotics routinely for prophylaxis as well as for therapy.

9.7 Mode of application

Parenteral and preferably intravenous administration of the antibiotic is primarily recommended to reach sufficient tissue concentrations, particularly in an emergency. However, modern antibiotics have sufficient bioavailability for oral preparations to be equally effective, e.g. fluoroquinolones (22). Local antibiotic irrigation is not recommended since the effects are not sustained.

9.8 Recommendations according to type of urological intervention

For peri-operative antibacterial prophylaxis, urological interventions are categorized into open and endoscopic-instrumental operations and diagnostic procedures (Table 19). The recommended antibiotics are summarized in Appendix 3.

Table 19: Classification of urological operations/interventions with regard to peri-operative antibacterial prophylaxis

<p>Open operations</p> <ul style="list-style-type: none"> • Urinary tract including bowel segments • Urinary tract without bowel segments • Special operations outside the urinary tract <ul style="list-style-type: none"> - Using implants: penis and sphincter prosthesis; testicular prosthesis - Reconstructive genital operations: acute operation; secondary operation
<p>Endoscopic-instrumental operations</p> <ul style="list-style-type: none"> • Urethra • Prostate • Bladder • Ureter and kidney • Percutaneous litholapaxy • Extracorporeal shock wave lithotripsy • Laparoscopic operations
<p>Diagnostic interventions</p> <ul style="list-style-type: none"> • Prostate biopsy <ul style="list-style-type: none"> - Transrectal - Perineal • Urethrocystoscopy • Ureterorenoscopy • Percutaneous pyeloscopy • Laparoscopic procedures

9.8.1 Urological operations including bowel segments

Intestinal organisms are usually responsible for the development of post-operative infections after operations that include intestinal segments. The organisms most frequently involved are *E. coli* and other Enterobacteriaceae, enterococci, anaerobes and streptococci, as well as staphylococci in wound infections. An aminopenicillin/acylaminopenicillin plus a BLI, or a second-generation cephalosporin plus metronidazole, is therefore recommended.

It is a matter of debate, but not proven in clinical studies, whether continent pouches or bladder replacements require prolonged post-operative antibiotic prophylaxis. Indwelling catheters and regular irrigation of the colonized intestinal segment (neobladder) could result in post-operative bacteraemia and, in exceptional circumstances, portal pyaemia.

9.8.2 Urological operations without bowel segments

General antibiotic prophylaxis is not required in open operations without bowel segments. It is necessary only in patients with an increased risk of infection (Table 16), or before a TURP if there is a history of a UTI. The most frequent infecting organism is *E. coli* followed by enterococci, *Proteus* spp. and *Klebsiella* spp. in the urinary tract, and staphylococci for wound infections. The bacterial spectrum of hospital-related UTIs must also be taken into consideration (Table 17), especially if the patient has an indwelling catheter.

A peri-operative antibiotic regimen recommended for prophylaxis according to the expected range of pathogens includes an oral/parenteral fluoroquinolone, an aminopenicillin plus a BLI, or a second-generation cephalosporin. A third-generation cephalosporin, or an acylaminopenicillin plus a BLI are alternatives for patients with an increased risk of infection, who have previously been treated with an antibiotic or who have a permanent catheter or nephrostomy drainage.

9.8.3 Urological operations outside the urinary tract

Peri-operative antibiotic prophylaxis is not generally recommended except in long reconstructive operations on the genital area or with implant surgery. It can be achieved with first- or second-generation cephalosporins, since staphylococcal infection predominates.

9.8.4 Endo-urological operations

Peri-operative prophylaxis is recommended only in cases at increased risk of infection (Table 17). For patients undergoing TURP, additional risk factors for morbidity are to be considered, such as size of prostate (> 45 g),

operative time (> 90 min) and acute urinary retention (32). Appropriate antibiotic regimens include a fluoroquinolone, an aminopenicillin plus a BLI, a second-generation cephalosporin, or co-trimoxazole. Comparative studies of short-term prophylaxis using fluoroquinolones versus co-trimoxazole are not available. Alternatives are fosfomycin trometamol and aminoglycosides. If the patient can take oral medication, a regimen including a single dose of a fluoroquinolone or two doses of fosfomycin trometamol can be considered as first choice (33,34). For laparoscopic operations (e.g. varicocele, lymphadenectomy, nephrectomy, radical prostatectomy), sufficiently powered studies are missing. It seems reasonable, however, to manage them in the same manner as the corresponding open procedures.

9.8.5 Diagnostic urological interventions

Peri-operative antibacterial prophylaxis, e.g. with an oral fluoroquinolone (35), an aminoglycoside, a second-generation cephalosporin plus metronidazole, or an aminopenicillin plus a BLI, is generally recommended only in transrectal prostate biopsy with a thick needle. In other diagnostic procedures of the urinary tract, prophylaxis is suggested in high-risk patients. An oral/parenteral fluoroquinolone or co-trimoxazole is appropriate.

9.8.6 Post-operative drainage of the urinary tract

When continuous urinary drainage (e.g. indwelling catheter, stent, nephrostomy, etc.), is left in place after an operation, the prolongation of peri-operative antibacterial prophylaxis is contra-indicated. If a symptomatic/febrile infection episode occurs, the patient has to be treated empirically until culture results are available. Asymptomatic bacteriuria has to be treated only prior to any urinary tract intervention or when the drainage tube is removed.

9.9 Pharmacoeconomics

The results of the largest study performed worldwide of the control of nosocomial infections have shown that UTIs (42%), followed by wound infections (24%), are the most frequent cause of infective post-operative complications (36). If these can be prevented, there is obviously great potential for cost-reduction in surgery. However, cost-benefit considerations of peri-operative antibacterial prophylaxis have not been fully addressed in urology. One exception is a meta-analysis of eight prospective, randomized, controlled trials in extracorporeal shockwave lithotripsy, where a 50% reduction in median risk of a UTI was indicated in patients treated with prophylaxis (2.1% vs a median risk of 5.7%). This difference was statistically significant ($p = 0.0005$) and the strategy added minimally to the overall cost of extracorporeal shockwave lithotripsy as it prevented serious UTIs requiring inpatient treatment (37). Similar studies for TURP and bladder tumours, for example, are missing. Nevertheless, an appreciation of cost-saving by peri-operative prophylaxis can only be evaluated by suitable studies.

A summary of the recommendations of peri-operative antibiotic prophylaxis is given in Appendix 3 (10).

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10. APPENDICES

1. Criteria for the diagnosis of a UTI (modified according to IDSA/ESCMID guidelines [1,2,3])

Category	Clinical	Laboratory
1. Acute uncomplicated UTI in women; acute uncomplicated cystitis in women	Dysuria, urgency, frequency, suprapubic pain, no urinary symptoms in the 4 weeks before this episode	≥ 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)	≥ 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)	≥ 10 WBC/mm ³ $\geq 10^5$ cfu/mL* in women $\geq 10^4$ cfu/mL* in men, or in straight catheter urine
4. Asymptomatic bacteriuria	No urinary symptoms	≥ 10 WBC/mm ³ $\geq 10^5$ cfu/mL* in two consecutive MSU cultures ≥ 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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2. Recommendations for antimicrobial therapy in urology (modified according to ref 1)

Diagnosis	Most frequent pathogen	Initial, empirical antimicrobial therapy	Therapy duration
Cystitis acute, uncomplicated	<ul style="list-style-type: none"> • Escherichia coli • Klebsiella • Proteus • Staphylococcus 	<ul style="list-style-type: none"> • Trimethoprim-sulphamethoxazole • Fluoroquinolone* Alternatives: <ul style="list-style-type: none"> • Fosfomycin trometamol • Pivmecillinam • Nitrofurantoin 	1-3 days
Pyelonephritis acute, uncomplicated	<ul style="list-style-type: none"> • E. coli • Proteus • Klebsiella • Other Enterobacteria • Staphylococcus 	<ul style="list-style-type: none"> • Fluoroquinolone* • Cephalosporin (group 2 or 3a) Alternatives: <ul style="list-style-type: none"> • Aminopenicillin/BLI • Aminoglycoside 	7-10 days
UTI with complicating factors Nosocomial UTI Pyelonephritis acute, complicated	<ul style="list-style-type: none"> • E. coli • Enterococcus • Pseudomonas • Staphylococcus • Klebsiella • Proteus • Enterobacter • Other Enterobacteria • (Candida) 	<ul style="list-style-type: none"> • Fluoroquinolone* • Aminopenicillin/BLI • Cephalosporin (group 2) • Cephalosporin (group 3a) • Aminoglycoside In case of failure of initial therapy within 1-3 days or in clinically severe cases: Anti- <i>Pseudomonas</i> active: <ul style="list-style-type: none"> • Fluoroquinolone, if not used initially • Acylaminopenicillin/BLI • Cephalosporin (group 3b) • Carbapenem • ± Aminoglycoside In case of Candida <ul style="list-style-type: none"> • Fluconazole • Amphotericin B 	3-5 days after defeverescence or control/elimination of complicating factor
Prostatitis acute, chronic Epididymitis acute	<ul style="list-style-type: none"> • E. coli • Other Enterobacteria • Pseudomonas • Enterococcus • Staphylococcus • Chlamydia • Ureaplasma 	<ul style="list-style-type: none"> • Fluoroquinolone* Alternative in acute bacterial prostatitis: <ul style="list-style-type: none"> • Cephalosporin (group 2) • Cephalosporin (group 3a/b) In case of Chlamydia or Ureaplasma: <ul style="list-style-type: none"> • Doxycycline • Macrolide 	Acute: 2 weeks Chronic: 4-6 weeks or longer
Urosepsis	<ul style="list-style-type: none"> • E. coli • Other Enterobacteria After urological interventions - multi-resistant pathogens: <ul style="list-style-type: none"> • Pseudomonas • Proteus • Serratia • Enterobacter 	<ul style="list-style-type: none"> • Cephalosporin (group 3a/b) • Fluoroquinolone* • Anti-<i>Pseudomonas</i> active acylaminopenicillin/BLI • Carbapenem • ± Aminoglycoside 	3-5 days after defeverescence or control/elimination of complicating factor

BLI = β -lactamase inhibitor; UTI = urinary tract infection. *Fluoroquinolone with mainly renal excretion.

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3. Recommendations for peri-operative antibacterial prophylaxis in urology (modified according to ref 1)

Procedure	Most common pathogen(s)	Antibiotic(s) of choice	Alternative antibiotic(s)	Remarks
1. Open operations				
Urinary tract including bowel segments	Enterobacteriaceae Enterococci Anaerobes Wound infection: Staphylococci	Aminopenicillin/BLI Cephalosporin (2 nd generation) /metronidazole	In high-risk patients: * Cephalosporin (3 rd generation) * Acylaminopenicillin/BLI	In all patients
Urinary tract without bowel segments	Enterobacteriaceae Enterococci Wound infection: Staphylococci	Fluoroquinolone* Cephalosporin (2 nd generation) Aminopenicillin/BLI	In high-risk patients: * Cephalosporin (3 rd generation) * Acylaminopenicillin/BLI	In patients with increased risk of infection
Implant/prosthesis: penis, sphincter	Staphylococci	Cephalosporin (1 st /2 nd generation)		In all patients
Reconstructive genital operation	Staphylococci	Cephalosporin (1 st /2 nd generation)		In secondary operations and in patients with increased risk of infection
Other interventions outside the urinary tract	Staphylococci	Cephalosporin (1 st /2 nd generation)		In patients with increased risk of infection
2. Endoscopic-instrumental operations				
Urethra, prostate, bladder, ureter, kidney, including percutaneous litholapaxy and ESWL	Enterobacteriaceae Staphylococci Enterococci	Fluoroquinolone* Aminopenicillin/BLI Cephalosporin (2 nd generation) Fosfomycin trometamol	Co-trimoxazole Aminoglycoside	In patients with increased risk of infection
3. Diagnostic interventions				
Transrectal biopsy of the prostate (with thick needle)	Enterobacteriaceae Enterococci Anaerobes Streptococci	Fluoroquinolone* Aminopenicillin/BLI Cephalosporin (2 nd generation)/ metronidazole	Aminoglycoside Co-trimoxazole	In all patients
Perineal biopsy of the prostate Urethrocystoscopy Ureterorenoscopy Percutaneous pyeloscopy Laparoscopic procedures	Enterobacteriaceae Enterococci Staphylococci	Fluoroquinolone* Aminopenicillin/BLI Cephalosporin (2 nd generation)	Co-trimoxazole	In patients with increased risk of infection

BLI = β -lactamase inhibitor; ESWL = extracorporeal shockwave lithotripsy.

*Fluoroquinolone with sufficient renal excretion.

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4. Antibacterial agents

Groups	Substances
Trimethoprim-sulphonamide Combinations	Trimethoprim, co-trimoxazole (TMP-SMX), co-tetroxoprim (TXP-SDX), sulphamerazine
Fluoroquinolones^{1,2}	
- group 1	Norfloxacin, pefloxacin
- group 2	Enoxacin, fleroxacin, ofloxacin, ciprofloxacin
- group 3	Levofloxacin, sparfloxacin
- group 4	Gatifloxacin, moxifloxacin
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
Tetracyclines	Doxycycline, minocycline, tetracycline
Fosfomycin	Fosfomycin-sodium, fosfomycin trometamol ³
Nitrofurantoin⁴	Nitrofurantoin
Penicillins	
Benzylpenicillin	Penicillin G
Phenoxyphenicillins	Penicillin V, propicillin, azidocillin
Isoxazolylpenicillins	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin
Aminobenzylpenicillins ⁵	Ampicillin, amoxicillin, bacampicillin
Aminopenicillins/BLI ⁶	Ampicillin/sulbactam, amoxicillin/clavulanic acid ⁷
Acylaminopenicillins	Apalcillin, azlocillin, mezlocillin, piperacillin
- + BLI ⁶	Piperacillin/tazobactam, sulbactam ⁶
Cephalosporins¹	
- group 1 (oral)	Cefalexin, cefadroxil, cefaclor
- group 2 (oral)	Cefprozil, loracarbef, cefuroxime axetile
- group 3 (oral)	Cefpodoxime proxetile, cefetamet pivoxile, ceftibuten, cefixime
- group 1 (parenteral)	Cefazolin, cefazedone
- group 2 (parenteral)	Cefamandole, cefuroxime, cefotiam
- group 3a (parenteral)	Cefmenoxime, cefodizime, cefotaxime, ceftizoxime, ceftriaxone
- group 3b (parenteral)	Cefoperazone, ceftazidime, cefepime, cefpirome
- group 4 (parenteral)	Cefsulodine
- group 5 (parenteral)	Cefoxitin, cefotetan, flomoxef
Monobactams	Aztreonam
Carbapenems	Imipenem, meropenem
Aminoglycosides	Gentamicin, netilmicin, tobramycin, amikacin
Glycopeptides	Vancomycin, teicoplanin

BLI = β -lactamase inhibitors.

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 Contra-indicated in renal failure and in the new-born.

⁵ In case of resistance the pathogen is most likely a β -lactamase producer.

⁶ BLIs can only be used in combination with β -lactam antibiotics.

⁷ In solution, storage instability.

4.1 Penicillins

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

Aminopenicillins, e.g. ampicillin and amoxicillin, have a broader spectrum of activity. Apart from streptococci and pneumococci, they cover enterococci, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Listeria*, *E. coli*, *P. mirabilis*, *Salmonella* and *Shigella* spp.; however, resistance may occur. Aminopenicillins are sensitive to β -lactamases. Therefore, they are 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). Amoxicillin/clavulanic acid and ampicillin/sulbactam are 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.

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 hydrolysed by β -lactamases and are therefore active only against β -lactamase-producing strains of staphylococci, *B. fragilis* and part of the enterobacteria, if used in combination with a BLI. This 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.

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

4.2 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 19).

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

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

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

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

Cefsulodine has a special position among *Group 4 cephalosporins* with its therapeutic relevance limited to *P. aeruginosa*.

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 20: Classification of parenteral cephalosporins according to the Paul Ehrlich Society for Chemotherapy (2)

	Generic names	Features of the group
Group 1 (1st generation)	Cefazolin Cefazedone	<ul style="list-style-type: none"> • Active against Gram-positive and partly also against Gram-negative bacteria • Stable against staphylococcal penicillinases • Unstable against β-lactamases of Gram-negative bacteria
Group 2 (2nd generation)	Cefuroxime Cefotiamе Cefamandole	<ul style="list-style-type: none"> • Activity against Gram-positive bacteria good, but weaker than Group 1 • Activity against Gram-negative bacteria superior to that of Group 1 • Stable against staphylococcal penicillinases • Limited stability against β-lactamases of Gram-negative bacteria
Group 3a (3rd generation)	Cefotaxime Ceftriaxone Ceftizoxime Cefmenoxime Cefodizime	<ul style="list-style-type: none"> • Activity against Gram-negative bacteria clearly superior to that of Groups 1 and 2 • Stable against numerous β-lactamases of Gram-negative bacteria • Microbiologically less active against staphylococci
Group 3b (3rd generation)	Ceftazidime Cefepime Cefpirome Cefoperazone	<ul style="list-style-type: none"> • Spectrum of antibacterial activity similar to that of Group 3a • Additional activity against <i>Pseudomonas aeruginosa</i>
Group 4	Cefsulodin	<ul style="list-style-type: none"> • Narrow antibacterial spectrum • Only activity against <i>P. aeruginosa</i> relevant therapeutically
Group 5 (*2nd and °3rd generation)	Cefoxitin* Cefotetan° Flomoxef°	<ul style="list-style-type: none"> • Active against anaerobe bacteria • Activity against Gram-negative bacteria superior to that of Group 2, but inferior to that of Group 3a/b • Activity against staphylococci unsatisfactory

4.3 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 21).

Table 21: Classification of oral cephalosporins (1)

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

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, in whom use of other antibiotics is limited.

Group 2 oral cephalosporins: The activity of cefprozil against *S. aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *H. influenzae* and *M. catarrhalis* is somewhat higher than that of cefaclor. Against *E. coli*, *Klebsiella pneumoniae* and *P. mirabilis*, however, cefprozil is less active than cefaclor.

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

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

Group 3 oral cephalosporins have a higher activity and a broader spectrum against Enterobacteria than those in group 2. 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 not active.

The main indications for the oral cephalosporins of group 3 are complicated infections of the respiratory tract, if 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.

4.4 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.

4.5 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 on the market.

4.6 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 21).

Table 22: Classification of fluoroquinolones (modified according to the Paul Ehrlich Society for Chemotherapy [3])

Generic name	Trade name*	Features of the group
Group 1	Norfloxacin Pefloxacin	• Indications essentially limited to UTIs in some countries, e.g. Germany. In France and other countries, pefloxacin is also available for systemic use.
Group 2	Enoxacin Fleroxacin** Ofloxacin Ciprofloxacin	• Broad indications for systemic use.
Group 3	Levofloxacin Sparfloxacin	• Improved activity against Gram-positive and 'atypical' pathogens
Group 4	Gatifloxacin Moxifloxacin	• Improved activity against Gram-positive and 'atypical' pathogens and anaerobes

UTI = urinary tract infections.

*Listed according to increasing *in vitro* activity (minimum inhibitory concentration) against indicative pathogens.

**Investigated in acute exacerbations of chronic bronchitis, UTIs, gonorrhoea and gastrointestinal infections.

The indication of *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.

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

The spectrum of activity of *Group 3 fluoroquinolones* (levofloxacin and sparfloxacin) and of Group 4 fluoroquinolones differs from that of Group 2 quinolones mainly in that they have a higher intrinsic activity against Gram-positive pathogens such as staphylococci, streptococci, pneumococci and enterococci - with 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. Grouping of levofloxacin is contradictory, because levofloxacin is the antibacterially active part of ofloxacin, which belongs to Group 2. 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, 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 is 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, as well as for 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. Therefore, it is 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%.

TMP-SMX

The main indication for TMP alone or in combination with a sulphonamide, e.g. SMX, is the treatment of UTIs. 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. Therefore, it is 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.

Fosfomycin

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

Nitrofurantoin

The antibacterial activity of nitrofurantoin is limited to the urinary tract because of its low serum concentrations. It is active against *E. coli*, *Citrobacter* and most strains of *Klebsiella* and *Enterobacter*, whereas *Providencia* and *Serratia* are mostly resistant. *Proteus*, *P. aeruginosa* and *Acinetobacter* are almost always resistant. It is active against Gram-positive cocci, e.g. enterococci and staphylococci. It is suitable only for the treatment or prophylaxis of uncomplicated UTIs. Short-term therapy for this indication has not been proven in sufficiently large studies. Little development of resistance has been observed over many years. Treatment can lead to severe although rare adverse events, such as chronic desquamative interstitial pneumonia with fibrosis.

4.7 Macrolides

The only macrolide available for oral and parenteral use is erythromycin. 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*.

4.8 Tetracyclines

The resistance against doxycycline and tetracycline of pneumococci, streptococci, *H. influenzae* and *E. coli* shows marked regional differences. Therefore, tetracyclines are 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*.

4.9 Aminoglycosides

Aminoglycosides are for parenteral use only and are among the drugs with 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 β -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.

4.10 Glycopeptides

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

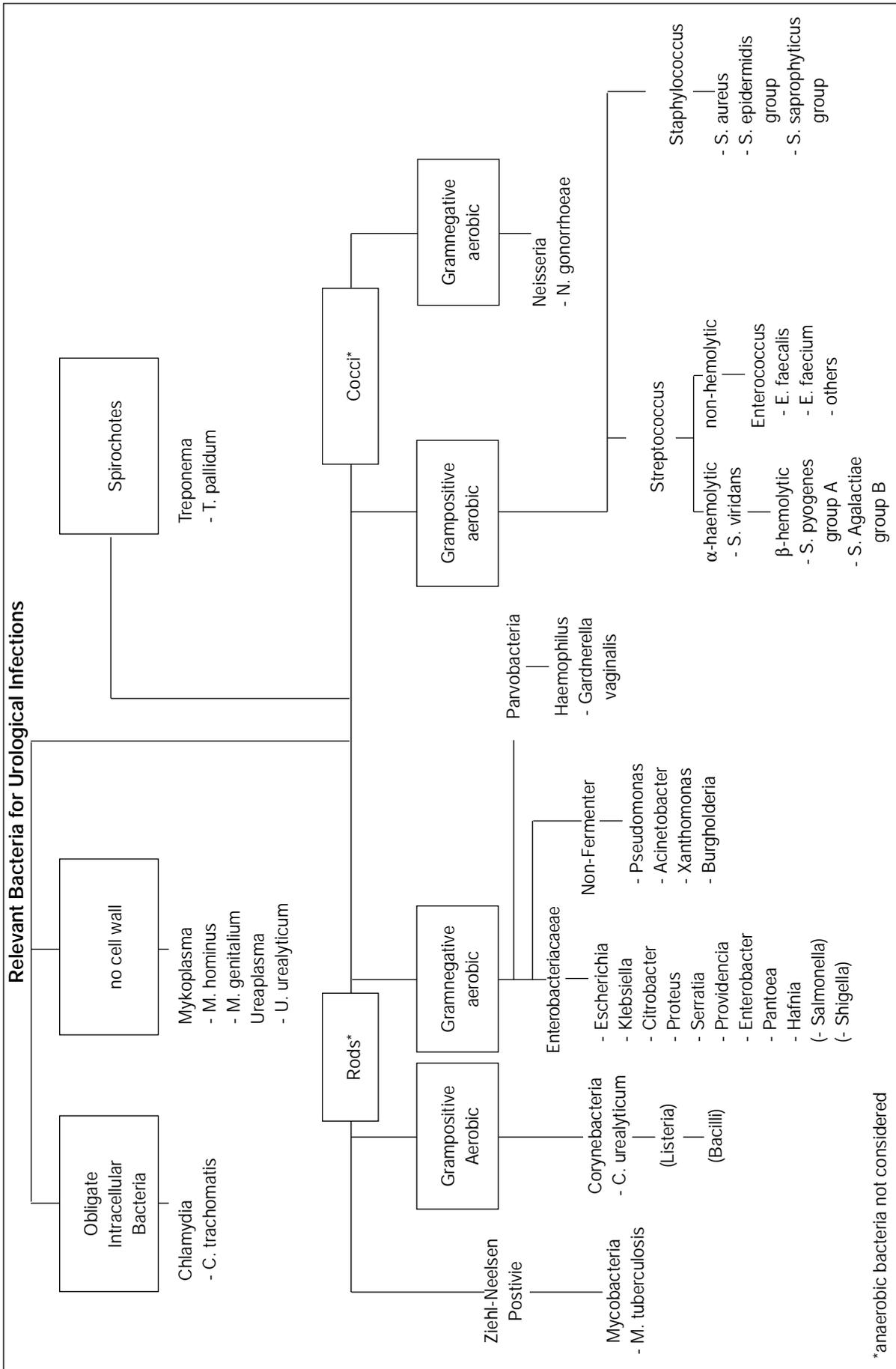
- In infections caused by the above-mentioned pathogens in case of allergy against all other suitable antibiotics.
- In case of infection by ampicillin-resistant enterococci or oxacillin-resistant staphylococci, or multi-resistant corynebacteria.
- As an alternative, in oral form, to metronidazole for the treatment of pseudomembranous colitis.

Because of the risk of selection of glycopeptide-resistant enterococci and staphylococci, glycopeptide use should be highly restricted. Similar to the aminoglycosides, glycopeptides have a narrow therapeutic window.

4.11 REFERENCES

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5. Relevant bacteria for urological infections



ABBREVIATIONS USED IN THE TEXT

ABP:	acute bacterial prostatitis
APCKD:	adult polycystic kidney disease
AUA:	American Urological Association
B. fragilis:	Bacteriodes fragilis
BLI:	β -lactamase inhibitor
BPH:	benign prostatic hyperplasia
CBP:	chronic bacterial prostatitis
Cfu:	colony-forming unit
CPPS:	chronic pelvic pain syndrome
CRP:	C-reactive protein
CT:	computed tomography
C. trachomatis:	Chlamydia trachomatis
DMSA:	dimercaptosuccinic acid
E. coli:	Escherichia coli
ESCMID:	European Society of Clinical Microbiology and Infectious Diseases
EPS:	expressed prostatic secretion
ESWL:	extracorporeal shockwave lithotripsy
G-CSF:	granulocyte-colony stimulating factor
GM-CSF:	granulocyte-macrophage-colony stimulating factor
HCO:	Health Care Office of the EAU
H. influenzae:	Haemophilus influenzae
IDSA:	Infectious Diseases Society of America
Ig:	immunoglobulin
IL:	interleukin
LUTS:	lower urinary tract symptoms
M. catarrhalis:	Moraxella catarrhalis
MRSA:	methicillin-resistant <i>Staphylococcus aureus</i>
MRSE:	methicillin-resistant coagulase negative staphylococci
MSU:	mid-stream sample of urine
M. tuberculosis:	Mycobacterium tuberculosis
N. gonorrhoeae:	Neisseria gonorrhoeae
NIDDK:	National Institute of Diabetes, Digestive and Kidney Diseases
NIH:	National Institutes of Health
PaCO ₂ :	partial pressure of carbon dioxide in alveolar gas
P. aeruginosa:	<i>Pseudomonas aeruginosa</i>
P. mirabilis:	<i>Proteus mirabilis</i>
PSA:	prostate-specific antigen
S. aureus:	Staphylococcus aureus
S. saprophyticus:	Staphylococcus saprophyticus
Tc:	technetium
TMP:	trimethoprim
TNF:	tumour necrosis factor
TURP:	transurethral resection of the prostate
T. vaginalis:	Trichomonas vaginalis
SIRS:	systemic inflammatory response syndrome
SMX:	sulphamethoxazole
STD:	sexually transmitted disease
UTI:	urinary tract infection(s)
VB1:	first-voided urine
VB2:	mid-stream urine
VB3:	voided bladder urine-3
VCU:	voiding cysto-urethography
VUR:	vesico-ureteric reflux
WBC:	white blood cells
WHO:	World Health Organisation

