ISKRA guidelines on antimicrobial treatment and prophylaxis of urinary tract infections – Croatian national guidelines

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1.0 Introduction

Urinary tract infections (UTI) are among the most common bacterial infections and one of the most common reasons for prescribing antimicrobial drugs.

UTI comprise a heterogeneous group of clinical syndromes and diseases that differ in epidemiology, etiology, location, severity of disturbed general condition and general symptoms of infection, expressed local symptoms, frequency of recurrence and relapse, presence of complicating factors and risks from their repeated occurrence, necessary antimicrobial therapy, outcome and prognosis.

The aim of the UTI treatment is the disappearance of clinical symptoms and eradication of infection in order to prevent relapse.
All symptomatic UTI and asymptomatic bacteriuria in certain individuals need to be treated.
Antimicrobial spectrum of administered drug has to cover a spectrum of detected or expected causative pathogen and as least as possible disturb normal human flora. Least toxic and at the same time the cheapest medication should be administered in adequate dosage and for a sufficiently long period of time in order to eradicate infection.

These guidelines refer to diagnosis, antimicrobial treatment and prophylaxis of UTIs in adults and children older than 12 years of age and cover lower urinary tract in females, uncomplicated pyelonephritis, complicated UTI with or without pyelonephritis, asymptomatic becteriuria and recurrent UTI. These guidelines do not cover sexually transmitted diseases, urethritis, epididymitis, orchitis or prostatitis caused by sexually transmitted organisms.

The guidelines are intended for use by general practitioners and specialists working in primary health care and hospitals.

Adherence to guideline recommendations will not ensure a successful outcome in every case, nor is the aim of this guideline to give an overview of all the available diagnostic and treatment options. The ultimate decision regarding diagnostic and therapeutic choice in a particular patient must be made by the appropriate healthcare professional.

2.0 Development of the guideline

2.1 The need for national guidelines – ISKRA initiative

The Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) of the Croatian Ministry of Health and Social Welfare has initiated the development of national guidelines on a series of topics where antimicrobial therapy plays an important role in the treatment of patients. The aim of this initiative is to provide optimal treatment options for infectious diseases patients, promote rational use of antibiotics and develop strategies for infection prevention and control of spread of resistant bacteria. These guidelines are in line with the Croatian strategy for antibiotic resistance control adopted by the Croatian Ministry of Health and Social Welfare according to the European Union Council Recommendation (2002/77/EC). When deciding on the choice of antibiotic therapy the Croatian national data on antibiotic resistance rates were taken into consideration as well as the existing 2004 Croatian guidelines for antimicrobial treatment and prophylaxis of urinary tract infections. The guidelines have been established based on the AGREE (Appraisal of Guidelines for Research and Evaluation) methodology.[1]

2.2 The guideline Working Group

The members of the Working Group (WG) for the development of guidelines on **antimicrobial treatment and prophylaxis of urinary tract infections** were appointed by the Croatian Ministry of Health and Social Welfare and are listed bellow together with the societies or institutions that they represent.

Members of the UTI Working Group (in alphabetical order):
Višnja Škerk, Chair, Reference Center for Urinary Tract Infections
Saša Andrašević, Croatian Society for Urinary Tract Infections and Sexually Transmitted Diseases
Jugoslav Bagatin, Croatian Society for Clinical Pharmacology
Mario Ćorić, Croatian Society for Urological Gynecology
Daniel Ferlin, Croatian Society for Family Medicine
Ivan Krhen, Croatian Society for Urology
Vesna Mađarić, Croatian Society for Chemotherapy
Slobodan Milutinović, Croatian Society for Nephrology
Ana Mlinarić Džepina, Croatian Society for Medical Microbiology
Ljiljana Perić, Croatian Society for Infectious Diseases
Edita Sušić, Croatian Committee for Antibiotic Resistance Surveillance of the Croatian Academy of Medical Sciences
Arjana Tambić Andrašević, Reference Center for Antibiotic Resistance Surveillance

2.3 Literature review, levels of evidence and grades of recommendations

2.3.1 Literature review

The evidence for this guideline is based on a systematic review of the literature. For the initial evidence search the Croatian UTI Working Group has used the existing Croatian guidelines for antimicrobial treatment and prophylaxis of urinary tract infections[2, 3]; IDSA guidelines for the antimicrobial treatment of acute uncomplicated bacterial cystitis and pyelonephritis in women[4]; Guidelines on the Management of Urinary and Male Genital Tract Infections developed by the European Association of Urology[5]; National Clinical Guideline SIGN 88 - Management of Suspected Bacterial Urinary Tract Infections in Adults developed by the Scottish Intercollegiate Guidelines Network in 2006[6]; Dutch Guidelines for Antimicrobial Therapy of Complicated Urinary Tract Infections[7] as well as papers listed in the literature section of these guidelines.

In addition, the following databases were also searched for articles written in English without time limit of publication: Medline, Evidence Based Medicine Reviews, Cochrane Database of Systematic Reviews. The following key words were used for literature search: urinary tract infections, diagnosis, treatment.

Local antibiotic resistance data were obtained from the Committee for Antibiotic Resistance Surveillance of the Croatian Academy of Medical Sciences.[8, 9, 10, 11, 12, 13]

These guidelines are also based on the existing clinical protocols on the treatment and prophylaxis of UTI, as well as suggestions and comments made by colleagues physicians during more than 50 continuous medical education courses held in the last three years on antimicrobial therapy and prophylaxis of UTIs.

2.3.2 Level of evidence

Table 1. Levels of evidence according to US Agency for Health Care Policy and Research[14]

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

2.3.3 Grade of recommendations

Table 2. Grades of guideline recommendations, modified according to the US Agency for Health Care Policy and Research[14]

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

2.4 Consultation and peer review

2.4.1 National Societies and Institutions supporting the guidelines

Presidents and heads of the societies and institutions listed under section 2.2 were first asked to delegate one of their members into the Working Group for guideline development. The Working Group produced a draft version of the guideline that represented a Working Group consensus document. The presidents and heads of the respected societies and institutions were asked to inform all the members that a draft version of the guideline is available for comments on the ISKRA web site: http://iskra.bfm.hr for a period of two months. General practitioners were also informed about the guidelines and asked for comments through a network of Health Care Centers` representatives. Comments received were analyzed by the Working Group members, who then, finalized the text and prepared the document for print.

2.4.2 Piloting of the guidelines

During the two-month piloting period the guidelines were used in everyday practice by five to ten specialists in urology, gynecology, infectious diseases, nephrology and 47 general practitioners. Physicians that used the guidelines in the pilot stage were asked to register their observations by filling in a predefined questionnaire with questions related to the feasibility of the guideline. Their suggestions and comments were discussed by the WG and taken into consideration when publishing the final version of the guidelines.

2.4.3 International consultants

As a part of the MATRA project “Antibiotic resistance surveillance in human medicine”, the assistance of international consultants was available throughout the guideline development. The project was financially supported by the Dutch government and was carried out by the Reference Center for Antibiotic Resistance Surveillance of the Croatian Ministry for Health and Social Welfare. International

consultants from the Netherlands Working Party on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid, SWAB) were involved in the development of these guidelines through a series of workshops on guideline writing and personal contacts with members of the Working Group.

2.4.4 ISKRA Board

The final version of the guideline was reviewed and accepted by the ISKRA board. Members of the ISKRA board are:
A. Tambić Andrašević, Chair of ISKRA, Reference Center for Antibiotic Resistance Surveillance
V. Stamenić, Croatian Ministry of Health and Social Welfare
B. Aleraj, Reference Center for Epidemiology
Lj. Betica Radić, Croatian Society for Infectious Diseases
T. Buble, Croatian Institute for Health Insurance
I. Francetić, Croatian Society for Clinical Pharmacology
S. Kalenić, Reference Center for Nosocomial Infections
V. Mađarić, Croatian Society for Chemotherapy
Lj. Maltar, Croatian Ministry of Agriculture, Forestry and Water
M. Payerl Pal, Croatian Committee for Antibiotic Resistance Surveillance
J. Škrlin, Croatian Society for Medical Microbiology
A. Tomljenović, Croatian Ministry of Science, Education and Sports
M. Vrca Botica, Croatian Society for Family Medicine

2.5 Updating guidelines

Guidelines will be updated every five years unless there is a significant reason for change sooner (e.g. change in resistance rates, new antibiotics).

3.0 Classification of UTI

These guidelines are in accordance with the IDSA[15] and ESCMID[16] classification of UTI as these UTI categories could easily be distinguished at the first visit of the patient when decision on therapy is made.

The UTI categories are as follows:

1. acute uncomplicated lower UTI in pre-menopausal, non pregnant women
2. acute uncomplicated pyelonephritis
3. complicated UTI including all UTI in men
4. asymptomatic bacteriuria
5. recurrent UTI (uncomplicated, without predisposing factors)

4.0 Diagnosis and antimicrobial treatment of UTI

Table 4.1. Criteria for the diagnosis and antimicrobial treatment of UTI

	Category	Clinical features	Laboratory investigations	Antimicrobial treatment *
1	**Acute uncomplicated lower urinary tract infections in pre-menopausal, non pregnant women**	Dysuria, urgency, frequency, suprapubic pain, no fever or low grade fever (< 37,5^{0}C), symptoms lasting less than 7 days, no urinary symptoms 4 weeks before this episode, uncomplicated sporadic episode	dipstick leukocyte esterase test and nitrite test ≥ 10 WBC/mm^3	**First choice:** nitrofurantoin 2x100 mg po. for 7 days **Alternative choice:** co-amoxiclav 2x1 g po. for 7 days cefalexin 2x1 g po. for 7 days norfloxacin 2x400 mg po. for 3 days
2	**Acute uncomplicated pyelonephritis**	Fever (>38^{0}C), chills, flank pain, other diagnoses excluded, no history or clinical evidence of urological abnormalities (ultrasonography, radiography)	≥ 10 WBC/mm^3 + ≥ 10^4 cfu/mL**	**AMBULATORY** **First choice:** co-amoxiclav 2x1 g po. for 10-14 days **Alternative choice:** II and III generation cephalosporins for 10-14 days (cefuroxime axetil 2x500 mg po., ceftibuten 1x400 mg po., cefixime 1x400 mg po.) ciprofloxacin 2x500 mg po. for 7-10 days*** **HOSPITAL** Indications for hospitalization are: severe clinical presentation that includes some of the following symptoms– prostration, fever >38.5^{0}C, urine retention, impossibility of antibiotic oral intake, indications for parenteral rehydration. **if hospitalization necessary** start parenteral therapy then switch to oral after clinical improvement (resolution of fever usually at 48-72h): **first choice:** co-amoxiclav 3x1.2 g iv. for 10-14 days in severe cases add gentamicin 1x4 mg/kg iv. (3 days) *** **Alternative choice:** gentamicin 1x4 mg/kg iv., im.*** II or III generation cephalosporins for 10-14 days (cefuroxime 3x750-1500 mg iv., ceftriaxone 1x1-2 g iv.) ciprofloxacin 2x400 mg iv. for 7-10 days***
3	**Complicated UTI including all UTI in men**	Any combination of symptoms from categories 1 and 2	≥ 10 WBC/mm^3 + ≥ 10^5 cfu/mL**	**AMBULATORY** **First choice:** co-amoxiclav 2x1 g po. for 10-14 days

		above; one or more factors associated with a complicated UTI (see text)	or ≥ 10^4 cfu/mL in straight catheter urine in pre-menopausal, non pregnant women ≥ 10^3 cfu/mL** in pregnant women ≥ 10^4 cfu/mL** in men	**Alternative choice:** II and III generation cephalosporins for 10-14 days (cefuroxime axetil 2x500 mg po., ceftibuten 1x400 mg po., cefixime 1x400 mg po.) ciprofloxacin 2x500 mg po. for 7-10 days*** **HOSPITAL** **First choice:** co-amoxiclav 3x1.2 g iv. for 10-14 days + gentamicin 1x4 mg/kg iv.*** for 10 days***[17, 18] **Alternative choice:** ciprofloxacin 2x400 mg iv. for 7-10 days*** II or III generation cephalosporins for 10-14 days (cefuroxime 3x750-1500 mg iv., ceftriaxone 1x1-2 g iv.) ***In males***: **AMBULATORY** ***Acute UTI and systemic symptoms (fever)*** **First choice:** ciprofloxacin 2x500 mg po. for 2 weeks*** **Alternative choice:** co-amoxiclav 2x1g po. for 2 weeks cefuroxime axetil 2x500 mg po. for 2 weeks ceftibuten 1x400 mg po., for 2 weeks cefixime 1x400 mg po., for 2 weeks ***UTI and complaints that correspond to chronic bacterial prostatitis (apart from dysuria, perineal pain and/or sexual dysfunction also present)*** **First choice:** ciprofloxacin 2x500 mg po. for 4 weeks*** **Alternative choice:** trimethoprim/sulfamethoxazole (TMP/SMX) 2x960 po. for 4 weeks if sensitivity of the agent is known co-amoxiclav 2x1g po. for 4 weeks cefuroxime axetil 2x500 mg po. for 4 weeks ceftibuten 1x400 mg po. for 4 weeks cefixime 1x400 mg po., for 4 weeks **HOSPITAL** **if hospitalization necessary** same as above except start parenteral therapy (ciprofloxacin 2x400 mg iv. ***, co-amoxiclav 3x1.2 g iv., cefuroxime 3x1.5g iv., ceftriaxone 1x1-2 g iv.) in severe cases add gentamicin (1x4 mg/kg iv.***) to beta-lactams

				In pregnant women**:* II (cefuroxime axetil) and III (ceftibuten or cefixime) generation cephalosporins or co-amoxiclav cystitis for 7 days pyelonephritis for 10-14 days (hospital treatment is recommended) nitrofurantoin 2-3x100 mg for 7 days in the first and second trimester for cystitis and asymptomatic bacteriuria only **if hospitalization necessary** same as above except start parenteral therapy ***In hospital acquired infections & foreign body (catheter) infections **First choice:** netilmycin 1x 4-6 mg/kg iv. + ceftazidim 3x1-2g iv. for 7-14 days*** **Alternative choice:** ciprofloxacin 2x400 mg iv. for 7-10 days***
4	**Asymptomatic bacteriuria**	No urinary symptoms	≥ 10 WBC/mm^3 **For females:** ≥ 10^5 cfu/mL** of the same bacterial strain in two consecutive MSU cultures ≥ 24 hours apart **For males:** ≥ 10^5 cfu/mL** in single MSU culture	No treatment except in pregnant women, before invasive urologic and gynecologic procedures, in kidney transplant recipients and in women with catheter associated bacteriuria that persists 48 h after indwelling catheter removal. Treatment according to antibiogram for 3-7 days.
5	**Recurrent UTI**	At least three episodes of uncomplicated infection documented by culture in the last 12 months or two episodes in the last 6 months: women only; no structural/functional abnormalities	≥ 10 WBC/mm^3 + Uncomplicated cystitis ≥ 10^3 cfu/mL** Uncomplicated pyelonephritis ≥ 10^4 cfu/mL** Patients suitable for prophylaxis should not have signs and symptoms of acute infection when prophylaxis is initiated	**Treatment** The same as sporadic episodes except that previous isolates and their sensitivity patterns should be taken into account. **Prophylaxis** In patients with recurrent UTI one of the following prophylactic regimens may be recommended: 1. selfmedication with antibiotics is recommended for 3-7 days according to finding of previous urinary culture and the success of treatment during the last urinary infection (in patients with ≤ 2 episodes of uncomplicated UTI in the last year) 2. in some patients taking prophylaxis is recommended after the sexual intercourse (in patients with ≥ 3 episodes of uncomplicated UTI in the last year) 3. continuous intake of prophylactic dose every evening or three times per week. Prophylaxis, according to antibiogram, should last for 6 months or longer and includes ¼ or ½ of therapeutic dose: nitrofurantoin 50-100 mg po. TMP/SMX 480 mg po. cefalexin 250 mg po. Fluoroquinolones should be saved for treatment of symptomatic infections and be used only

				exceptionally norfloxacin 200 mg po. ciprofloxacin 125 mg po. **Alternative ways of prophylaxis** cranberry products (2 times daily) intravaginal estrogen administration intravaginal administration of lactobacillus suspension (under research at the moment, not standard of care)
MSU = mid-stream urine sample; UTI = urinary tract infection; WBC = white blood cells. All leukocyturia counts refer to unspun urine.				

*Doses are adjusted according to[19, 20] if not indicated differently; doses are stated for an average adult body weight and normal kidney function;
**Uropathogen in MSU culture;
***Dosing should be adapted in patients with impaired kidney function (see Section: General recommendations)

General recommendations for the therapy approach in all UTI categories:

After clinical improvement (resolution of fever, usually after 48-72h), therapy should be switched to oral.[2, 3, 5, 21, 22, 23, 24, 25]

Empirical therapy should be modified according to antibiogram as soon as urine culture results are available (antibiotic therapy should be switched to an antibiotic that has narrowest spectrum and is effective against the causative agent).[2, 3, 26]

Aminoglycosides should not be used for longer than 10 days in patients with normal kidney function. After clinical improvement (usually after 72h), aminoglycosides should be replaced with perooral antibiotic. In case aminoglycoside is added to beta-lactam antibiotic for synergistic effect, after 3 days of clinical improvement, aminoglycoside therapy should be stopped and only beta-lactam antibiotic continued. In patients with impaired kidney function dose should be modified accordingly.[7, 27, 28, 29] (Ib, A) Aminoglycosides have limited tissue distribution and are renally cleared. Dosing is based on a patient's ideal or adjusted body weight and renal function. Careful selection of empiric dosing regimens and serum level monitoring when warranted are needed to ensure safety and efficacy of these drugs. Patients anticipated to receive aminoglycosides for > 2 weeks should be considerd for audiometry.

Antimicrobial effect of aminoglycosides depends on antibiotic concentration. Single dosing achieves the same effect as multiple dosing, however, toxic effect of aminoglycosides is decreased when single dose is used. Single dose is administered in patients with creatinine clearance >60 ml/min. Gentamycin is administered in a single dose of 4-7 mg/kg[17, 18] (IIa, B). Infections caused by Pseudomonas require gentamicin dose of 7 mg/kg.[30, 31] (IIa, B)

In patients with impaired kidney function, dosing should be adapted to creatinine clearance. (Table 4.2)

Table 4.2 Aminoglycoside dosing in patients with impaired kidney function

Creatinine Clearance	Dose (gentamicin, tobramycin)
40-60 ml/min	1.2 - 1.5 mg/kg/dose IV q12h
20-40 ml/min	1.2-1.5 mg/kg/dose IV q12-24h
<20 ml/min	2 mg/kg loading dose

A 2 mg/kg loading dose may be administered in patients with severe infections.

4.1 Acute uncomplicated lower urinary tract infections (cystitis) in pre-menopausal, non pregnant women

The most common cause of acute uncomplicated lower urinary tract infections (cystitis) in pre-menopausal, non pregnant women is *E.coli* (80% of cases). *Staphylococcus saprophyticus* is also recognized as a primary uropathogen in young women (5-10% of UTI in this population).[32, 33] In Croatia, the incidence of *S.*

saprophyticus is low (less than 5%).[34] Other microorganisms (other enterobacteriaceae, enterococci) usually cause infection in the presence of underlying conditions.[23, 35]
In women with clear symptoms of uncomplicated cystitis, ≥ 10^3 cfu/mL of uropathogens in midstream urine (MSU) is thought to be the best cut off for significant bacteriuria with sensitivity of approx. 80% and specificity of approx. 90%.[5, 36, 37] (IV, C) In case the UTI symptoms are not clear it should be kept in mind that a low bacterial count (10^3 cfu/mL) is frequently found in healthy women as a consequence of urine contamination during voiding.

Urine culture should not be performed in young women with sporadic uncomplicated cystitis as the causative agent is highly predictable.[2, 3, 5, 6, 23] (IV, C) If the patient does not improve while on empirical therapy, a urine sample should be taken for culture.

The diagnosis should be based on characteristic symptoms (described in table 3) and a dipstick test finding. According to literature, a positive nitrite test and/or leukocyte esterase test indicate the presence of an infection.[38] (Ia). Therefore, the WG recommends the use of both - dipstick tests for leukocyte esterase as well as nitrite test (A).

Although leukocyturia speaks in favor of infection diagnosis, positive finding does not always confirm infection, nor the lack of it rules it out.[39] In laboratory practice, leukocyturia is detected most commonly through the detection of leukocytes in large visible urine sediment (magnification 10x40), where the finding od 5-10 leukocytes in large visible sediment is considered the upper limit of normal finding in urine of healthy individuals.[40] By using this method for the detection of leukocyturia, a large number of patients with significant bacteriuria will have a negative finding, therefeore this method is considered not sensitive enough. The method of leukocyte counting in noncentrifuged urine is considered more sensitive, where the number of >10 leukocytes/mm^3 presents a pathological finding.[15] The simplest method for the detection of leukocyturia is the detection of leukocyte esterase. Leukocyte esterase test has a high sensitivity and specificity if performed in symptomatic patients (75-96% sensitivity, 94-98% specificity).[36, 37] Although the probability of UTI is reduced to a less than 20% by a negative dipstick test, UTI cannot be excluded in symptomatic women[38], so clinical judgement should be used to decide whether to obtain urine for culture or invite the patient to a control visit, if symptoms persist or worsen.

Increased number of leukocytes in urine is usually a sign of urinary tract infection, however it can also reflect some other factors such as the presence of a catheter, stones, vulvovaginitis, erosion of vaginal and cervical mucosa or dehydration.[41] In such cases further investigation of sexually transmitted diseases or gynecological pathology should be indicated.

The UTI WG has decided to use nitrofurantoin as the first choice therapy for acute uncomplicated lower urinary tract infections (cystitis) in pre-menopausal, non pregnant women since *E.coli* is still highly susceptible to this agent (97% in Croatia), the resistance to this agent seems to be developing slowly after many years of its clinical use[13], its affordable price and low toxicity. There have been concerns about the toxicity of nitrofurantoin, acute and chronic pulmonary disease in particular. The

incidence of these side effects seems to be low based on literature[33, 42, 43] and personal experience of the members of the working group.[2, 3] Symptoms are reversible after the discontinuation of the drug. However, attention should be paid not to miss the symptoms of side effects and the drug should be stopped if they appear. The WG recommends nitrofrantoin to be administered twice daily because of drug efficacy and better patient compliance. [44, 45]
Nitrofurantoin should be used for 7 days as there is no good evidence that shorter therapy is as effective.[4, 46] (IIb, B)

There is no good evidence that shorter therapy is as effective as a 7-day therapy with co-amoxiclav, so the WG has accepted the general 7-day treatment for beta-lactam therapy for this indication.[47, 48, 49, 50] (Ib, A)

At present, the resistance of *E.coli* to fluoroquinolones in Croatia is 10% and fluoroquinolones should be saved for more serious infections.[13] If used for uncomplicated cystitis norfloxacin should be used for no longer than 3 days, as this therapy is proved to be as effective as a 7-day therapy. Longer therapy is more likely to select resistance in a normal flora and therefore should be avoided.[51, 52, 53, 54] (Ia, A)

The resistance rates of *E. coli* to most commonly used antibiotics for the treatment of UTI in the period from 2001 to 2006 are shown in Table 4.2.

Table 4.2. The resistance of *E. coli* to most common antibitiotics in Croatia in the period from 2002-2006[13]

Antibiotic	Resistant (intermediate) %				
	2002	**2003**	**2004**	**2005**	**2006**
nitrofurantoin	4 (1)	3 (1)	3 (1)	3 (1)	2 (1)
TMP/SMX	25 (0)	22 (0)	25 (0)	24 (1)	24 (0)
amoxicillin	47 (1)	47 (1)	44 (1)	49 (1)	52 (1)
cephalexin	11 (5)	9 (4)	9 (6)	11 (8)	8 (5)
co-amoxiclav	8 (4)	6 (4)	5 (3)	5 (4)	4 (4)
cefuroxim	5 (1)	3 (1)	3 (1)	3 (2)	2 (2)
ceftibuten	3 (0)	2 (0)	2 (0)	1 (0)	2 (0)
ceftriakson	3 (0)	2 (0)	2 (0)	1 (0)	2 (0)
gentamicin	7 (1)	5 (0)	5 (0)	6 (0)	6 (0)
norfloksacin	8 (0)	8 (0)	7 (0)	10 (0)	10 (1)
ciprofloksacin	7 (0)	8 (0)	7 (0)	10 (0)	10 (1)

4.2 Acute uncomplicated pyelonephritis

Although the criteria of significant bacteriuria with ≥ 10^4 cfu/mL uropathogens in MSU is recommended in routine diagnostics, in 80-95% of acute pyelonephritis cases, ≥ 10^5 cfu/mL uropathogens in MSU are found.[55]

The UTI WG has decided to choose co-amoxiclav as the first choice therapy for the treatment of acute uncomplicated pyelonephritis due to its low resistance rate in *E.coli* (4% resistant and 4% intermediately sensitive in Croatia in 2005),[13] relative narrow spectrum and nontoxicity. In hospitals the therapy should start parenterally

(3x1.2 g), and in outpatients orally (2x1 g).[56] (Ib) While twice daily dosing of co-amoxiclav (2x1g) is clearly more efficient than 3x625 mg dosing for the treatment of pneumococcal (respiratory) infections, the opposite goes for gram-negative (UTI) infections. The content of clavulanic acid is higher in 3x625 mg dosing regimen and this is important for gram-negative agents (UTI infections), but irrelevant for gram-positive organisms (respiratory tract infections). However, some studies have demonstrated equal clinical effectiveness of both regiments in the treatment of UTI [57] so the WG has decided to recommend 2x1 g of co-amoxiclav counting on better compliance and less side effects linked with this dosing regimen.

Alternative therapy includes 2nd and 3rd generation cephalosporins and ciprofloxacin. However, these drugs should be preserved for persons allergic to penicillins with regards to possible resistance development.[58, 59, 60, 61] (IIa, B)
In case of an anaphylactic reaction to penicillin, beta-lactams should not be given and ciprofloxacin should be the drug of choice.[58] Beta-lactam therapy should last for 10-14 days.[26, 62, 63] (IV, C) Ciprofloxacin should be used for 7-10 days.[64, 65] (Ib, A)

In patients who need to be hospitalized parenteral therapy should be initiated and in severe cases co-amoxiclav could be combined with gentamycin for synergistic effect and broader spectrum of the combination.[62] (IV, C)
The only combination of antibiotics with proved synergy is a combination of a beta-lactam and an amynoglycoside.[66, 67] (IIb, B) After many years of use there is still a low resistance rate to aminoglycosides in *E.coli*, 6% for gentamicin and 1% for netilmicin.[13] Once daily dosing of aminoglycozides is at least as effective as multiple dosing and is less toxic, so it is recommended to use aminoglycosides in once daily dosing regimen.[17, 18] (Ib, A)

4.3 Complicated UTI

Factors that suggest a potential complicated UTI

1. Male sex
2. Pregnancy
3. Hospital acquired infection
4. The presence of an indwelling catheter, stent or splint (urethral, ureteral, renal) or the use of intermittent bladder catheterization
5. Vesicoureteric reflux or other functional or anatomical abnormalities of the urinary tract (e.g. a post-void residual urine of >100 ml; chemical or radiation injuries of the uroepithelium; an obstructive uropathy of any aetiology such as bladder outlet obstruction, including neurogenic urinary bladder, stones and tumour; urinary tract modifications, such as an ileal loop or pouch)
6. Renal insufficiency (creatinine clearance < 30 mL/min) and transplantation
7. Recent urinary tract intervention (in the last 15 days)
8. Recent antibiotic use (in the last 2-3 months)
9. Symptoms for > 7 days at presentation
10. Diabetes mellitus
11. Immunosuppression or immunocompromised diseases

4.3.1 UTI in men

In older men, UTIs are common and usually related to instrumentation and bllader outlet obstruction while in men younger than 50 years of age UTI are very rare and mostly related to urinary tract abnormalities. Therefore all UTI in men are classified as complicated UTI. UTI in men can also be uncomplicated with an easy eradication of the pathogen, however such infections are very rare.[55] In most men, in whom a urinary tract infection is accompanied by fever, a subclinical infection of the prostate is also present.[68] Apart form dysuria, prostatitis symptoms include perineal pain and sexual dysfunction.
TMP/SMX and ciprofloxacin are antibiotics that penetrate well into the prostate and are therefore recommended for the treatment of UTI in men.[69, 70, 71, 72] (IIb, B) Since the resistance of *E. coli* to TMP/SMX in Croatia is greater than 20%, the UTI WG has decided to use ciprofloxacin in empirical therapy. If antibiogram of the causative pathogen shows that the isolate is susceptible to TMP/SMX it is recommended for targeted therapy. Ciprofloxacin or TMP/SMX therapy for UTI in men should last at least 2 weeks, and in case of expressed prostatitis symptoms for 4 weeks.[73, 74] (Ib, A)

In case of pathogen resistance to both of these two antibiotics, co-amoxiclav or cephalosporin alone or in combination with aminoglycoside can be used, since these have shown to penetrate somewhat better into the prostate during acute inflammation.[70, 72]

4.3.2 Complicated UTI in the presence of functional or anatomical abnormalities

First step in the treatment of complicated UTIs should be to find and eliminate the predisposing factor.[2, 3, 5]
Only symptomatic episodes of complicated UTIs should be treated with antibiotics.[5, 75]

Acute symptomatic episodes should be treated with co-amoxiclav and gentamicin in hospitalized patients or ciprofloxacin if treated ambulatory. Urine should be taken for culture before starting antibiotic therapy. Empirical antibiotic therapy should be adjusted according to the previous urine culture findings and antibiogram.

4.3.3 Nosocomial UTI and UTI in the presence of a foreign body (catheter)

UTIs associated with foreign body are often hospital acquired or share the same pathogens as hospital acquired UTIs. Any invasive diagnostic or therapeutic intervention can also result in a nosocomial infection. The longer the catheter is in place the greater are the chances for bacteriuria. After 30 days of catheterization (long term catheterization) bacteriuria (often with more than two organisms) is commonly present in almost all patients with an indwelling catheter.[5, 76, 77] Intermittent catheterization is related to lower frequency of asymptomatic bacteriuria.[78]

In asymptomatic patients with an indwelling catheter, urine culture is not recommended as a routine test, since bacteriuria and leukocyturia are most commonly present.[6, 79] (IIa, B)

Bacteriuria without symptoms should not be treated with antibiotics.[78, 79] (Ib, A)

In patients with long term indwelling catheters asymptomatic bacteriuria as well as leukocyturia are common and should not be treated with antibiotics.[5, 6, 79, 80, 81] (Ib, A)
Long-term antibiotic prophylaxis in catheterized patients is not recommended since it can also lead to an infection with resistant pathogens.[81, 82, 83] (Ib, A)
Urine culture should be done only in acute symptomatic episodes.[5] Exceptions to these rules are commented under asymptomatic bacteriuria chapter.

Symptoms of acute UTI in patients with urinary catheter are sometimes difficult to determine.[84]

Elevated temperature is a nonspecific sign of UTI, however when other possible causes are lacking, and in combination with suprapubic or lumbal pain and general severity of the clinical picture, worsened mental state, it can be the reason for initiation of antimicrobial treatment of presupposed UTI.[6, 85, 86] (IIa, B)

When deciding on empirical therapy, a wider spectum of causative pathogens should be taken into accont, including *P. aeruginosa*. Therefore the UTI WG has chosen ceftazidime and aminoglycoside as the first choice therapy. Empirical therapy should be adapted to previous findings and local resistance data. Urine culture should be done prior to initiation or change of current therapy. Catheter removal should be considered as part of the treatment, due to bacteria sequestered within the biofilm coating and catheter surface.[5]
In case of ambulatory treatment, the only oral antibiotic with antipseudomonas efficacy is ciprofloxacin. Duration of therapy is the same as for any other complicated UTI.
Irigation of the bladder with antibiotics is not effective and is not recommended.[83] (IIb, B)

4.3.4 UTI in pregnant women

Pregnant women should be screened for asymptomatic bacteriuria (≥ 10^5 cfu/mL in two consecutive MSU cultures, ≥ 24 hours apart) in the first trimester of pregnancy and if known to have a UTI or asymptomatic bacteriuria on every visit to the doctor until delivery.[75, 87, 88] (Ia, A)
Pregnant women who do not have positive urine culture on screening in the first trimester do not need to have repeat urine cultures.[6]
Most symptomatic UTIs in pregnant women present as acute cystitis. The UTI WG is recommending the use of beta-lactam antibiotics (7 days for cystitis, 14 days for pyelonephritis) as these agents are effective for UTI and safe for use in pregnancy.[89, 90] (Ib, A) Quinolones, tetracyclines and TMP/SMX should NOT be used in pregnancy.[19, 56] Nitrofurantoin could be used for cystitis and asymptomatic bacteriuria for 7 days in the first and second trimester only.[91, 92]

4.3.5 UTI in post-menopausal women

UTIs in post-menopausal women should be treated the same as in pre-menopausal women.[5] However, thorough examination for urological or gynaecological disorders should be performed and predisposing factors should be treated accordingly.

4.4 Asymptomatic bacteriuria

Asymptomatic bacteriuria is common in healthy individuals and especially in populations with structural or functional abnormalities.[5, 93]
The only patients who are at higher risk for developing an symptomatic infection with serious outcome are pregnant women and patients undergoing invasive urological interventions. Therefore treating asymptomatic bacteriuria in these patients is recommended.[33, 75, 94] (Ia, A)

Asymptomatic bacteriuria in elderly is quite common and should not be treated.[5, 80, 82] (Ib, A)

In patients with long term indwelling catheters asymptomatic bacteriuria as well as leukocyturia are common and should not be treated with antibiotics.[5, 6, 79, 80, 81] (Ib, A)
The only exceptions are patients who are at high risk of serious complications (neutropenic), patients undergoing urological surgery, patients infected with *Serratia marcescens* as this species has a high potential for causing bacteriemia and sometimes treatment could be justified if the aim is eradication of a particularly dangerous microorganisam from the ward.[95, 96, 97] In patients with an indwelling catheter, urine culture is not recommended as a routine test, since bacteriuria and leukocyturia are most commonly present.[6, 79] (IIa, B)

There is good evidence that a short term antibiotic treatment of women with asymptomatic bacteriuria after short term catheterization significantly reduces the risk of symptomatic infection.[5, 98] (Ib) The WG recommends screening for bacteriuria in these patients (A).

Guidelines for preparation of patients for large joint surgery (hips and knee) include urine analysis and recommend treatment of asymptomatic bacteriuria in these patients. [99, 100] (IV, C). A prospective study has shown that preoperative presence of bacteria in urine rarely causes wound or joint infection after hip surgery [101] (IIa), and that the finding of asymptomatic bacteriuria is not an indication for postponing the surgery (B).

4.5 Recurrent UTI

It is estimated that 20-30% of women who have UTI will have a recurrent UTI.[102] Predisposition for recurrent UTI can partially be attributed to genetics, and partially depends on behavioral risk factors. The occurrence of UTI in age younger than 15 years, history of UTI in mother, spermicide use and frequency of sexual intercourse are risk factors associated with recurrent UTI.[5, 103]

Episodes of recurrent UTI should be treated the same way as sporadic episodes of cystitis or pyelonephritis. However, microbiological results from the previous episodes should be taken into account and urine should be sent for culture before starting therapy.

For asymptomatic reinfecton, the same therapeutic approach is valid as for asymptomatic bacteriuria, and in the majority of women it should not be treated.[23, 103]

In some women acute exacerbations of UTI are so frequent that they disturb their normal everyday life, and in such cases UTI prophylaxis is tried.[104, 105, 106]

Long term prophylactic antimicrobials taken daily or postcoital proved to be effective in reducing clinical recurrences as compared with placebo.[107] However, the risks of side effects (oral or vagnal candidiasis, gastrointestinal symptoms) should be taken in consideration. Also the risk of selecting resistant organisms is considerable.[103] Prophylaxis does not appear to modify the natural history of a recurrent UTI and as soon as the prophylaxis is discontinued most women are susceptible to reinfections again. In patients with lower recurrence rates, who are cooperative, patient initiated treatment is a prefered option.[108] In such cases care should be taken that patients are well educated to recognize the symptoms of a true UTI.
Long-term antibiotic prophylaxis in patients with indwelling catheters is not recommended since it can lead to an infection with resistant pathogens.[81, 82, 83] (Ib, A)
Antimicrobial prophylaxis may be considered in patients where frequency and severity of symptomatic episodes is such that it seriously impairs the patient's quality of life.[6]

Prolonged therapy with low doses of antibiotics is very likely to select resistant bacteria and in that respect alternative ways of prophylaxis should be encouraged.

Cranberry products vary greatly in strenght but there is good evidence to support effectivness of these products in prophylaxis of recurrent UTI.[6, 109, 110, 111] (Ia, A)

Oestrogen plays an important role in maintaining normal vaginal flora and prevents atrophic changes in the vaginal epithelium. In some studies oestrogens were shown to reduce the rate of recurrences in post-menopausal women.[5, 34, 112] (Ib) However, one meta-analysis study on the safety and efficacy of vaginal oestrogen preparations showed conflicting results in reducing UTI symptoms.[113] The safety of long term oestrogens use still needs to be tested. The WG does not recommend the use of oestrogen routinely in every postmenopausal women with recurrent UTI, but some patients may benefit from it.

The administration of intravaginal *Lactobacillus* vaginal suppositories aims to regenerate normal vaginal flora in order to reduce the colonization of this area with other bacteria. The effectiveneness of these preparations is still under research.[114, 115, 116]

5.0 Key points on interpretaton of microbiological findings and treatment of UTI

- **The presence of bacteria in urine does not automatically imply a disease**

Urine is normally sterile, however a distal part of the uretra is colonized with saprophitic flora of the surrounding region and even carefully collected mid stream urine sample can be contaminated with microorganisms. Since these same microorganisms can be possible causative pathogens of urinary tract infections it is sometimes difficult to differentiate a true bacteriuria from contamination of urine with saprophitic flora of the distal uretra. Kass has showed in 1957 that a finding greater than 10^5 cfu/ml bacteria in voided urine correlaties well with the finding of bacteria in urine obtained after bladder catheterization, while a smaller number of bacteria in voided urine most frequently indicates a contamination.[117] This is when the term „significant bacteriuria" has originated and it signifies a finding of $\geq 10^5$ cfu/ml urine, and with the presence of symptoms indicates a urinary tract infection.

Today, the accepted criteria for „significant bacteriuria" have been administratively set taking into consideration that in some categories of UTI sometimes a smaller number of bacteria combined with specific clinical symptoms can be a significant finding. However, we should keep in mind that a smaller number of bacteria even in these categories, presents a contamination in the majority of cases. Since microbiology laboratory has no complete clinical data on the patient`s condition, findings are issued for a small number of bacteria ($\geq 10^3$ cfu/mLl). However, such policy leads to issuing a large number of false positive findings that often cause unnecessary prescriptions of antibiotics.

Uropathogen bacteria primarily refer to *E. coli,* and in younger women *S. saprophyticus* as well, while for other bacterial species (other enterobacteria, enterococci), more firm criteria should be sought (larger number of bacteria) in order to relate it to clinical symptoms.[118]

In 95% of cases the infection is caused by one bacterial species, while a larger number of bacterial species in urine finding usually presents a contamination.

- **Correct sampling of the midsteam urine**

First morning sample or urine sample after four hours of nonurination should be collected. Before sampling, local cleansing of the genitals should be done with sterile isotonic saline (disinfectants should not be used).

- **Urine should be analyzed within two hours from collection**

False positive urine cultures can be obtained if urine is not analyzed immediatelly after collection because a small number of contaminating bacteria quickly multiplies to significant concentrations. Therefore, urine should be immediatelly cultured, if not then urine sample should be stored at $+4^0$ C up to 24 hours.

- **The diagnosis of UTI is primarily based on symptoms and signs**

The diagnosis of UTI is primarily based on the clinical presentation of the disease and microbiological finding is not so important for making the diagnosis as much as it is important for pathogen identification and its sensitivity to antibiotics when clinical signs indicate an infection. The main value of urine culture is to identify bacteria and their sensitivity to antibiotics.[6]
The symptoms of frequent and painful urination do not need to be related to urinary tract infection, but can be a reflection of urethritis or vaginitis with simultaneous bacterial contamination of the urine.

Routine urine culture after administered therapy is not recommended in asymptomatic patients except in pregnant women.[41]

- **Asymptomatic bacteriuria most frequently does not require antimicrobial treatment**

Bacteriuria is common in elderly and people with long term indwelling urinary catheters.[5, 6]

Asymptomatic bacteriuria should be treated with antibiotics only where there is a convincing evidence that eradication of bacteriuria results in meaningful health gain at acceptable risk. In elderly patients, asymptomatic bacteriuria is common and there is evidence that treatment is more harmful than benefical. In contrast, during pregnancy there is evidence that treatment of bacteriuria does more good than harm.

Asymptomatic bacteriuria should not be declared upon finding of any number of bacteria in urine or in only one urine sample in women (critera for diagnosis and therapy of asymptomatic bacteriuria are described in Table 4).

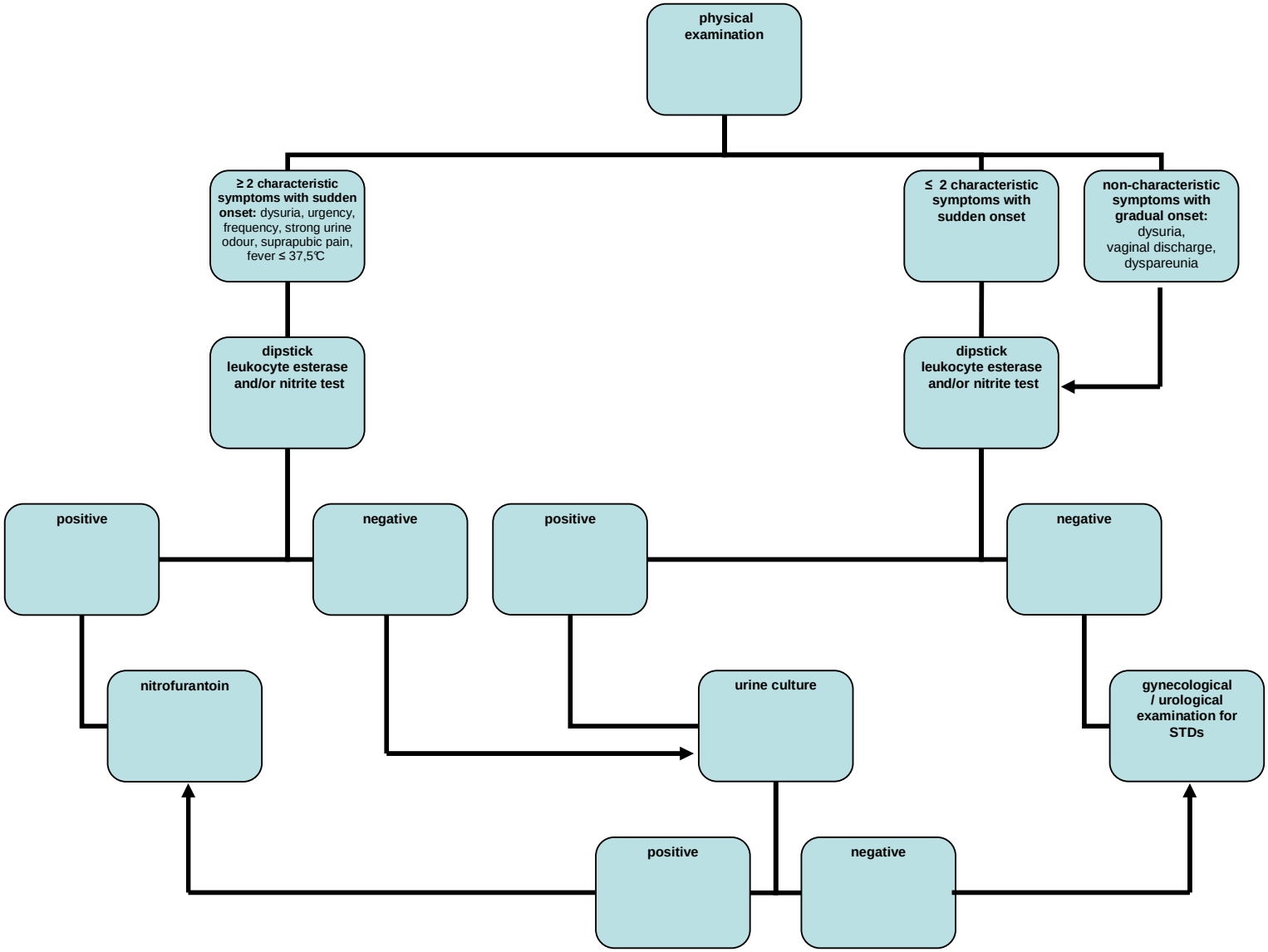
Leukocyturia accompaning asymptomatic bacteriuria is not an indication for antimicrobial treatment.[4, 15]

6.0 Conclusions from the literature

Level of recommendation	Statement (reference/ level of evidence)
Level IV	There is no need for urine culture in young women with sporadic uncomplicated cystitis as the causative agent is highly predictable.[2, 3, 5, 6, 23]
Level IV	Nitrofurantoin is first choice therapy for acute uncomplicated lower urinary tract infections (cystitis) in pre-menopausal, non pregnant women since *E.coli* is still highly susceptible to this agent.[2, 3, 13]
Level II	Nitrofurantoin should be used for 7 days as there is no good evidence that shorter therapy is as effective.[4, 46]
Level IV	The UTI WG has decided to choose co-amoxiclav as the first choice therapy for the treatment of acute uncomplicated pyelonephritis due to its low resistance rate in *E.coli* (4% resistant and 4% intermediately sensitive in Croatia in 2005),[13] relative narrow spectrum and nontoxicity.
Level IV	Empirical therapy should be modified according to the antibiogram as soon as the urine culture results are available.[2, 3, 26, 62]
Level IV	Depending on the severity of disease, parenteral therapy should be initiated and in some cases co-amoxiclav could be combined with gentamycin for synergistic effect and broader spectrum of the combination.[66, 70, 72]
Level I	In males, therapy with ciprofloxacin or TMP/SMX should last at least 2 weeks, and in case of expressed prostatitis symptoms for 4 weeks.[73, 74]
Level IV	Only symptomatic episodes of complicated UTI should be treated with antibiotics.[5, 75]
Level II	In patients with an indwelling catheter, urine culture is not recommended as a routine test, since bacteriuria and leukocyturia are most commonly present.[6, 79]
Level I	Antibiotic prophylaxis in patients with indwelling catheters is not recommended.[81, 82, 83]
Level II	Elevated temperature is a nonspecific sign of UTI, however when other possible causes are lacking, and in combination with suprapubic or lumbal pain and general severity of the clinical picture, worsened mental state, it can be the reason for initiation of antimicrobial treatment of presupposed UTI.[6, 85, 86]
Level I	Beta-lactam antibiotics (7 days for cystitis, 14 days for pyelonephritis) are effective for UTI and safe for use in pregnancy.[89, 90]

Level I	Asymptomatic bacteriuria should not be treated with antibiotics, except in specific patients group (see table 4.1) [78, 79]
Level I	The only patients who are at higher risk for developing a symptomatic infection with serious outcome are pregnant women and patients undergoing invasive urological interventions.[33, 75, 94]
Level I	Pregnant women should be screened for asymptomatic bacteriuria (≥ 10^5 cfu/mL in two consecutive MSU cultures, ≥ 24 hours apart) in the first trimester of pregnancy and if known to have a UTI or asymptomatic bacteriuria on every visit to the doctor thereafter.[75, 87, 88]
Level I	Asymptomatic bacteriuria in elderly is quite common and should not be treated.[5, 80, 82]
Level II	In some women acute exacerbations of UTI are so frequent that they disturb their normal everyday life, and in such cases UTI prophylaxis is tried. [104, 105, 106]
Level I	Cranberry products vary greatly in strenght but there is good evidence to support effectivness of these products in prophylaxis of recurrent UTI.[6, 109, 110, 111]
Level I	The WG does not recommend the use of oestrogen routinely in every postmenopausal women with recurrent UTI, but some patients may benefit from it.[5, 34, 112, 113]
Level IV	The administration of intravaginal *Lactobacillus* vaginal suppositories aims to regenerate normal vaginal flora in order to reduce the colonization of this area with other bacteria. The effectiveneness of these preparations is still under research. [114, 115, 116]

7.0. Appendix 1. Diagnosis and treatment of uncomplicated UTI in non-pregnant women



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9.0 Conflicts of interest

There were no conflicts of interest.

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