GUIDELINES ON UROLOGICAL INFECTIONS

(Limited text update March 2015)

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Introduction

Urinary tract infections (UTIs) pose a serious health problem for patients with high cost to society. UTIs are also the most frequent healthcare associated infections.
E. coli is the predominant pathogen in uncomplicated UTIs. Besides *E. coli*, other *Enterobacteriaceae, Enterococcus spp*, and *Pseudomonas aeruginosa* are also cultured in patients with urological diseases. Microbial resistance is developing at an alarming rate with country-specific resistance rates related to the amount of antibiotics used. Particularly of concern is the increasing resistance to broad spectrum antibiotics. It is thus essential to limit the use of antibiotics in general and fluoroquinolones and cephalosporins in particular, especially in uncomplicated infections and asymptomatic bacteriuria.

Classification and definitions

For practical clinical reasons, UTIs and male genital tract infections are classified into entities defined by the predominant location of clinical symptoms and underlying risk factors (Table 1).

Table 1: Classification of urinary tract and male genital infections
Uncomplicated lower UTI: cystitis (acute, sporadic or recurrent)
Uncomplicated upper UTI: Pyelonephritis (acute, sporadic, no risk factor identified)
Complicated UTI with or without pyelonephritis (underlying urological, nephrological or other medical risk factors)
Urosepsis
Urethritis
MAGI: Prostatitis, epididymitis, orchitis

MAGI: male accessory gland infection.

The definitions of bacteriuria are listed in Table 2.

Table 2: Relevant bacterial growth in adults
1. ≥ 10^3 uropathogens/mL in midstream urine in acute uncomplicated cystitis in women.
2. ≥ 10^4 uropathogens/mL in midstream urine in acute uncomplicated pyelonephritis in women.
3. ≥ 10^5 uropathogens/mL in midstream urine in women or ≥ 10^4 uropathogens/mL in midstream urine in men (or in straight catheter urine in women) with complicated UTI.
4. In a suprapubic bladder puncture specimen, any count of bacteria is relevant.

Asymptomatic bacteriuria (ABU)

Asymptomatic bacteriuria is defined as two positive urine cultures taken more than 24 hours apart containing ≥ 10^5 uropathogens/mL of the same bacterial strain (in a patient without any clinical symptoms), irrespective of an accompanying pyuria. ABU is not considered an infection but rather a commensal colonisation, and in some clinical

situations a risk factor. Therefore ABU should not be treated and not screened for. There is some evidence that ABU in recurrent UTI could even be protective.

Pyuria

The diagnostic requirement for pyuria is 10 white blood cells per high-power field (HPF) (x400) in the re-suspended sediment of a centrifuged aliquot of urine or per mm^3 in unspun urine. For routine investigation, a dipstick method can also be used, including a leukocyte esterase test and assessment of haemoglobin and nitrites.

Classification of prostatitis/chronic pelvic pain syndrome

It is recommended to use the classification according to NIDDK/NIH (Table 3). Only acute and chronic bacterial prostatitis are covered in these Guidelines.

Table 3: Classification of prostatitis according to NIDDK/NIH

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

Epididymitis, orchitis

Most cases of epididymitis, with or without orchitis, are caused by common urinary pathogens. Bladder outlet obstruction and urogenital malformations are risk factors. Consider Chlamydia trachomatis infection in the younger male population.

Diagnosis

UTI (general)

A disease history, assessment of symptoms, physical examination and dipstick urine analysis, including white and red blood cells and nitrite reaction, is recommended for routine diagnosis. A urine culture is recommended in all types of UTI before treatment, except for sporadic episodes of uncomplicated cystitis in premenopausal women, in order to adjust antimicrobial therapy if necessary.

Pyelonephritis

Acute Pyelonephritis is suggested by flank pain, nausea and vomiting, fever (>38°C), costovertebral angle tenderness, and it can occur both with and without symptoms of cystitis. It may be necessary to evaluate the urinary tract to rule out upper urinary tract obstruction or stone disease.

Urethritis

Symptomatic urethritis is characterised by alguria and purulent discharge. Pyogenic urethritis is indicated by a Gram stain of secretion or urethral smear that shows more than five leukocytes per HPF (x1,000) and in case of gonorrhoea, gonococci are located intracellularly as Gram-negative diplococci. A positive leukocyte esterase test or more than 10 leukocytes per HPF (x400) in the first voiding urine specimen is diagnostic.

Bacterial Prostatitis

Acute bacterial prostatitis is a usually febrile infection of the prostate that can be severe and the diagnosis is based on the clinical symptoms and signs and positive urine culture. Chronic bacterial prostatitis is usually characterised by recurrent symptoms and UTI. In patients with prostatitis-like symptoms, an attempt should be made to differentiate between bacterial prostatitis and CPPS. This

is best done by the four glass test according to Meares & Stamey, if acute UTI and STD can be ruled out.

Treatment

Treatment of UTI depends on a variety of factors. Table 4 provides an overview of the most common pathogens, antimicrobial agents and duration of treatment for different conditions.

Table 4: Recommendations for antimicrobial therapy in urology

Diagnosis	Most frequent pathogen/species
Asymptomatic bacteriuria	• *E. coli* (usually low virulent) • Other species can also be found
Cystitis acute, sporadic and uncomplicated in otherwise healthy women	• *E. coli* • *Klebsiella sp.* • *Proteus sp.* • Staphylococci
Pyelonephritis, acute, sporadic, usually febrile (Uncomplicated)	• *E. coli* • *Proteus sp.* • *Klebsiella sp.* • Other enterobacteriaceae
(Febrile) UTI with urological complicating factors	• *E. coli* • *Klebsiella sp.*

Initial, empirical antimicrobial therapy	Therapy duration
No treatment Exception: before urological surgery entering the urinary tract and during pregnancy (low evidence)	3-5 days treatment of bacteriuria prior to urological surgery according to sensitivity testing[4] For pregnancy: refer to national recommendation if available
• Fosfomycin trometamol • Nitrofurantoin macrocrystal • Pivmecillinam Alternative: • Cephalosporin (group 1, 2) • TMP-SMX[1] • Fluoroquinolone[2,3]	1 dose 5 days 3 days 3 days 3 days (1-)3 days
• Fluoroquinolone[2] • Cephalosporin (group 3a) Alternatives: • Aminopenicillin/BLI • Aminoglycoside • TMP-SMX[1]	7-10 days After improvement, switch to oral therapy according to sensitivity testing
• Fluoroquinolone[2] • Aminopenicillin/BLI • Cephalosporin (group 3a) • Aminoglycoside • TMP-SMX[1]	7-14 days As for pyelonephritis consider combination of two antibiotics in severe infections

Pyelonephritis, acute, febrile, severe with complicating factors Healthcare associated (Nosocomial) UTI Catheter-associated febrile UTI	• *Proteus sp.* • *Enterobacter sp.* • *Serratia* • Other enterobacteriaceae • *Pseudomonas* • *Enterococci* • *Staphylococci* High risk of multi-resistant strains • In case of *Candida sp.*	
Urosepsis	Pathogen as above	

[1]Only in areas with resistance rate < 20% (for E. coli).
[2]Fluoroquinolone with mainly renal excretion (see text).
[3]Avoid Fluoroquinolones in uncomplicated cystitis whenever possible.
[4]Bacteriuria is a risk factor, though no clear regimen has been defined in available literature. The given recommendation is based on a reasonable expert opinion.
BLI = beta-lactamase inhibitor; UTI = urinary tract infection.

	In case of failure of initial therapy within 1-3 days or in clinical cases: Anti-*Pseudomonas* active: • Fluoroquinolone, if not used initially • Piperacillin/tazobactam • Cephalosporin (group 3b) • Carbapenem • ± Aminoglycoside • Fluconazole • Amphotericin B	3-5 days after defervescence or control/ elimination of complicating factor (drainage, surgery as required)
	• Cephalosporin (group 3a/b) • Fluoroquinolone[2] • Anti-Pseudomonas active acylaminopenicillin/BLI • Carbapenem • ± Aminoglycoside	As above Consider combination of two antibiotics in severe infection

Table 5: Summary of male accessory gland infections		
Diagnosis	**Most frequent pathogen/species**	
Prostatitis, acute bacterial (febrile) NIH type I Acute febrile Epididymitis	*E. coli* Other enterobacteriaceae *Pseudomonas* *Enterococcus feacalis* Staphylococci	
Prostatitis, chronic bacterial NIH type II	As above	
Prostatitis, acute or chronic Epididymitis Urethritis, caused by	*Chlamydia sp* *Ureaplasma sp*	

Special situations

UTI in pregnancy

A urine culture is recommended. Only antimicrobials considered safe in pregnancy should be used, e.g. penicillins, cephalosporins, fosfomycin; trimethoprim not in the first and sulphonamides not in the third trimenon; nitrofuantoin not in the last weeks of pregnancy to avoid glucose-6-phosphate deficiency of the embryo.

	(MAGI) management	
	Initial, empirical antimicrobial therapy	**Therapy duration**
	Fluoroquinolone Cephalosporin (group 3a or b) Aminoglycoside TMP-SMX	Initial parenteral Consider combination of two antibiotics in severe infections After improvement, switch to oral therapy according to sensitivity test for 2 (-4) weeks
	Fluoroquinolone Alternative to consider based on isolated pathogen TMP-SMX Doxycycline Macrolide	Oral 4 - 6 weeks
	Doxycycline Fluoroquinolone active on species (e.g. ofloxacin, levofloxacin) Macrolide	7 (-14) days (Follow national guidelines if available)

UTI in children

Treatment periods should be extended to 7-10 days. Tetracyclines and fluoroquinolones should not be used because of adverse effects on teeth and cartilage.

Acute uncomplicated UTI in young men

A urine culture is recommended. Treatment should last at least 7 days for uncomplicated UTI. Consider the option of a bacterial prostatitis that requires a longer treatment.

Complicated UTI due to urological disorders

The underlying disorder must be managed if a permanent cure is to be achieved. Whenever possible, treatment should be guided by urine culture to avoid missing and/or inducing resistant strains.

Sepsis in urology (urosepsis)

Patients with complicated UTI may develop sepsis. Early signs of systemic inflammatory response (fever or hypothermia, tachycardia, tachypnoea, hypotension, oliguria, leukopenia) should be recognised as the first signs of possible multi-organ failure. As well as appropriate antibiotic therapy, life-support therapy in collaboration with an intensive care specialist may be necessary. Any obstruction in the urinary tract must be drained.

Follow-up of patients with UTI

- For routine follow-up after uncomplicated UTI and pyelonephritis in women, assessment of symptoms and dipstick urine analysis is sufficient.
- In women with a recurrence of UTI within 2 weeks, repeated urinary culture with antimicrobial testing and urinary tract evaluation is recommended.
- In the elderly, newly developed recurrent UTI may warrant a full evaluation of the urinary tract.
- In men with UTI, a urological evaluation should be performed in adolescent patients, cases of recurrent infection and all cases of pyelonephritis. This recommendation should also be followed in patients with prostatitis, epididymitis and orchitis.
- In children, urological investigations are recommended after two episodes of UTI in girls and one episode in boys. Recommended investigations are ultrasound of the urinary tract supplemented by voiding cystourethrography.

Prevention of recurrent UTI (rUTI)

Prevention of rUTI includes i) counselling and behavioural modifications, i.e. avoidance of risk factors, ii) non-antimicrobial measures and iii) antimicrobial prophylaxis, which should be attempted also in this order. Urological risk factors need to be looked for and eliminated as far as possible. Significant residual urine should be treated optimally, which also includes clean intermittent catheterisation (CIC) when valued necessary.

Non-antimicrobial prophylaxis

Hormonal replacement

Local oestriol replacement, especially in postmenopausal women (GR: C)

Immunoactive prophylaxis

OM-89 (Urovaxom®) is documented with several placebo-controlled studies and useful in clinical practice (GR: B). The vaginal vaccine (Urovac®) and the parenteral products (StroVac® and SolcoUrovac®) demonstrated efficacy in only smaller controlled studies (GR: C).

Probiotics

Only in clinically proven studies are probiotics recommended (GR: C).

D-Mannose

To be used only in clinical trials for further evaluation. Cannot be recommended presently.

Endovesical instillation

Glycosaminoglycan (GAG) layer replenishement is used but recent review shows insufficient background for any recommendation.

Antimicrobial prophylaxis of rUTI

Antimicrobial prophylaxis can be given continuously (daily, weekly) for longer periods of time (3-6 months), as short courses after self-diagnosis in cooperative women or as a

single post-coital dose. It should be considered only after counselling and behavioural modification has been attempted, and when non-antimicrobial measures have been unsuccessful (GR: B).
Regimens for women with rUTIs include e.g. cotrimoxazole (TMP/SMX) 40/200 mg once daily or thrice weekly, nitrofurantoin 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every 10 days, and during pregnancy e.g. cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily.

Urethritis

The following guidelines for therapy comply with the recommendations of the Center for Disease Control and Prevention (2010 and later update). For the treatment of gonorrhoea, the following antimicrobials can be recommended (Table 6):

Table 6: Antibiotic therapy for treatment of gonorrhoea[1]

First choice	Second choice[2]
Ceftriaxone[3] 1.0 g iv/im (with local anaesthesia) plus Azithromycin 1.0 - 1.5 g p.o. as SD	Cefixime 400 mg p.o. SD Azithromycin 1.5 g p.o. SD Cefuroxime 400 mg p.o. SD Ciprofloxacin 500 mg p.o. SD Levofloxacin 250 mg p.o. SD

[1]always culture and susceptibility testing before therapy and PCR 2 weeks after therapy
[2]only if susceptibility is shown by culture
[3]if i.m. injection contraindicated and i.v. administration not possible: cefixime 800 mg p.o.

As gonorrhoea is often accompanied by chlamydial infection, an anti-chlamydial active therapy should be added.
The following treatment has been successfully applied in *Chlamydia trachomatis* infections (Table 7):

Table 7: Antibiotic therapy for *Chlamydia trachomatis* infections

First choice	Second choice
Azithromycin 1.5 g (= 3 caps @ 500 mg) orally as single dose	Erythromycin 4 times daily 500 mg orally for 7 days
Doxycycline[1] 2 times daily 100 mg orally for 7 (-14) days	Ofloxacin 2 times daily 300 mg orally or Levofloxacin once daily 500 mg orally for 7 days

[1]*contraindicated in children less than 8 years, in pregnant breast feeding women.*

If therapy fails, infections with *Trichomonas vaginalis* and/or *Mycoplasma* spp. should be considered. These can be treated with a combination of metronidazole (2 g orally as a single dose) and erythromycin (500 mg orally, 4 times daily, for 7 days).

Bacterial Prostatitis

Acute bacterial prostatitis has increased as a result of diagnostic trans-rectal prostate biopsy and can be a serious infection. The parenteral administration of high doses of bactericidal antibiotics, such as an aminoglycoside and a penicillin derivative or a third-generation cephalosporin, is required until defervescence occurs and infection parameters return to normal. In less severe cases, a fluoroquinolone may be given orally for at least 10-14 days.

In chronic bacterial prostatitis and inflammatory CPPS, a fluoroquinolone or trimethoprim should be given orally for 2 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics only continued if the pre-treatment cultures were positive or if the patient has reported positive

effects from the treatment. A total treatment period of 4-6 weeks is recommended.

Drainage/Surgery
Bladder catheter drainage might be needed in case of residual urine. Abscess of the prostate may develop in rare situations and require drainage.

Epididymitis, orchitis

Prior to antimicrobial therapy, a urethral swab and midstream urine sample should be obtained for microbiological investigation. The first choice of drug therapy should be fluoroquinolones, preferably those agents that react well against *C. trachomatis* (e.g. ofloxacin, levofloxacin), because of their broad antibacterial spectra and favourable penetration into urogenital tract tissues.
In cases caused by *C. trachomatis*, treatment may also be continued with doxycycline, 200 mg/day, for a total treatment period of at least 2 weeks. Macrolides are alternative agents.
In cases of *C. trachomatis* infection, the sexual partner should also be treated.

Perioperative antibacterial prophylaxis in urological surgery

The aim of antimicrobial prophylaxis in urological surgery is to reduce the load of bacteria at the site of surgery and thus to prevent symptomatic or febrile urogenital infections, such as acute pyelonephritis, prostatitis, epididymitis and urosepsis, as well as serious wound infections in conjunction with surgery. In recent years increased resistance of the faecal flora, especially against fluoroquinolones, has been reported which may impact on prophylaxis mode. It is recommended to assess the risk, e.g. prior to prostate biopsy. A urine culture is recommended prior to urological surgery when the urinary tract is entered both to identify ABU and any resistant strain.

The basic recommendations for short-term peri-operative antibacterial prophylaxis in standard urological interventions are listed in Table 8.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-80-9), available to all members of the European Association of Urology at their website, http://www.uroweb.org.

Table 8: Basic recommendations for peri-operative text Guidelines (Tables 19-24)

Procedure	Pathogens (expected)	Prophylaxis (standard)
Diagnostic procedures		
Transrectal biopsy of the prostate[1]	Enterobacteriaceae (Anaerobes?)	All patients
Cystoscopy Urodynamic study	Enterobacteriaceae Enterococci Staphylococci	No
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No
Endourological surgery and SWL		
SWL	Enterobacteriaceae Enterococci	No
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients
TUR of the prostate	Enterobacteriaceae Enterococci	All patients

antibacterial prophylaxis in urology. For details, see full

Antibiotics	Remarks
Fluoroquinolones[1] TMP ± SMX Metronidazole[2]	Single dose effective in low risk. Consider prolonged course in risk patients
TMP ± SMX Cephalosporin	Consider in risk patients
TMP ± SMX Cephalosporin	Consider in risk patients
TMP ± SMX Cephalosporin Aminopenicillin/BLI[3]	In patients with stent or nephrostomy tube or other known risk factor
TMP ± SMX Cephalosporin Aminopenicillin/BLI	Consider in risk patients
TMP ± SMX Cephalosporin Aminopenicillin/BLI (Fluoroquinolones)	Single dose or short course
TMP ± SMX Cephalosporin Aminopenicillin/BLI	Low-risk patients and small-size prostate require no prophylaxis

TUR of bladder tumour	Enterobacteriaceae Enterococci	No (see remarks)
Open or laparoscopic urological surgery[4]		
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens	No
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended
Clean-contaminated/ contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients

BLI = beta-lactamase inhibitor; TMP ± SMX = trimethoprim with thral resection.
[1]Increased resistance of faecal flora recorded (see text).
[2]No evidence for the use of metronidazole in prostate core biopsies.
[3]Gram-negative bacteria excluding Pseudomonas aeruginosa.
[4]Classifications of surgical field contamination (CDC).

	TMP ± SMX Cephalosporin Aminopenicillin/BLI	Consider in risk patients and large resections tumours and necrotic tumours
		Consider in high-risk patients. Short post-operative catheter requires no treatment
	TMP ± SMX Cephalosporin Aminopenicillin/BLI	Single peri-operative course
	Cephalosporin Metronidazole	As for colonic surgery
	Cephalosporin Penicillin (penicillinase stable)	

or without sulphamethoxale (co-trimoxazole); TUR = transure-