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ARTICLE FOR PRACTITIONERS / РАД ЗА ПРАКСУ

# National clinical practise guidelines – prevention and treatment of uncomplicated urinary tract infections

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**SUMMARY**
Uncomplicated urinary tract infections occur in persons with morphologically and functionally normal lower and upper urinary tract, normal kidney function, and a competent immune system. They are one of the leading reasons of antibiotics misuse. There is much controversy regarding the screening, diagnosis, and treatment of urinary tract infection. This article summarizes the most common urinary tract infections and those that cause the most doubts in daily clinical practice. The goal is to stimulate physicians in using the latest recommendations of the national guidelines that may help them in daily clinical practice.
**Keywords:** uncomplicated urinary tract infection; recommendations; national guidelines

## INTRODUCTION

Urinary tract infections (UTIs) are one of the leading cause of antibiotics use worldwide. On the annual level, UTIs are found in more than 150 million people globally, which ranks them among the most common infectious diseases [1]. The true incidence of UTIs in Serbia is not easily determined because they are not subject to mandatory reporting.

Uncomplicated UTIs are defined as UTIs occurring in persons with morphologically and functionally normal lower and upper urinary tract, normal kidney function, and a competent immune system. There is much controversy regarding the screening, diagnosis, and treatment of these infections. The new national guidelines have given recommendations for uncomplicated UTIs [2]. This overview summarizes the most common topics that cause the most doubts for treatment in clinical practice. The goal is to stimulate physicians in using the guidelines in appropriate medical situations so that the practice of all doctors in our country could be uniform.

## ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria (AB) is a significant concern in current guidelines due to its link to unnecessary antibiotic use. AB is defined as the presence of one or more bacterial species in urine taken properly ($\geq 10^5$ colony-forming units per ml) regardless of the presence of pyuria and without symptoms of urinary infection [3]. In some cases, especially among the elderly, AB can be mistaken for a UTI when patients show general deterioration (e.g., mental state changes, lethargy, loss of appetite). However, these symptoms might be caused by factors other than a UTI. Therefore, it is crucial to explore other potential causes before attributing such conditions to UTI and initiating antibiotic treatment [3].

Screening for AB is not recommended except for pregnant women (when it is treated and controlled) and before urological interventions that are accompanied by bleeding (such as transurethral resection of the prostate). A single dose of antibiotics is given before the intervention, and the drug is possibly used for a short time or while a temporary urinary catheter is in place. Screening and treatment of AB before spinal surgery is recommended for patients with a urinary catheter, neurogenic bladder or urinary incontinence in order to reduce the risk of Gram-negative infection at the surgical site.

## ACUTE UNCOMPLICATED CYSTITIS

Acute uncomplicated cystitis refers to sudden inflammation of the bladder without underlying health issues or urinary tract abnormalities. Around half of women experience it at least once in their lives, and a third have it by the age of 24. Diagnosis is often based on symptoms like pain during urination and urgency without vaginal discharge or pain [4]. In typical cases, urine analysis might not be necessary [4]. However, in older women, symptoms might not always signify cystitis, requiring laboratory confirmation [5]. The presence of leukocytes in urine is not specific for UTI, but detecting nitrites is highly indicative of bacterial presence. However, some bacteria types (*Staphylococcus*, *Enterococcus*, *Pseudomonas*)

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do not convert nitrates to nitrites, and the absence of nitrites does not rule out infection (e.g., due to diluted urine or certain bacteria types).

Urine culture is indicated when the diagnosis of acute uncomplicated cystitis is not clear, in case of persistence of symptoms, early return of infection, suspected resistant infection or when therapeutic options are limited due to multiple allergies.

The first-choice drugs for uncomplicated cystitis treatment are fosfomycin trometamol in a single dose of 3 g, nitrofurantoin 100 mg twice a day for five to seven days, and pivmecillinam 400 mg three times a day for three to five days [6]. Trimethoprim + sulfamethoxazole, the most commonly used drug for this indication, can only be used empirically if the local *E. coli* resistance rate is less than 20% [7]. Fluoroquinolones are extremely effective in three-day regimens, but they should be considered as alternative antibacterial drugs because of side effects.

## RECURRENT URINARY TRACT INFECTIONS

Recurrent UTIs (rUTI) are common in women across various demographics. Around 60% of women experience an acute bladder infection in their lifetime, 20–40% of them might have recurrent episodes, and almost half experiencing multiple recurrences [8]. A diagnosis of rUTI typically requires two infections in the past six months or three within the previous year [8].

To identify the underlying causes of rUTI, medical examinations are crucial including pelvic, gynecological, and urological evaluations. These examinations may detect anatomical or functional issues like stones, diverticula, or nerve-related bladder problems. Bowel issues, prior antibiotic use, *Clostridium difficile* infection, antibiotic resistance, allergies, menopausal status, contraceptive use, sexual activity, and genital tract symptoms should be taken into consideration. Additionally, conditions like bladder or vaginal prolapse, rectal issues, cysts, and infections in genital areas need consideration. Examining pelvic floor muscles, especially in elderly and women who have given birth multiple times, is essential [9]. Neurological conditions (brain and spinal cord damage, diabetes and vegetative polyneuropathy) and ongoing therapies affecting urine flow should also be taken into account. Treating the primary issue often resolves the recurring infections.

Positive urine culture is necessary for diagnosing rUTI. Routine cystoscopy and upper urinary tract imaging are not routinely advised but might be considered in case of poor response to therapy or if infections return rapidly with the same microorganism. It is recommended to wait for urine culture results before starting treatment [10]. Antibiotic selection relies on prior culture results, favoring first line therapy like nitrofurantoin, trimethoprim-sulfamethoxazole, or fosfomycin for shorter courses, typically lasting up to seven days. Prophylactic antibiotics might be considered after discussing the risks and benefits either on the daily basis or during the risk conditions (sexual intercourse, travel, all-day work, diarrhea, or constipation). The duration of prophylaxis varies from three to 12 months with periodic patient monitoring. Immunoprophylaxis with polyvalent vaccines [Uro-Vaxom® (OM-89, OM Pharma, Meyrin, Switzerland)] or autovaccines can be advised. Peri- and postmenopausal women, without contraindications, may consider using vaginal estrogen [11, 12]. Post-treatment, urine analysis is needed only for those with persistent symptoms.

## ACUTE UNCOMPLICATED PYELONEPHRITIS

Acute uncomplicated pyelonephritis is an inflammation of the renal pelvis, calyces, and tubules, typically caused by bacteria and presenting with fever and signs of systemic infection [13]. Urine analysis is crucial for diagnosis, which reveals blood, leukocytes, and nitrites via a test strip. Microscopic urine analysis shows high leukocyte counts, leukocyte cylinders, and bacteria. In *E. Coli* infections, erythrocytes might be present. Initial Gram staining may help in selecting the most suitable therapy. Urine culture confirms the infection and identifies the causative agent and its sensitivity [14]. Blood tests often show increased leukocytes, neutrophils, sometimes anemia, rarely low platelets. Inflammation is indicated by increased values of C-reactive protein, D-dimer and accelerated sedimentation. Electrolyte imbalances, kidney failure, and elevated procalcitonin levels are indicators of systemic infection or even sepsis [15].

Acute uncomplicated pyelonephritis treatment can be on outpatient or in hospital basis depending on the severity of the disease. Outpatient treatment begins after urine sampling with empirical antibiotics like fluoroquinolones or third-generation cephalosporin. Mild form of the disease may start with a single dose of intravenous antibiotics initially [16].

Moderate form of the disease can be treated on an outpatient basis if the patient can consume liquids, food, and medications orally or if home-based intravenous therapy is feasible. Otherwise, hospitalization is recommended. Severe, septic form of pyelonephritis requires hospital treatment with carbenicillin or ureidopenicillin with/without aminoglycosides (adjusted to kidney function) along with supportive measures [16].

## URINARY TRACT INFECTIONS DURING PREGNANCY

UTIs often occur during pregnancy and present a risk factor for maternal and fetal morbidity [17]. Pregnancy increases the risk of UTI due to changes in the function of the endocrine and immune systems, but also due to the mechanical compression of the ureters and bladder by the enlarged uterus.

Screening for AB by urine culture is recommended for all pregnant women during the first trimester of pregnancy with the aim of reducing the risk of pyelonephritis, premature birth, and low birth weight [18]. In pregnant women with AB, empirical use of antibiotics and one-day

use of antibiotics is not recommended (exception is fosfomycin-trometamol in single dose of 3 g). Women with proven group B streptococcal bacteriuria should be treated with appropriate intravenous antibiotics, aiming to prevent diseases in newborns, and the drugs of choice are penicillin, Cephalexin (Hemofarm AD, Vršac, Serbia) and Clindamycin (CHEPHASAAR chem. - pharm. Fabrik GmbH, St. Ingbert, Germany) [19]. Urine culture control is advised until delivery.

Cystitis in pregnant women requires empiric therapy (after urine is taken for analysis) with cefpodoxime, amoxicillin-clavulanate, and fosfomycin for three to seven days, unless fosfomycin is used. Urine culture is advised one week after the end of therapy [20]. Antimicrobial prophylaxis is advised if pregnant women have three or more episodes of cystitis during pregnancy.

Most episodes of acute pyelonephritis (AP) occur during the second and third trimester of pregnancy, and are accompanied by numerous complications. For pregnant women who have fever and/or pain in the loins or back, some other obstetric complications should be considered such as: intra-amniotic infection, placental abruption, nephrolithiasis and acute abdomen [20]. Radiological diagnostics of the kidneys and urinary tract may be justified when AP recurs or responds slowly to treatment [20]. Treatment of AP is carried out in hospital setting for the first 48 hours, where empiric antibiotic therapy with parenteral beta-lactam antibiotics is started. Fluoroquinolones and aminoglycosides should be avoided. If bacterial resistance to the empirical antibiotic is found, a change of antibiotic is necessary regardless of whether the symptoms of the infection improve or not. The duration of AP treatment is 10–14 days, and antibiotic prophylaxis is recommended for women who have had at least two episodes of AP during pregnancy.

## URINARY TRACT INFECTIONS IN ELDERLY PEOPLE

UTIs are responsible for about 15.5% of hospitalizations due to infectious diseases in persons ≥ 65 years of age and are the cause of death in about 6% [21]. Elderly individuals face increased infection risks due to hormonal changes, prostate hypertrophy, reduced mobility, incontinence, and urinary catheter use. Obtaining urine samples from the elderly is challenging, often requiring single-time catheterization for women and clean condom catheters for men. Diagnosing UTIs in the elderly is challenging due to atypical symptoms. Urine characteristics (color, odor, turbidity) may not always indicate infection but could relate to dehydration or incontinence. Laboratory tests are crucial for diagnosis and treatment, especially considering high microorganism resistance [22].

Screening and treatment of AB is not recommended. Diagnosis of UTI in this group relies on the recognition of atypical symptoms, especially in nursing homes. Initiation of therapy is based on acute symptoms like dysuria, high fever, confusion, or worsening of genitourinary symptoms. Parenteral therapy is necessary for unstable patients, impaired oral absorption, or resistant infections. If aminoglycosides are indicated for more than a week, monitoring of drug levels and kidney function is necessary.

Long-term antimicrobial prophylaxis lasting 6–12 months can prevent repeated infections. The first line is nitrofurantoin 50 or 100 mg per day or trimethoprim-sulfamethoxazole half a tablet per day or every other day. Proper hydration is essential.

In elderly with a urinary catheter, AB is common and does not require screening or treatment. Symptoms of infection might differ, typically showing high fever, malaise, confusion, back pain, and sometimes catheter blockage or blood in urine. When infection is suspected, a urine sample should be taken after catheter replacement if it lasts for over two weeks. Treatment starts after catheter replacement and usually lasts seven days, occasionally 10–14 days if the response to therapy is delayed. Systemic antibiotic prophylaxis is advised only if catheter insertion, replacement or removal is accompanied by hematuria [23].

This article was written in accordance with the ethical standards of the institutions and the journal.

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## Националне смернице клиничке праксе – превенција и лечење некомпликованих инфекција мокраћних путева

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**САЖЕТАК**

Некомпликоване инфекције мокраћних путева се односе на особе са морфолошки и функционално нормалним уринарним трактом и очуваним имунским системом. Оне су и најчешћи разлог злоупотребе антибиотика. Постоји више контроверзи о скринингу, дијагностиковању и лечењу некомпликованих инфекција мокраћних путева. У овом чланку сажете су препоруке о дијагностиковању и лечењу најчешћих инфекција мокраћних путева које су и најчешћи узрок дилема у клиничкој пракси. Циљ је да се лекари подстакну да користе препоруке најновијег водича у свакодневном клиничком раду.

**Кључне речи**: некомпликоване инфекције мокраћних путева; препоруке; национални водич