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Analysis of the Significance of Infection in Diseases of the Urinary System

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Abstract: One of the most common infections in clinical practice is urinary tract infections (UTIs). Limiting unnecessary antibiotic use and improving clinical care for many patients will result from accurate diagnosis and evidence-based treatment of UTIs. Crops and urine tests are useful for the diagnosis of UTIs; however, it is necessary to keep in mind their disadvantages. Due to the fact that most non-pregnant patients with asymptomatic bacteriuria do not require antibiotics and may even be harmful when prescribed, it is extremely important to distinguish true UTI from asymptomatic bacteriuria. The scope of UTI syndromes, such as acute uncomplicated cystitis, pyelonephritis, prostatitis and catheter-associated UTIs, determines the choice of antibiotics and the duration of their administration. Treatment methods also depend on the patient's immunosuppression and the characteristics of their genitourinary system. Therefore, patients with urological obstruction or patients receiving kidney transplantation may need a specialized management approach that includes working with various disciplines. Some preventive measures can be used for people prone to frequent UTIs, but there is often no universal method. Thus, urinary tract infection is very common among urology doctors. The frequency of this pathology does not decrease, despite the existing methods of diagnosis and treatment. There are conflicting opinions about the etiology and pathogenesis of the disease, early signs of diagnosis and risk factors.

Keywords: Bacteriuria, urosepsis, cystitis, urethritis, leukocyturia, urinalysis.

Relevance. It is known that viral diseases are nosologies with intensive spread, which manifest themselves suddenly and make you think about the specifics of any other diseases with their various symptoms. An example is pandemics, which in recent years have caused worldwide not only medical, but also extremely serious social and economic problems. It should be noted here

that pathologies caused by upper respiratory tract infections have always created difficulties and problems for clinicians due to their complexity [1, 2, 3]. However, the addition of infection at a time when the pathological process occurs in other organs also leads to insufficient medical problems. Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, affecting 150 million people annually. These infections, which can occur in the urethra, bladder or kidneys, are one of the most common infectious diseases in the world, with significant morbidity and high medical costs. Numerous constitutive and induced antimicrobial peptides and proteins are expressed in the urinary tract. Most UTIs are usually treated empirically, although the clinical symptoms of the disease are diverse and range from uncomplicated to complicated. The main causative agents of these infections are bacteria, but in rarer cases other microorganisms, such as fungi and some viruses, are responsible for UTIs [4, 5, 6]. More than 90% of acquired diseases of the excretory organs are associated with urinary tract infections (UTIs), which occur in all age groups. It should be noted that pathologies of the urinary system in adolescents develop much faster than in young children and adults. Morphological abnormalities and metabolic disorders that cause inflammation, and factors that lead to recurrence and chronization of the process, are closely related to each other and create a vicious circle. Metabolic disorders do not disappear with age or with remission of IC, that is, with the disappearance of laboratory signs and clinical manifestations of the syndrome, such as bacteriuria and leukocyturia. These problems begin during intrauterine development and in the early postnatal period [7, 8, 9, 10]. The researchers note that there is an increase in mutations in the genomes of bacteria that cause infectious diseases, which leads to the creation of increasingly aggressive types of pathogens. In addition, the search for resistant strains puts the reasonable use of antibacterial drugs and the search for alternative treatments in the first place. The rate of development of antibiotic resistance is significantly lagging behind the rate of production of new antibacterial and antimicrobial drugs. In modern clinical practice, rational and adequate prescription of drugs is a difficult task, and specialists are required to comply with the basic principles and recommendations of UTI diagnosis, as well as strict adherence to accepted treatment algorithms. Together, all this will reduce the resistance of uropathogens [11, 12, 13, 14, 15].

Epidemiology of urinary tract infection. UTIs occur between the ages of 20 and 50 years and are observed at least once in a lifetime in more than half of all women and under the age of 24, more than 30% of women have an episode of this disease. These infections also quite often affect elderly patients and it is noteworthy that they often do not cause clinical symptoms. UTIs are the second most common type of infection among the elderly population, accounting for almost 25% of all infections among the elderly. 50% of older women suffer from asymptomatic bacteriuria and in many cases one of the factors is bladder catheterization. 38% of patients require permanent catheterization of the bladder, which is the reason for an increase in the frequency of UTIs in the elderly. The child population also suffers from UTIs and bacteriuria is present in 2.7% of boys and 0.7% of girls. A study conducted showed that 35% of boys and 32% of girls who had their first episode of UTI before the age of 1 became ill with recurrent UTIs over the next 3 years. Other risk factors in children are hospitalization and catheterization. In children aged 1 to 5 years, the frequency of bacteriuria increases by 4,5% [15, 16, 17, 18].

Functions of the urinary tract. There are two subtypes of the urinary tract: the lower and upper urinary tracts. The lower urinary tract is of special concern due to its propensity for various inflammatory diseases. The main purposes of the urinary system are to filter blood and expel waste through urination. The literature that is currently available does not include thorough reviews of the most prevalent infections and inflammatory conditions that affect the lower urinary tract. An overview of these illnesses, as well as associated immunological and microbiological elements that are essential for the creation of novel treatment options, will be given in this review. We'll also talk about management challenges, new opportunities, and current medical standards. Urinary tract infections (UTIs), urosepsis, interstitial cystitis, and urethritis are among the conditions taken into consideration [11, 14, 15, 18].

The main causative agents of urinary tract infection. The main causes of urinary tract infections The most common causative agent of both the urinary tract and cuticle is uropathogenic *E. coli* (UPEC). It is followed by other pathogens such as *Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis* and *Staphylococcus spp.* In addition, the incidence of UTIs caused by multidrug resistance (MDR) is increasing. This leads to the spread of antibiotic resistance and increases the financial burden of these infections. Here we discuss various aspects of UTI, such as the mechanisms of pathogenicity of UTI-causing bacteria and the growth of resistance in UTI pathogens [4, 5]. Urinary tract infections (UTIs) are a serious public health problem and are caused by many pathogens, but the most common of them are *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis* and *Staphylococcus saprophyticus.* Recurrent infections and the increasing antimicrobial resistance of uropathogens threaten to significantly increase the financial burden of these infections. In this review, we discuss how basic scientific research clarifies the molecular details of crosstalk at the host-pathogen interface. We also discuss how these interactions affect the pathophysiology of UTIs. In addition, we are reviewing ongoing efforts to integrate this knowledge into new clinical approaches to the treatment of UTIs [17, 18, 19]. In addition, it was found that *Staphylococcus saprophyticus* is seeded in the urine mainly in young women, and *Staphylococcus epidermidis* is seeded in patients with prolonged catheterization of the bladder. The presence of *Staphylococcus aureus* in the urine of most patients with UTIs is caused by a single pathogen, but with prolonged catheterization of the bladder, this may be the result of a staphylococcal infection [20, 21].

Microbiological and laboratory diagnostics of urinary tract infection. Detection of bacteriuria by microscopy. Bacteriuria can be detected microscopically by staining gram-by-gram non-centered urine samples, gram-by-gram centrifuged samples, or by directly observing bacteria in urine samples. To do this, a microscope slide is applied to a certain volume of urine, allowed to dry in the air, and then stained by gram and microscoped. Leukocyturia and the urothelial response to bacterial invasion are an important diagnostic sign of UTI. In the absence of bacteriuria, leukocyturia should be examined for the presence of chlamydia, candidiasis or mycobacterium tuberculosis. Bacteriuria without leukocyturia indicates colonization of the urinary tract, but this does not mean invasion of the urothelium. The gold standard for the diagnosis of UTI is a cultural, microbiological examination of urine with the isolation of the pathogen and an assessment of the level of bacteriuria. A sign of a diagnosis of UTI is the presence of at least 105 colony—forming units of bacteria in a milliliter of fresh urine. However, the detection of bacteriuria, which is diagnostically significant, does not allow us to determine the degree of infection of the urinary system. When problems arise with making a topical diagnosis, they often lead to overdiagnosis, which affects the subsequent treatment of the disease. According to foreign data, lower urinary tract infections make up a large part of the UTI structure. Ultrasound of the urinary system and excretory urography are additional diagnostic methods [22, 23, 24].

The main factors of virulence of uropathogens. The ability of various uropathogens to adhere and colonize the epithelium of the lower urinary tract depends on how well they express certain virulence factors. The most common pathogen of both the urinary tract and cuticle is uropathogenic *E. coli*. Gram-negative and gram-positive bacteria found in the colon, such as *Escherichia coli, Enterococcus faecalis, Proteus mirabilis* and *Klebsiella pneumoniae*, are the cause of most UTIs. *Staphylococcus saprophyticus, group B streptococcus* and *Pseudomonas aeruginosa* are other pathogens. Many adhesion proteins are present on the cell surface of uropathogens. These proteins play an important role in the beginning of the interaction between the host and the pathogen. In addition, adhesives have recently been found to help bacteria attach to host tissues and infect them into the urinary tract. The most well-known adhesion factor is the villi of uropathogenic bacteria, which can be gram-negative or gram-positive bacteria. Gram-negative and gram-positive bacteria require two separate pili assembly pathways: the chaperone/usher pathway and the pili assembly pathway using sortase. These uropathogens use

various types of adhesives to promote the formation and binding of biofilms on both biotic and abiotic surfaces. In this context, it is important to note that most UTIs are biofilm-related infections in which uropathogens colonize both the mucous membrane of the urinary tract and stationary devices such as urinary catheters [25, 26, 27].

Special measures of treatment and prophylaxis. At the first signs of UTI, antibacterial therapy should be started. Treatment started after four days does not prevent the appearance of scarring in the kidney. Nevertheless, the task of choosing an adequate therapy is becoming more and more difficult. Bacteria that do not respond to antibiotics are a global problem. In most countries, the sensitivity of gram-negative flora to ampicillin and cotrimoxazole has decreased. American pediatricians report that even in combination with clavulanate, there is a low sensitivity to ampicillin. In addition, the maximum activity to the latest generation of cephalosporins remains (ceftriaxone and cefazolin, respectively, reach 97% and 90%, respectively). Although nitrofuran derivatives have high activity (up to 95%), they cannot penetrate the renal parenchyma. Fluoroquinolones act very well on Gram-positive and Gram-negative bacteria, and moxifloxacin, a 4th generation drug, also kills Mycobacterium tuberculosis. However, admission to this group is allowed only to persons over the age of 18. Indian microbiologists claim that most strains are resistant to four or more antibiotics. Targeted selection of antibiotics requires constant monitoring of the sensitivity of strains circulating in this area. The question of whether probiotics affect the risk of developing or relapsing IC remains open, despite the generally recognized fact that the intestinal flora serves as the main reservoir of pathogenic bacteria for the urinary system. E.M. Schoenberg et al., in particular, deny the usefulness of probiotics for both primary and secondary prevention of UTI [28, 29, 30, 31].

Improvement of urodynamics is necessary for successful treatment of IC. The primary task in any type of neurogenic bladder dysfunction is to eliminate detrusor hypoxia and eliminate hypovitaminosis B2 and B6, which are usually associated with bladder pathology. Since the age of 5, oxybutynin hydrochloride ("Driptan") has been used to treat hyperreflective dysfunction, and propiverine ("Mictonorm") is allowed for children with a body weight of more than 35 kg (10-12 years old). Hyporeflective dysfunction is much more difficult to treat. This variant is usually accompanied by severe neurological pathology, is often accompanied by encopresis and requires the supervision of a neurologist. Therapeutic effects are aimed at increasing the sensitivity, tone and contractile activity of the MP. Distigmine bromide, also known as "ubretide", which is part of the group of M-cholinomimetics, has a number of side effects that limit its use. The only plant recognized by evidence—based medicine for the treatment of IC is cranberry (Vaccinium macracarpon Aiton). Proanthocyanidins are a group of substances that have recently been obtained from cranberries. They fight strains of uropathogenic bacteria, which are both sensitive and resistant to antibiotics, and have anti-adhesive properties [32, 33, 34].

Discussion. In clinical microbiology laboratories, urinary tract infections (UTIs) are among the most common bacterial infections. Although the spread of pathogens that cause UTIs is changing, the most common cause of infection remains intestinal bacteria, in particular E. coli. Increased resistance to certain antimicrobial drugs, especially trimethoprim-sulfamethoxazole, which is observed in E. coli, is of greater importance. Doctors use a small number of tests to distinguish UTIs from other diseases with similar clinical manifestations. None of these tests have sufficient sensitivity and specificity for individual use. Urine analysis is useful mainly to exclude bacteriuria from diagnostic tests. For the examination of outpatient patients with uncomplicated UTIs, urine culture may not be necessary; however, for outpatient patients with recurrent UTIs, unsuccessful treatment or complicated UTIs, as well as inpatient patients with UTIs. Men and women can have urinary tract infections at any age, but due to the anatomy of women, infections are more common in women than in men. UTI is diagnosed in most patients who go to outpatient clinics complaining of dysuria, although some patients with UTI symptoms may instead have an overactive bladder or interstitial cystitis. Diagnosis is not always an easy task. Intermediate urine culture has been considered the gold standard for the diagnosis of UTIs

for many decades. However, about a third of the cases do not receive a positive culture, which makes it increasingly clear that the bacteria may be in a healthy bladder. Because infections negatively affect people's mental health and well-being, the impact of UTIs on individuals is significant. The problem of UTI in urology has always been extremely relevant and is still in the focus of attention of specialists all over the world. Currently, adequate and reasonable use of antibacterial drugs is especially important for the treatment of urological patients and improving the quality of life, as well as for the health of the general population, given the increasingly increasing resistance to antibacterial drugs. But at the moment this is a difficult task in modern clinical practice, and specialists are required to comply with the basic principles and recommendations in the diagnosis of UTI, as well as strict adherence to accepted treatment algorithms. Together, all this will reduce the resistance of uropathogens [14, 24, 26, 35, 36, 37, 38].

Conclusions. Thus, urinary tract infection is a very common problem in urological practice. The frequency of this pathology does not decrease, despite the existing methods of diagnosis and treatment. There are conflicting opinions about the etiology and pathogenesis of the disease, early signs of diagnosis and risk factors.

Despite the large number of studies on UTI in children and adolescents, the results of treatment and follow-up are unsatisfactory. It is necessary to develop pathogenetically determined dispensary monitoring schemes that take into account the premorbid condition of the patient, his "metabolic portrait" and age. It is necessary to expand the list of laboratory parameters that can determine the degree of inflammation of the CUT. These actions will help slow the spread of CHKD in children, adolescents and adults.

References

1. Khateri S, Mohammadi H, Khateri R, Moradi Y. The Prevalence of Underlying Diseases and Comorbidities in COVID-19 Patients; an Updated Systematic Review and Meta-analysis. Arch Acad Emerg Med. 2020 Sep 12;8(1):e72.
2. Kaur H, Thakur JS, Paika R, Advani SM. Impact of Underlying Comorbidities on Mortality in SARS-COV-2 Infected Cancer Patients: A Systematic Review and Meta-Analysis. Asian Pac J Cancer Prev. 2021 May 1;22(5):1333-1349. doi: 10.31557/APJCP.2021.22.5.1333.
3. Nikolaeva S.V., Khlypovka Yu.N., Gorelov A.V. Effect of various treatment regimens on the course of viral respiratory infections in children. Russian Medical Inquiry. 2023;7(11):713–717 (in Russ.). DOI: 10.32364/2587-6821-2023-7-11-1.
4. Mancuso G, Midiri A, Gerace E, Marra M, Zummo S, Biondo C. Urinary Tract Infections: The Current Scenario and Future Prospects. Pathogens. 2023 Apr 20;12(4):623. doi: 10.3390/pathogens12040623.
5. McCann E., Sung A.H., Ye G., Vankeepuram L., Tabak Y.P. Contributing Factors to the Clinical and Economic Burden of Patients with Laboratory-Confirmed Carbapenem-Nonsusceptible Gram-Negative Urinary Tract Infections. Clin. Outcomes Res. CEOR. 2020;12:191–200. doi: 10.2147/CEOR.S234840.
6. Flores-Mireles A.L., Walker J.N., Caparon M., Hultgren S.J. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. Nat. Rev. Microbiol. 2015;13:269–284. doi: 10.1038/nrmicro3432.
7. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015 May;13(5):269-84. doi: 10.1038/nrmicro3432. Epub 2015 Apr 8.
8. Dickson K, Zhou J, Lehmann C. Lower Urinary Tract Inflammation and Infection: Key Microbiological and Immunological Aspects. Journal of Clinical Medicine. 2024; 13(2):315. https://doi.org/10.3390/jcm13020315

9. Kauffman CA. Diagnosis and management of fungal urinary tract infection. Infect Dis Clin North Am. 2014;28(1):61-74. https://doi.org/10.1016/j.idc.2013.09.004
10. Michael L. Wilson, Loretta Gaido, Laboratory Diagnosis of Urinary Tract Infections in Adult Patients, Clinical Infectious Diseases, Volume 38, Issue 8, 15 April 2004, Pages 1150–1158, https://doi.org/10.1086/383029
11. Hawra Al Lawati, MD, Barbra M. Blair, MD, and Jeffrey Larnard, MD. Urinary Tract Infections: Core Curriculum 2024. Core curriculum in nephrology| Volume 83, Issue 1, P90-100, 2023DOI:https://doi.org/10.1053/j.ajkd.2023.08.009
12. Kuprienko N.B., Smirnova N.N. Urinary tract infection in adolescents. modern approaches to diagnostics, treatment and dispensary observation. Nephrology (Saint-Petersburg). 2018;22(4):108-115. (In Russ.) https://doi.org/10.24884/1561-6274-2018-22-4-108-115
13. Santajit S., Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. BioMed Res Intern. 2016;2:1–8.
14. Hooton T.M. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366:1028–1037.
15. Rowe T.A., Juthani-Mehta M. Urinary tract infection in older adults. Aging health. 2013;9(5). DOI: 10.2217/ahe.13.38.
16. Wu Y.R., Rego L.L., Christie A.L. et al. Recurrent Urinary Tract Infections Due to Bacterial Persistence or Reinfection in Women-Does This Factor Impact Upper Tract Imaging Findings. J Urol. 2016;196:422–428.
17. Eidelshtein M.V., Sukhorukova M.V., Skleenova E. Yu. et al. Antibiotic resistance of nosocomial strains of Pseudomonas aeruginosa in Russian hospitals: results of the multicenter epidemiological study “Marathon” 2013–2014. Clinical Microbiology and Antimicrobial Chemotherapy. 2017;19(1):37–41.
18. Glover M., Moreira C.G., Sperandio V., Zimmern P. Recurrent urinary tract infections in healthy and nonpregnant women. Urol Sci. 2014;25:1–8.
19. Plekhanov A.N., Dambaev A.B. Urinary tract infections: epidemiology, etiology, pathogenesis, risk factors, diagnosis (review). Бюллетень ВСНЦ со РАМН, 2016, № 1 (107), с. 70-74.
20. Al Mohajer M, Musher DM, Minard CG (2013). Clinical significance of Staphylococcus aureus bacteriuria at a tertiary care hospital. Scand. J. Infect. Dis., 45 (9), 688-695.
21. CiesielczukH, Betts J, Phee L (2015). Comparative virulence of urinary bloodstream isolates of extra-intestinal pathogenic Escherichia coli in Galleria mellonella model. Virulence, 6 (2), 145-151.
22. Kovavisarach E, Vichaipruck M, Kanjarahareutai S (2009). Risk factors related to asymptomatic bacteriuria in pregnant women. J. Med. Assoc. Thai., 92 (5), 606-610.
23. Fahimazed A, Taherian M, Da Li Rani R (2010). Diaper type as a risk factor in urinary tract infection of children. Iran J. Pediatr., 20 (1), 97-100.
24. Haider G, Zehra N, Munir AA (2010). Risk factors of urinary tract infection in pregnancy. J. Pak. Med. Assoc., 60 (3), 213-216.
25. Flores-Mireles A.L., Walker J.N., Caparon M., Hultgren S.J. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. Nat. Rev. Microbiol. 2015;13:269–284. doi: 10.1038/nrmicro3432.
26. Govindarajan D.K., Kandaswamy K. Virulence factors of uropathogens and their role in host pathogen interactions. Cell Surf. 2022;8:100075. doi: 10.1016/j.tcsw.2022.100075.

27. Shrestha L.B., Baral R., Khanal B. Comparative study of antimicrobial resistance and biofilm formation among Gram-positive uropathogens isolated from community-acquired urinary tract infections and catheter-associated urinary tract infections. Infect. Drug Resist. 2019;12:957–963. doi: 10.2147/IDR.S200988.

28. Malcolm G Coulthard, Heather J Lambert, Susan J Vernon et al. Does prompt treatment of urinary tract infection in preschool children prevent renal scarring: mixed retrospective and prospective audits. Arc Dis Child 2014; 99: 342-347 https://doi.org/10.1136/archdischild-2013304428

29. Roberts KB. Urinary tract infection: clinical practice guidline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2014; 128: 595-610

30. Mary Anne Jackson, MD, FAAP, Gordon E. Schutze The Use of Systemic and Topical Fluoroquinolones. Pediatrics 2016;138(5):e20162706

31. Mohammed Akram, Mohammed Shahid, Asad U Khan. Etiology and antibiotic resistance patterns of community-acquired urinary tract infection in JNMC Hospital Aliga. J Annals of Clinical Microbiology and Antimicrobials 2007; 6:4. https://doi.org/10. 1186/1476-0711-6-4

32. Тэц ВВ. Микроорганизмы и антибиотики. КЛЕ-Т. СПб., 2009; 168 с. [Tech VV. Microorganisme i antibiotici. KLE-T. SPb., 2009; 168]

33. Smirnova NN, Kuprienko NB. Zabolevania organov mochevoj sistemi vrogdennogo I priobretennogo haractera na fone displasii soedinitelnoj tkani u detej I podrostrov. Izdatelstvo PSPbGMU, SPb., 2014, 40 s.

34. Jarmo Salo, Matti Uhari, Merja Helminen et al. Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial. Clinical Infectious Diseases 2012; 54(3):340-346.

35. Grigoryan L., Mulgirigama A., Powell M., Schmiemann G. The emotional impact of urinary tract infections in women: A qualitative analysis. BMC Women's Health. 2022;22:182. doi: 10.1186/s12905-022-01757-3.

36. Grundy L., Caldwell A., Brierley S.M. Mechanisms Underlying Overactive Bladder and Interstitial Cystitis/Painful Bladder Syndrome. Front. Neurosci. 2018;12:931. doi: 10.3389/fnins.2018.00931.

37. Andolfi C., Bloodworth J.C., Papachristos A., Sweis R.F. The Urinary Microbiome and Bladder Cancer: Susceptibility and Immune Responsiveness. Bladder Cancer. 2020;6:225–235. doi: 10.3233/BLC-200277.

38. Barlam T.F., Cosgrove S.E., Abbo L.M., MacDougall C., Schuetz A.N., Septimus E.J., Srinivasan A., Dellit T.H., Falck-Ytter Y.T., Fishman N.O., et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2016;62:e51–e77. doi: 10.1093/cid/ciw118.