

BACTERIAL CYSTITIS

¹Sarkisova Victoria Vladimirovna, ²Yusupova Dildora Uktamovna, ³Shernazarov Farrukh,
⁴Hasibur Rehman

^{1,2}Lecturer of Samarkand State Medical University

^{3,4}Student of Samarkand State Medical University

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Abstract. *Every year, the development of bacterial cystitis is the reason for seeking medical help for 7 million women around the world.*

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Such a high prevalence of pathology among the fair sex is not accidental and is associated with a number of risk factors, which include sexual intercourse, the presence of inflammatory diseases of the vulva and vagina, incompetence of the pelvic floor muscles, atrophic vaginitis caused by estrogen deficiency during menopause [6]. Gynecologists often encounter the presented reasons for the possible development of an inflammatory process in the bladder in their practice and must take measures aimed at preventing the development of bacterial cystitis. Despite the apparent simplicity of diagnosis and treatment of bladder inflammation, the selection of adequate therapy is associated with a whole complex of difficult problems. Firstly, for a long time, experts have noted an increase in antibiotic resistance of leading microorganisms that provoke the occurrence of urinary tract infections (UTIs), and secondly, treatment of the latter in women often leads to disruption of the microbiome of the vulva and vagina, which leads to an increased risk of re-infection of the lower parts of the urinary system [7]. Previously, researchers had already established the identity of the microflora of the vagina and urethra in 80% of cases [8]. This confirmed the fact that the ascending route of infection in women is dominant. It is known that the location of the external opening of the urethra near the reservoirs of uropathogens - the anus and vagina - predisposes to infection of the periurethral area. Then there is a sequential migration of microorganisms into the bladder, where they can be colonized or eliminated, depending on the result of the host-pathogen interaction. There is no doubt that the development of such a mechanism is facilitated by the weakening of the primary protective barrier. The effectiveness of the latter is ensured by lactobacilli, which normally make up 96-98% of the total microbiome in healthy women, both from the vagina and from the distal urethra. The described microorganisms in the mucous membrane adhere tightly to epithelial cells, forming a biofilm consisting of microcolonies of lactobacilli surrounded by the products of their metabolism - the glycocalyx. Unfortunately, the hormonal changes that women undergo throughout their lives, namely puberty, menstruation, pregnancy, menopause, can have a negative impact on the quantitative characteristics of the microbiome. Violation of its constant composition not only leads to a weakening of the protective barrier, but also increases the possibility of adhesion and reproduction of opportunistic microorganisms [10-14]. It is important to note that a number of antibacterial drugs used for the treatment of cystitis can also have a negative effect on the quantitative composition of lactobacilli. This entails the formation of vaginal dysbiosis, manifested in the form of bacterial vaginosis (BV) or even vaginitis, which can provoke frequent exacerbations and a protracted course of the inflammatory process in the urogenital tract. To overcome such a vicious circle, it is advisable to use medications that do not disrupt the normal biocenosis of the genital

mucosa. The use of drugs that do not lead to the development of vaginal dysbiosis during UTI treatment is also supported by the fact that *Gardnerella vaginalis* can act as a trigger for exacerbation of chronic cystitis in women. Before describing this mechanism, we note that the most common cause of the disease remains enterobacteria, mainly *Escherichia coli* (80%). The latter is a representative of the normal intestinal microflora, but its uropathogenic strains are capable of adhesion to the urothelium and can interfere with the development of the immune response. In addition, this type of microorganism is capable of tissue invasion into the bladder mucosa. This feature makes the pathogen resistant to antimicrobial therapy and allows it to form dormant intracellular bacterial reservoirs. The urinary tract is regularly exposed to vaginal bacteria, including *Gardnerella vaginalis*. Moreover, as studies have shown, even a short stay of *Gardnerella vaginalis* in the bladder can provoke reactivation of latent *E. coli* cells [15, 16]. Understanding this possible development of the clinical situation should not only be a reason for timely detection and treatment of vaginal infections by a gynecologist, but also requires a differentiated approach to the selection of therapy for patients with a history of recurrent cystitis. The anatomical and physiological features of the structure of the female urinary and reproductive systems, the presence of risk factors for possible reinfection, as well as the continuous increase in antibiotic resistance of microorganisms significantly complicate the selection of adequate and effective therapy for patients. In order to find ways to solve this problem, a prospective multicenter microbiological study DARMIS was conducted in 2018. Its implementation made it possible to once again confirm that the main causative agent of uncomplicated urinary tract infection remains *E. coli*, reaching 74.6% of observations. With the development of a complicated urinary tract infection, this microorganism was isolated in 67.2% of cases. The remaining bacteria leading to the development of uncomplicated and complicated forms of the infectious disease were *Klebsiella pneumoniae* in 9.6% and 12.7% of observations, *P. mirabilis* - in 3% and 4.6% of observations, *Enterococcus faecalis* - in 5% and 6% of cases, 3% of observations, *Staphylococcus spp.* – in 2.3% and 1.2% of observations.

Every year, the development of bacterial cystitis is the reason for seeking medical help for 7 million women around the world. On the territory of the Russian Federation, the occurrence of this disease is recorded in 15-20 thousand per 1 million people per year, while in 10% inflammation of the bladder takes on a recurrent form [1-5]. Such a high prevalence of pathology among the fair sex is not accidental and is associated with a number of risk factors, which include sexual intercourse, the presence of inflammatory diseases of the vulva and vagina, incompetence of the pelvic floor muscles, atrophic vaginitis caused by estrogen deficiency during menopause (Table) [6]. Gynecologists often encounter the presented reasons for the possible development of an inflammatory process in the bladder in their practice and must take measures aimed at preventing the development of bacterial cystitis. Despite the apparent simplicity of diagnosis and treatment of bladder inflammation, the selection of adequate therapy is associated with a whole complex of difficult problems. Firstly, for a long time, experts have noted an increase in antibiotic resistance of leading microorganisms that provoke the occurrence of urinary tract infections (UTIs), and secondly, treatment of the latter in women often leads to disruption of the microbiome of the vulva and vagina, which leads to an increased risk of re-infection of the lower parts of the urinary system [7]. Previously, researchers had already established the identity of the microflora of the vagina and urethra in 80% of cases [8].

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The anatomical and physiological features of the structure of the female urinary and reproductive systems, the presence of risk factors for possible reinfection, as well as the continuous increase in antibiotic resistance of microorganisms significantly complicate the selection of adequate and effective therapy for patients. In order to find ways to solve this problem, a prospective multicenter microbiological study DARMIS was conducted in 2018. Its implementation made it possible to once again confirm that the main causative agent of uncomplicated urinary tract infection remains *E. coli*, reaching 74.6% of observations. With the development of a complicated urinary tract infection, this microorganism was isolated in 67.2% of cases. The remaining bacteria leading to the development of uncomplicated and complicated

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was not detected. In all women, normal vaginal coenosis was restored with a sufficient amount of *Lactobacillus* spp. Achieving absolute normalization of urine tests and vaginal microbiota, as well as the cessation of bacteriuria, allowed the author to confirm the bidirectional effect of nifuratel [25]. The study proved its high effectiveness in relation to both nosologies. The presented results of studies assessing the effectiveness of nifuratel and carried out during 2000-2020 suggest that it has high activity against the main causative agents of acute urogenital infections, including not only the main uropathogens (*E. coli*, *Enterococcus* spp., *Klebsiella* spp., *Staphylococcus aureus*, *Enterococcus* spp., etc.), but also causative agents of vaginal infections (causative agents of BV, including *Atopobium vaginae*, fungi of the genus *Candida albicans*, *Trichomonas vaginalis*) [26]. The undeniable advantage of nifuratel is the absence of its activity against *Lactobacillus* spp., which makes it possible to normalize the microflora of adjacent reservoirs of infection, vagina and intestines, thereby preventing relapses of cystitis [27]. An important aspect is the possibility of using nifuratel in pregnant women based on a benefit/risk assessment.

Obviously, the treatment of acute and recurrent forms of cystitis is not the task of gynecologists. However, timely identification and selection of drugs to eliminate vulvovaginal infections are the direct responsibility of these specialists and lead to a reduction in the risk of developing bladder inflammation. For this purpose, in case of recurrent cystitis, it is advisable to recommend nifuratel in the form of vaginal dosage forms, in combination with nystatin (for example, Macmiror complex, capsules, cream). This treatment regimen will not only completely eliminate the pathogenic microorganism from the mucous membrane of the vulva and vagina, but will also not require a second stage of treatment aimed at restoring the microbiome of the genital tract. As a result, the doctor will be able to significantly reduce the duration of therapy, providing a personalized approach to the patient, which in turn will lead to improved quality of medical care at the outpatient stage.

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