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EAU Guidelines for the Management of Urinary and Male Genital Tract Infections[1]

Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU)

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Abstract

A short version of the UTI Guidelines elaborated by the Urinary Tract Infection Working Group of the Health Care Office of the European Association of Urology is presented. The topics include classification, diagnosis, treatment and follow-up of uncomplicated UTI, UTI in children, UTI in diabetes mellitus, renal insufficiency, renal transplant recipients and immunosuppression, complicated UTI due to urological disorders, sepsis syndrome, urosepsis, urethritis, prostatitis, epididymitis, orchitis and principles of perioperative prophylaxis in urology.

[1] For more extensive information, consult the EAU Guidelines presented at the XVIth EAU Annual Congress, Geneva, Switzerland (ISBN 90–806179–3–9).

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Table 1. Factors that suggest potential complicated UTI [modified according to Johnson et al., 1987]

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

Classification of Urinary and Male Genital Tract Infections

For practical clinical reasons, urinary tract infections (UTIs) and male genital tract infections are classified according to entities with predominating clinical symptoms: (1) uncomplicated lower UTI (cystitis); (2) uncomplicated pyelonephritis; (3) complicated UTI with or without pyelonephritis; (4) urosepsis; (5) urethritis, and (6) prostatitis, epididymitis, orchitis.

Definitions

The definitions of bacteriuria and pyuria are as follows:

Significant bacteriuria in adults:

1. $\geq 10^3$ uropathogens/ml of midstream urine in acute uncomplicated cytstitis in female;
2. $\geq 10^4$ uropathogens/ml of midstream urine in acute uncomplicated pyelonephritis in female;
3. $\geq 10^5$ uropathogens/ml in midstream urine of women or 10^4 uropathogens/ml of midstream urine in men (or in straight catheter urine in women) with complicated UTI.

In a suprapubic bladder puncture specimen any count of bacteria is relevant.

Asymptomatic bacteriuria (ABU).

ABU is defined as two positive urine cultures taken more than 24 h apart with 10^5 uropathogens/ml of the same bacterial strain (mostly only the species is available).

Pyuria.

The requirement for pyuria is 10 white blood cells per high-power field (×400) in the resuspended sediment of a centrifuged aliquot of urine or per mm^3 in unspun urine. For the routine also a dipstick method can be used, including leukocyte esterase test, hemoglobin and probably nitrite reaction.

Uncomplicated UTIs in Adults

Definition. Acute, uncomplicated UTIs in adults include episodes of actute cystitis and acute pyelonephritis occurring in otherwise healthy individuals, most of whom are women who have none of the risk factors, i.e. structural or functional abnormalities within the urinary tract or without underlying diseases known to increase the risk for acquiring infection or failing therapy. Several factors have been identified, however, that are markers for potential complicated UTI (table 1).

Etiologic Spectrum. The spectrum of etiologic agents is similar in uncomplicated upper and lower UTI, with *Escherichia coli* the pathogen in approximately 70–95% and *Staphylococcus saprophyticus* in over 5% of the cases. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* species or enterococci, are isolated. In as many as 10–15% of symptomatic patients, bacteriuria cannot be detected with routine methods.

Acute Uncomplicated Cystitis in Premenopausal, Nonpregnant Women

Diagnosis and Follow-Up. Acute cystitis is likely if the women complains of urgency and suprapubic pain and has suprapubic tenderness. Although approximately 40% of women with cystitis have hematuria, this is not a predictor of complicated infection.

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 so predictable and culture results become available only after the patient's symptoms have resolved or are considerably improved. Voided midstream or straight catheter (by trained urological personnel) urine cultures probably should be performed if the patient's symptoms are not characteristic of UTI. The laboratory must be instructed to look for 'low count' bacteriuria if such UTIs are to be detected.

Besides physical examination, a urinalysis, e.g. using a dipstick method, including white and red blood cells as well as nitrite reaction is recommended for routine diagnosis. Urinalysis including a dipstick method is also sufficient as a routine for follow-up. In women whose symptoms do not resolve or recur within 2 weeks, a urine culture and antimicrobial susceptibility testing has to be performed.

Treatment. Short courses of antimicrobials are highly effective and are desirable because of the improved compliance that they promote, lower cost, and lower frequency of adverse reactions. Single-dose therapy is generally less effective than longer courses with the same antibiotic. How-

ever, most antimicrobials given for 3 days are as effective as longer courses. Longer treatment usually shows a higher rate of adverse events.

The resistance pattern of *E. coli* strains causing uncomplicated UTI may vary considerably between European regions and countries, therefore no general recommendations concerning the choice of antibiotic are suitable throughout Europe:

(1)Trimethoprim/sulfamethoxazole (TMP/SMZ) is the most intensively studied drug and was equally effective to trimethroprim. All 3-day regimen with trimethoprim (or TMP/SMZ) can be recommended as first-line drugs for empiric therapy, but only in communities with resistance rates of uropathogens to trimethoprim $<10\%$ (–20%).

(2)The fluoroquinolones (ciprofloxacin, fleroxacin, norfloxacin and ofloxacin) are equivalent to TMP/SMZ when given as a 3-day regimen. Fluoroquinolones are more expensive than TMP and TMP/SMZ and thus not recommended as first-line drugs for empiric therapy except in communities with resistance rates of uropathogens causing uncomplicated UTI to trimethoprim of $>10\%$. With any of these agents, one should expect $>90\%$ eradication of the bacteriuria.

(3)β-Lactams as a group are less effective than the foregoing drugs. With 2nd and 3rd generation oral cephalosporins or with aminopenicillins combined with a β-lactamase inhibitor (BLI) no large enough studies are available. Only a large study with pivmecillinam showed equivalent rates of bacterial eradication but higher rates of recurrence when a 3-day course was compared with a 7-day course. Thus, a 7-day course is recommended, when pivmecillinam is used.

(4)Nitrofurantoin needs more study. Nitrofurantoin cannot yet be considered as a suitable drug for short-term therapy of acute uncomplicated cystitis and if used should be given for 7 days.

(5)Fosfomycin trometamol used as single-dose treatment may be an interesting alternative. However, large enough trials are necessary to demonstrate equivalence with standard agents, e.g. trimethoprim, TMP/SMZ or one of the fluoroquinolones administered as 3-day regimen.

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

The treatment options are summarized in table 2.

Acute Uncomplicated Pyelonephritis in Premenopausal, Nonpregnant Women

Diagnosis and Follow-Up. Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever ($>38\,^{\circ}C$), or costovertebral angle tenderness and may occur with or in the absence of cystitis symptoms, e.g. dysuria and frequency. The presentation of an acute uncomplicated pyelonephritis usually varies from a mild to moderate illness. A life-threatening condition with multiple organ system dysfunction, including a sepsis syndrome with or without shock and renal failure, must be considered as a complicated case.

Besides physical examination, a urinalysis, e.g. using a dipstick method, including white and red blood cells as well as nitrite reaction, is recommended for routine diagnosis. If urine culture is performed, colony counts of $\geq 10^4$ cfu/ml uropathogens can be considered as 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, CT or DMSA scan should be considered if the patient remains febrile after 72 h of treatment to rule out further complicating factors, e.g. renal or perinephric abscesses.

For follow-up, urinalysis including a dipstick method is sufficient as a routine. In women whose pyelonephritis symptoms do resolve, but recur within 2 weeks, a repeat urine culture, antimicrobial susceptibility testing, and renal ultrasound, excretory urography, CT or a DMSA scan should be performed to rule out abnormalities within the urinary tract.

Treatment. For mild cases, an oral fluoroquinolone for 7 days is recommended as first-line drug. If a Gram-positive organisms is seen on the initial Gram's stain, an aminopenicillin plus a BLI may be recommended. More severe cases of acute uncomplicated pyelonephritis should be admitted to a hospital and treated parenterally. With improvement, the patient can be switched to an oral regimen using a fluoroquinolone or TMP/SMZ (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 contraindicated, e.g. pregnancy, lactating women, adolescence, a 2nd or 3rd generation oral cephalosporin is recommended. The treatment options are summarized in table 2.

Treatment of Recurrent (Uncomplicated) UTIs

Recurrent UTIs are common among young, healthy women even though they generally have anatomically and physiologically normal urinary tracts. The following pro-

Table 2. Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

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

[a] Fluroquinolone with mainly renal excretion; BLI = β-lactamase inhibitor.

phylactic antimicrobial regimens are recommended (table 3): (i) the use of long-term, low-dose prophylactic antimicrobials taken at bedtime, and (ii) postintercourse prophylaxis for women in whom episodes of infection are associated with sexual intercourse.

Prophylactic Alternative Methods. Alternative methods, such as acidification of urine, cranberry juice, extract from Uvae ursi, and vaginal application of lactobacilli show variable effects.

Reports on immunostimulating extracts of *E. coli* showed a reduction of the frequency of recurrent infections and decrease the degree of bacteriuria in paraplegic patients.

Water diuresis may be effective in some women with uncomplicated UTI, but it often delays more effective management with antimicrobial drugs until the patient becomes more ill. The evidence is also too weak to recommend that women change their body habits and menstrual practices or void after intercourse.

UTIs in Pregnancy

Most women acquire bacteriuria before pregnancy. 20–40% of women with asymptomatic bacteriuria will develop pyelonephritis during pregnancy. The false-positive rate of a single midstream specimen of urine 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 midstream or straight catheter urine specimen for culture is obtained.

Treatment of asymptomatic bacteriuria lowers the risk of pyelonephritis. Bacteriuria of pregnancy is associated with a significant increase in low-birth-weight infants (<2,500 g), decreased gestational age (<37 weeks) and neonatal mortality. Women with persistent infection despite treatment or evidence of 'tissue invasion' are at higher risk of delivering premature infants. It should, however, be mentioned that bacterial vaginosis is also an important independent risk factor for permature birth.

Treatment and Follow-Up. Treatment of asymptomatic bacteriuria should be based on antibiotic sensitivity testing. Usually a 7-day course of antibiotics is recommended, but some authors recommend short-term therapy as for acute cystitis. One to 4 weeks after treatment and at least once more before delivery, follow-up cultures should be obtained.

Most symptomatic UTIs in pregnant women represent acute cystitis. Short-term therapy is not as well established yet as in nonpregnant women.

For acute pyelonephritis 2nd or 3rd generation cephalosporins, an aminoglycoside or an aminopenicillin plus a BLI may be recommended. Quinolones, tetracyclines, trimethoprim in the first trimester and sulfonamides 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.

For recurrent UTI low-dose cephalexin (125–250 mg) or nitrofurantoin (50 mg) at night are recommended for reinfection prophylaxis. Postintercourse prophylaxis may be an alternative approach.

Table 3. Antimicrobial regimens of documented prophylactic efficacy for prevention of acute uncomplicated urinary infection in women

Agent	Dose
Standard regimens (taken at bedtime)	
Trimethoprim/sulfamethoxazole	40/200 mg/day or 3 times weekly
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

UTI in Postmenopausal Women

In case of acute UTI, the antimicrobial treatment policy is similar to that in premenopausal women. Short-term therapy in postmenopausal women is, however, not as well documented as in younger women. In postmenopausal women with recurrent UTI therapy intravaginal estriol is able to reduce the rate of recurrences significantly. For the remaining patients an antimicrobial prophylactic regimen should be recommended.

Acute Uncomplicated UTI in Young Men

It has been conventional to consider all UTI in men as complicated, because most of them that occur in the newborn, the infant, or the elderly are associated with urologic abnormalities, bladder outlet obstruction, or instrumentation. UTI in otherwise healthy adult men 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 was reported.

Urologic evaluation should be done routinely in adolescents and men with pyelonephritis, recurrent infections, or whenever a complicating factor is present. Such men should receive, at a minimum, a 7-day antibiotic regimen.

Urinary analgesics, such as phenazopyridine 200 mg 3 times daily can be administered for those patients with severe dysuria for 1 or 2 days. Women with cystitis usually have 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 for women with UTI must be individualized.

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

UTI in Children

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

Chronic pyelonephritic renal scarring develops very early in life due to the combination of UTI, intrarenal 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 litte consequence.

E. coli is responsible for 90% of the episodes of UTI. Gram-positive organisms represent 5–7%, particularly *Enterococcus* and *Staphylococcus* species. Hospital-acquired infections show a wider pattern of aggressive organisms like *Klebsiella*, *Serratia* and *Pseudomonas*. Group A or B *Streptococcus* are relatively common in the newborn. There is an increasing trend to isolate *S. saprophyticus* as responsible organism of UTI in children although its role is still debatable.

Diagnosis of UTI. Diagnosis is as follows: (a) Collecting bag: negative culture is indicative only. (b) Suprapubic bladder aspiration: any positive culture. (c) Coagulase-negative Staphylococcus: $\geq$300 cfu/ml. (d) Catheter urine: 10^4–5×10^4 cfu/ml. (e) Midstream urine: 10^4 in symptomatic children, 10^5 cfu/ml on 2 different days in asymptomatic children. (f) Significant pyuria with 10 WBC/mm^3 and 5×10^4 cfu/ml in catheter urine in febrile children discriminate between infection and contamination; discrimination between pyelonephritis and asymptomatic bacteriura; elevated CRP $>$20 μg/ml. (g) N-acetyl-β-glucosaminidase: marker of tubular damage (also elevated in VUR).

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

Treatment Principles. The treatment has four main goals: (1) elimination of symptoms and bacteriuria in the acute episode; (2) prevention of renal scarring; (3) prevention of recurrent UTI, and (4) correction of associated urological lesions.

The principles of treatment of UTI in children are slightly different from 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 on account of effects on teeth and cartilage.

Severe febrile UTI (fever of 39 °C, ill sensation, persistent vomiting, moderate or severe dehydration, in case of low compliance children should be treated like severe UTI) is differentiated from simple UTI (mild pyrexia but be able to take fluids and oral medications, slightly or not dehydrated, good expected level of compliance).

VUR is treated with long-term prophylactic antibiotics and surgical reimplantation reserved for the small number of children with breakthrough infection.

Treatment of Severe Febrile UTI. It requires an adequate parenteral fluid reposition and appropriate antimicrobial treatment preferably with cephalosporins. If a Gram-positive UTI is suspected it is useful to associate aminoglycosides, ampicillin or amoxicillin/clavulanate. In case of 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 represent the treatment of choice.

In newborns, surveillance of antimicrobial serum concentrations and subsequent dosage adjustment to compensate for renal function deficit is mandatory. Chloramphenicol, sulfonamides, tetracyclines, rifampin, amphotericin B and quinolones should be avoided. In newborns the use of ceftriaxone must also be avoided due to its unwanted effect of jaundice.

In older children a wide variety of antimicrobials can be used except tetracyclines because of teeth staining and fluorinated quinolones due to cartilage toxicity. For a safety period of 24–36 h, parenteral therapy should be administered. After the child is doing well and afebrile and she or he is able to take fluids, the child may be given an oral agent to complete the 10–14 days of treatment. The preferred oral antimicrobials are: amoxicillin, cephalexin, cefixime or trimethoprim. In children younger than 3 years of age with difficult oral intake, a 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 (1–2 mg/kg/day), trimethoprim (1–2 mg/kg/day), cephalexin (10 mg/kg/day) and cefaclor (10 mg/kg/day).

Simple UTI. It is considered a low-risk infection and thus a single parenteral dose of a cephalosporin such as ceftriax-

one will be enough. In case of allergy, aztreonam (30–50 mg/kg/6–8 h) followed by trimethoprim, cephalexin or amoxicillin for 10 days will warrant an effective therapy. Once the treatment is completed an 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 the hospital and a parenteral treatment started.

UTI in Diabetes mellitus, Renal Insufficiency, Transplant Recipients and Immunosuppression

Diabetes mellitus, Renal Insufficiency

Diabetic patients are susceptible to rapid progression of parenchymal infection and clearance of asymptomatic bacteriuria should be attempted and then prevented with long-term antibiotics. Overwhelming infection can predispose to pyogenic infection with intrarenal perinephric abscess formation and very rarely a specific form of infective interstitial nephritis. Papillary necrosis is a common consequence of pyelonephritis in diabetics.

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.

In acute pyelonephritis, infected cysts (presenting as recurrent bacteremia or 'local sepsis') a high dose of systemic fluoroquinolones should be used as a long course and followed by prophylaxis. Bilateral nephrectomy is performed as a last resort.

As for patients without renal impairment, stone clearance should be attempted where possible. If the calculus cannot be removed, antibiotic treatment should be used but limited as far as possible. Nephrectomy may be performed as 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 disease end-stage kidney is more pressing in a patient enlisted for renal transplantation. Even so, the results of nephrectomy for scarred or hydronephrotic kidney may be disappointing.

Renal Transplantation and Immunosuppression

UTI is common after renal transplantation. Bacteriuria is present in 35–80% of transplant recipients. Early factors predisposing to UTI include infection in the donor kidney. Infection in the native kidneys may worsen considerably with maximum immunosuppression. This problem is most troublesome with papillary necrosis, particularly in diabetes mellitus, massive infective VUR polycystic disease and with infective calculi. Also of concern is the increasing number of children with congenital uropathies, often in association with neuropathic bladder dysfunction and the sinister combination of intravesical obstruction, poor bladder compliance, residual urine and VUR. A full urodynamic assessment, establishing a routine of intermittent self-catheterization and any necessary bladder surgery must be completed well in advance of renal transplantation. Urinary diversions and bladder augmentation and substitution have also been successfully completed in patients on dialysis treatment and after transplantation, though bacteriuria is common and may require antibiotic treatment.

Treatment and Prevention of Bacterial UTI in Renal Transplant Recipients. The treatment of a symptomatic UTI is similar to that given in nontransplant patients, but with a 10- to 14-day course of treatment in most cases, preferably with fluoroquinolones which penetrate well into the renal parenchyma.

For prevention of infection, TMP-SMX (cotrimoxazole) is recommended which will also prevent *Pneumocystis carinii* pneumonia and infection with other rare fastidious organisms. Low-dose cotrimoxazole (to prevent added nephrotoxicity with cyclosporin A) has been recommended for 6 months after transplantation. A number of other drug interactions need to be considered, e.g. gentamicin, TMP-SMX and amphotericin B promote cyclosporine toxicity, rifampicin induces cytochrome P_{450} synthetase and erythromycin inhibits hepatic cyclosporin A metabolism.

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

Complicated UTIs due to Urological Disorders

A complicated UTI is an infection associated with a condition that increases the risk for acquiring infection or failing therapy such as structural or functional abnormalities of the genitourinary tract and the presence of underlying diseases which interfere with host defense mechanisms.

The spectrum of pathogens (with *E. coli* and other Enterobacteriaceae dominating, but also *P. aeruginosa*, staphylococci and enterococci) is much larger than in uncomplicated UTI, and bacteria are more likely to be antimi-

crobial-resistant, especially in treatment-related complicated UTI.

Treatment Strategies. Treatment encompasses three goals: management of the urological abnormality; antimicrobial therapy, and supporting care when needed. Hospitalization is often required. To avoid emergence of resistant strains, therapy should be guided by urine culture whenever possible.

In catheter-associated UTI, biofilm has to be considered. Antimicrobial therapy may only be effective in early stages of this infection. It is advisable to stratify complicated UTI due to urological disorders at least into two groups: (1) patients in whom the complicating factors could be eliminated by therapy (e.g., stone extraction, removal of an indwelling catheter) and (2) patients in whom the complicating factor could not be or is not removed satisfactory during therapy (e.g., permanent indwelling catheter, stone residual after treatment, neurogenic bladder).

The duration of therapy is usually 7–14 days, but is sometimes prolonged up to 21 days. Until predisposing factors are completely removed, true cure without recurrent infection is usually not possible. Therefore, a urine culture has to be done 5–9 days after the completion of therapy and also 4–6 weeks later. Recurrent infection is the rule when underlying urological abnormality cannot be removed: either relapse (e.g., with the same infection organism) or a reinfection (e.g., with a new microorganism). The treatment options are summarized in table 2.

Sepsis Syndrome in Urology (Urosepsis)

Principles (table 4)

(1) Patients with urosepsis should be diagnosed at an early stage and especially in case of complicated UTI. Systemic inflammatory response (fever or hypothermia, tachycardia, tachypnea, hypotension, oliguria, leukocyturia or leukopenia) is recognized as the first event in a cascade to multiorgan failure.

(2) Urosepsis treatment calls for the combination of adequate life-supporting care, appropriate antibiotic therapy, adjunctive measures, such as sympathomimetic amines, corticosteroids, anticoagulation, G-CSF or GM-CSF, naloxone, and optimal management of urinary tract disorders.

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

(4) Much of 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, attention to simple daily techniques of hygiene in order to avoid cross-infection).

Preventive Measures of Proven or Probable Efficacy

(1) Prudent 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.

(2) Reduction in hospital stay. It is well known that long inpatient periods prior to surgery lead to a greater incidence of nosocomial infections.

(3) Isolation of all patients infected with multiresistant organisms to avoid cross-infection.

(4) Early removal of indwelling urethral catheters, as soon as allowed by the patient's conditions. Nosocomial UTI is promoted by bladder catheterization as well as ureteral stenting. Antibiotic prophylaxis does not prevent stent colonization, which appears in 100% of patients with a permanent ureteral stent and in 70% if temporarily stented.

(5) Use of closed catheter drainage and minimize breaking the integrity of the system, e.g., for urine sampling or bladder washout.

(6) Use of least invasive method to release urinary tract obstruction until the patient is stabilized.

(7) Attention to simple everyday techniques to assure asepsis: the routine use of protective, disposable gloves, frequent hand washing and respect of infectious disease control measures to prevent cross-infections.

Appropriate perioperative antimicrobial prophylaxis (see below): The potential side effects of antibiotics must be considered prior to their administration in a prophylactic regimen.

Preventative measures of debatable efficacy: (a) instillation of antibiotic or antiseptic drugs into catheters and drainage bas, and (b) use of urinary catheters coated with antibiotics or silver nitrate.

Ineffective or counterproductive measures: (a) continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics which increase the risk of infection with resistant bacteria, and (b) routine administration of antimicrobial drugs to catheterized patients which reduces the incidence of bacteriuria only for a few days and increase the risk of infection with multiresistant bacteria; its use is reserved to immunosuppressed patients.

Table 4. Clinical diagnostic criteria of sepsis and septic shock

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response
Bacteremia	Bacteria present in blood as confirmed by culture may be transient
Septicemia	Same as bacteremia, 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: Temperature $>38\,°C$ or $<36\,°C$ Heart rate >90 beats/min Respiratory rate >20 breaths/min or $PaCO_2 < 32$ mm Hg (<4.3 kPa) WBC $>12{,}000$ cells/mm^3 $<4{,}000$ cells/mm^3 or 10% immature (band) forms
Sepsis syndrome	Infection plus evidence of altered organ perfusion with at least one of the following: hypoxemia, elevated lactate, oliguria, altered mentation
Hypotension	A systolic blood pressure of <90 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes of hypotension
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute alteration on mental status
Septic shock	Sepsis with hypotension despite adequate fluide resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressore agents may not be hypotensive at the time that perfusion abnormalities are measured
Refractory septic shock	Septic shock that lasts for more than 1 h and does not respond to fluid administration or pharmacologic intervention
Systemic inflammatory response syndrome	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but can be noninfectious in etiology (e.g., burns, pancreatitis)

Urethritis

Symptomatic urethritis is characterized by alguria and purulent discharge. Many infections of the urethra are asymptomatic. Pathogens of primary urethritis include *Neisseria gonorrheae, C. trachomatis, Mycoplasma genitalium* and *Trichomonas vaginalis. Mycoplasma hominis* does probably not, *Ureaplasma urealyticum* does not frequently cause urethritis. In most cases the evidence of *Mycoplasma* or *Ureaplasma* represents an asymptomatic colonization of the urogenital tract.

Diagnosis. The Gram stain of secretion or urethral smear showing more than 5 leukocytes per high-power field (HPF) (×1,000) and eventually gonococci located intracellularly as Gram-negative diplococci indicate a pyogenic urethritis. A positive leukocyte esterase test or more than 10 leukocytes per high-power field (×400) in the first voiding urine specimen are diagnostic. In all patients with urethritis and where sexual transmission is suspected, identification of the pathogenic organisms should be aimed at. If for identifying the pathogens an amplification system is used, the first voiding urine specimen can be taken instead of urethral smear. Trichomonas can usually be identified microscopically.

Therapy. The following guidelines for therapy comply with the recommendations of the Center for Disease Control and Prevention (1998).

For the treatment of gonorrhea the following antimicrobials can be recommended:

Cefixime 400 mg orally as a single dose	Ciprofloxacin 500 mg orally as single dose
Ceftriaxone 250 mg i.m. as a single dose (i.m. with local anaesthetic)	Ofloxacin 400 mg orally as single dose

As gonorrhea is frequently accompanied by chlamydial infection, an antichlamydial active therapy should be added. The following treatment has been successfully applied in *C. trachomatis* infections:

First choice	*Second choice*
Azithromycin 1 g (= 4 caps.@ 250 mg) orally as single dose	Erythromycin 4 times daily 500 mg orally for 7 days
Doxycycline 2 times daily 100 mg orally for 7 days	Ofloxacin 2 times daily 200 mg orally for 7 days

If therapy fails, one should consider infections by *T. vaginalis* and/or *Mycoplasma*, which can be treated with a combination of metronidazole (2 g orally as single dose) and erythromycin (4 times daily 500 mg orally for 7 days). Treatment of the sexual partner is necessary, as in other sexually transmitted diseases.

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

Prostatitis, Epididymitis and Orchitis

Prostatitis

Prostatitis is a disease entity diagnosed by symptoms, microscopy of expressed prostatic secretion (EPS), culture tests of EPS and segmented urine samples as described by Meares and Stamey. According to the duration of symptoms, prostatitis is described as acute or chronic with symptoms for at least 3 months. We recommend the classification of prostatitis suggested by the NIDDK/NIH (table 5) in which bacterial prostatitis (acute and chronic) is discerned from chronic pelvic pain syndrome (CPPS).

Treatment. Acute bacterial prostatitis can be a serious infection and parenteral administration of high doses of bactericidal antibiotic such as aminoglycosides and a penicillin derivative or a 3rd generation cephalosporin are required until defervescence and normalization of infection parameters. In less severe cases a fluoroquinolone may be given orally for 10 days.

In chronic bacterial prostatitis and chronic inflammatory pelvic pain syndrome a fluoroquinolone or trimethoprim should be given orally for 2 weeks after the initial diagnosis. Then the patient should be reassessed and antibiotics only continued if pretreatment cultures were positive or the patient reports positive effect of the treatment. A total treatment period of 4–6 weeks is recommended.

Table 5. Classification of prostatitis according to NIDDK/NIH

I.	Acute bacterial prostatitis (ABP)
II.	Chronic bacterial prostatitis (CBP)
III.	Chronic pelvic pain syndrome (CPPS)
	A. Inflammatory CPPS: WBC in semen/EPS/voided bladder urine-3 (VB3)
	B. Noninflammatory CPPS: no WBC semen/EPS/VB3
IV.	Asymptomatic inflammatory prostatitis (histological prostatitis)

Epididymitis, Orchitis

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 hematogenous orgin. Epididymo-orchitis is also seen in systemic infections such as tuberculosis, lues, brucellosis and cryptococcus disease. Antimicrobials should be selected on the empiric basis that in young, sexually active men, *C. trachomatis* is usually causative, and in older men with BPH or other micturation disturbances, the most common uropathogens are the etiologic agents.

Treatment. Prior to antimicrobial therapy an urethral swab and midstream urine should be obtained for microbiological investigation. Fluoroquinolones, preferably those with good activity against *C. trachomatis*, e.g. ofloxacin, levofloxacin, should be first-choice drugs because of their broad antibacterial spectra and their favorable penetration into the tissues of the urogenital tract. In case *C. trachomatis* has been detected as etiologic agent, treatment could also be continued with doxycycline 200 mg/day for a total treatment period of at least 2 weeks. Macrolides may be alternative agents in this case. In case of *C. trachomatis* epididymitis, the sexual partner should be treated as well.

Antibiotics and α-Blockers in Combination. Urodynamic studies have shown increased urethral closing pressure in patients with chronic prostatitis. A combination treatment of α-blockers and antibiotics is reported to have a higher cure rate than antibiotics alone in inflammatory CPPS. This is a treatment option favored by many urologists.

Intraprostatic Injection of Antibiotics. This treatments has not been evaluated in controlled trials and should be considered only if oral treatment fails to eradicate the infection.

Surgery. In acute prostatitis some patients need bladder drainage, preferably with a suprapubic catheter. A positive

Table 6. Recommendations for perioperative antibacterial prophylaxis in urology [modified according to Naber et al., Chemother J 2000;9: 165–170]

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°+ metronidazole	In high-risk patients: Cephalosporin 3° Acylaminopenicillin + BLI	In all patients
Urinary tract without bowel segments	Enterbacteriaceae Enterococci Wound infection: staphylococci	Fluoroquinolone[a] Cephalosporin 2° Aminopenicillin + BLI	In high-risk patients: Cephalosporin 3° Acylaminopenicillin + BLI	In patients with increased risk of infection
Implant/prosthesis: penis, sphincter	Staphylococci	Cephalosporin 1°/2°		In all patients
Reconstructive genital operation	Staphylococci	Cephalosporin 1°/2°		In secondary operations and in patients with increased risk of infection
Other interventions outside of the urinary tract	Staphylococci	Cephalosporin 1°/2°		In patients with increased risk of infection
2. Endoscopic-instrumental operations				
Urethra, prostate, bladder, ureter, kidney, incl. percutaneous litholapaxy and ESWL	Enterobacteriaceae Staphylococci Enterococci	Fluoroquinolone[a] Aminopenicillin + BLI, Cephalosporin 2° Fosfomycin Trometamol	Cotrimoxazole Aminoglycoside	In patients with increased risk of infection
3. Diagnostic intervention				
Transrectal biopsy of the prostate (with thick needle)	Enterobacteriaceae Enterococci Anaerobes Streptococci	Fluoroquinolone[a] Aminopenicillin + BLI Cephalosporin 2° + metronidazole	Aminoglycoside Cotrimoxazole	In all patients
Perineal biopsy of the prostate, urethrocystoscopy, ureterorenoscopy, percutaneous pyeloscopy, laparoscopic procedures	Enterobacteriacea Enterococci Staphylococci	Fluoroquinolone[a] Aminopenicillin + BLI Cephalosporin 2°	Cotrimoxazole	In patients with increased risk of infection

BLI = β-Lactamase inhibitor; ESWL = extracorporeal shock-wave lithotripsy. 1°, 2°, 3° = 1st, 2nd, and 3rd generation, respectively.

[a] Fluroquinolone with sufficient renal excretion.

effect of transurethral resection (TUR) of the prostate was observed by some authors in patients with CBP and severe discomfort. Even radical prostatovesiculectomies have been carried out to relieve the pain, the results of which are dubious. In general, surgery should be avoided in the treatment of prostatitis patients except for drainage of prostatic abscesses.

Perioperative Antibacterial Prophylaxis in Urological Surgery

The main aim of antimicrobial prophylaxis in urology is to prevent symptomatic/febrile genitourinary 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 except in long or secondary interventions or in implant surgery. Prophylaxis should always be considered in patients with an increased risk of infection. For patients undergoing TUR of the prostate, additional risk factors for morbidity are also to be taken into account, such as size of prostate (>45 g), operative time (>90 min), and acute urinary retention. For diagnostic interventions, perioperative antibacterial prophylaxis

is generally recommended only in transrectal prostate biopsy with a thick needle.

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 prolonged intervention (>3 h) is an additional dose required whose size and timing are dictated by the pharmacokinetics. Antibiotic prophylaxis should not be continued for more than 24 h. It is a matter of discussion but not proved by clinical studies whether continent pouches or bladder replacements require prolonged postoperative antibiotic prophylaxis. Indwelling catheters and regular irrigation of the colonized intestinal segment (neobladder) could results in postoperative bacteremia and, in exceptional circumstances, portal pyemia.

When continuous urinary drainage, e.g. indwelling catheter, stent, nephrostomy etc., is left in place after operation, prolongation of perioperative antibacterial prophylaxis is contraindicated. If a symptomatic/febrile infection episode occurs, the patient has to be treated empirically until culture results are available. Asymptomatic bacteriuria has only to be treated before any urinary tract intervention or when the drainage tube is removed. Local antibiotic irrigation is not recommended since the effect is not sustained.

The most frequent infecting organism is *E. coli* followed by enterocci, *Proteus* spp. and *Klebsiella* spp. in the urinary tract and staphylococci for wound infections. The bacterial spectrum of hospital-related UTI must also be taken into consideration, especially if the patient has an indwelling catheter.

Many antibiotics meet the criteria for use in prophylaxis (table 6), e.g. 2nd 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 3rd generation cephalosporins, acylaminopenicillins plus BLI and carbapenems, should only be used sparingly, e.g. if the site of operation is contaminated with multiresistant nosocomial bacteria. Usually their administration should be restricted to the treatment of severe infections. 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 vancomyin-resistant enterococci and staphylococci.

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Regarding each chapter, selected references are offered for further reading. The complete list of references used to establish these guidelines is found in the full-length version of the 'EAU Guidelines for the Management of Urinary and Male Genital Tract Infections'.

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