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MODERN THERAPEUTIC OPTIONS IN THE TREATMENT OF BACTERIAL VAGINOSIS

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▪ This article reviews the pathogenetic aspects of bacterial vaginosis and modern methods of diagnosis and treatment of vaginal microbiocenosis disorders. The advantages and disadvantages of the available therapeutic approaches are discussed, and new opportunities and prospects in the treatment of bacterial vaginosis are highlighted.

▪ **Keywords:** antibacterial drug; antiseptic; bacterial vaginosis; combination drug; lactic acid.

СОВРЕМЕННЫЕ ТЕРАПЕВТИЧЕСКИЕ ВОЗМОЖНОСТИ ЛЕЧЕНИЯ БАКТЕРИАЛЬНОГО ВАГИНОЗА

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▪ В обзорной статье представлены патогенетические аспекты бактериального вагиноза, современные методы диагностики и лечения нарушений микробиоценоза влагалища. Рассмотрены преимущества и недостатки терапевтических подходов, отмечены новые возможности и перспективы в лечении бактериального вагиноза.

▪ **Ключевые слова:** антибактериальный препарат; антисептик; бактериальный вагиноз; комбинированный препарат; молочная кислота.

Large-scale international studies have shown that the human body is a habitat of various microorganisms, the total genome of which is more than 9.9 million microbial cells, which is approximately 500 times larger than the genome of the cells of the human body [1].

Knowledge of the peculiarities of the interaction of the microbiota of various localizations expands the understanding of the pathophysiology of many diseases and can determine the quality and length of life. Thus, the mechanism by which the microbiome can influence structural changes in the human genome and alter the function of the immune system and metabolism in general is studied actively [2–4].

The vaginal microbiocenosis represents a complex dynamic biosystem that maintains colonization resistance [5]. In healthy women of reproductive age, the predominant bacteria of the vaginal environment are lactobacilli, which make up 95%–98% of the biotope [3, 6–8]. The stability of vaginal microbiocenosis is provided by the ability of lactobacilli to participate in acidogenesis [9, 10].

In bacterial vaginosis (BV), the microecological state of the vagina changes, which is accompanied by a decrease and increase in the number of lactobacilli and anaerobic microorganisms, respectively; as a result, the pH of the vaginal fluid rises [5, 7]. The most common BV-associated microorganisms are *Gardnerella vaginalis, Mobiluncus* spp., *Sneathia* spp., *Leptotrichia* spp., *Atopobium vaginae*, as well as some other species of anaerobic microorganisms [10, 11].

BV firmly established itself at a leading position in the range of infectious diseases of the vagina. In women with complaints of discharge from the genital tract, the detection rate of BV varies from 16% to 65%, and this rate ranges from 15% to 37% in pregnant women and up to 87% in case of pathological leucorrhea. The disease often relapses, as 60% of women experience relapses within 12 months after treatment [12].

An extended list of predisposing factors contributing to the destabilization of the vaginal microbiocenosis explains the high prevalence of BV. These include hygiene, different sexual partners, hormonal imbalance, history of inflammatory diseases of the female genital organs, use of antibacterial drugs, endocrinopathy, and stress [7, 13].

BV is mainly clinically manifested as vaginal discharge with a specific fishy odor due to amines, which are waste products of anaerobic microorganisms. Signs of inflammation are not typical for BV [12].

BV itself is not life-threatening, but the presence of prolonged and profuse vaginal discharge can provoke disorders in the reproductive and sexual domains and reduce the quality of life of patients [14].

For the clinical diagnosis of BV, the criteria of Amsel et al. (1983) are used. The diagnosis is established based on at least three of the four criteria, namely, homogeneous vaginal discharge with an unpleasant odor, an increase in vaginal pH (>4.5), presence of clue cells, and a positive amino test result [7, 8, 12]. The diagnostic method using the criteria defined by Nugent et al. (1991), based on the detection of bacterial morphotypes by microscopy of Gram-stained preparations, is less popular in Russia [3, 11, 12, 15]. A phase contrast microscopic diagnostic method was proposed by Donders (1999). This method enables assessment of the ratio of lactobacillus and non-lactobacillary microflora to compare the leukocyte count and their ratio with the count of epithelial cells. The authors preferred the use and study of the native preparation, rather than the stained one, since the lactobacillary microflora can be destroyed partially during sample preparation, and its adequate assessment is the first step of microscopic analysis [16].

In 1995, Kira proposed a classification of the microscopic assessment of the vaginal microbiocenosis and described its four types. The classification combines microscopic interpretation and clinical characteristics corresponding to a specific nosological form. It is simple and practical to use; therefore, it has become widespread and generally recognized [7].

Advances in molecular biology associated with the development of a real-time polymerase chain reaction method are being actively implemented in the diagnosis of urogenital infections, including those associated with opportunistic pathogens [17]. This diagnostics has a number of advantages over traditional methods for detecting disorders of the vaginal microbiocenosis. They include a high level of standardization of the analysis and interpretation of results, exclusion of subjectivity, accurate quantitative assessment, and quick achievement of the result.

The cultural method of diagnosing BV is almost not used, because it is associated with the difficulties of cultivating anaerobic microorganisms. BV-associated microorganisms are also found in small amounts in healthy women [18].

According to the federal clinical guidelines for the diagnosis and treatment of patients with diseases accompanied by pathological discharge from the genital tract, treatment is based on an established diagnosis of BV grounded on complaints and results of clinical laboratory tests [12].

The approach to BV treatment has not changed dramatically for a long time and includes the use of antibacterial drugs. Since anaerobic microorganisms play an important role in the development of BV, the main drugs used in the treatment are agents of the 5-nitroimidazole group or lincosamides [8].

The first drug of choice from the nitroimidazole group was metronidazole. Subsequently, tinidazole,

ornidazole, and secnidazole were created, including the topical preparation ternidazole. For a long time, metronidazole was the main drug for most anaerobic microorganisms. The nitro group of the molecule, which is an electron acceptor, is incorporated into the respiratory chain, which disrupts the respiratory processes and causes the death of bacterial cells. Nevertheless, many studies have demonstrated that the nitroimidazole group is significantly inferior in efficacy compared to clindamycin against bacteria associated with BV, such as *G. vaginalis, A. vaginae,* and *Mobiluncus* spp. [19]. After metronidazole therapy, BV recurs immediately in 30% of women, and within 6 months after treatment, this index can reach 50% [20].

Compared with metronidazole, clindamycin is characterized by a wider spectrum of antibacterial activity, it is more effective against main BV-associated bacteria, and its side effects were noted in a smaller number of cases [19]. The molecule of this lincosamide binds to the 50S ribosomal subunit of a microbial cell and inhibits protein synthesis in microorganisms sensitive to it.

The use of antibacterial drugs can have a number of limitations, particularly because of its embryonic and fetotoxic properties, which is itself a risk factor for the development of microbial imbalance in the treatment of recurrent BV [7]. For this reason, the search for new alternative methods for the prevention and treatment of BV is necessary.

The current tendency in the pathogenetic treatment of BV is represented by substitution therapy with probiotics, for example, the use of lactobacilli that have positive effects on the biochemical and immunological parameters of the vaginal environment [20].

An important pathogenetic justification for the use of lactobacilli to correct microbial imbalance in the vaginal biotope is related to their ability to affect adversely the cells of opportunistic pathogens with antimicrobial peptides [21]. The metabolites of probiotic strains of lactobacilli were found to contribute to the destruction of bacterial films formed by *G. vaginalis* and *A. vaginae*, which, in combination with antibacterial drugs, improves the treatment and reduces the probability of relapse [18].

It is a naturally accepted belief that the greatest effect can be obtained with the use of lactobacilli, which more often colonize the vaginal biotope under normal conditions, such as during infection with *L. crispatus* [21].

Taking into account many years of clinical experience and research results in Russia, a two-stage method of BV treatment was adopted. This method was introduced in 1987, its efficacy was proved in 1990, and it was then introduced actively into clinical practice [7]. Stage I of treatment mainly aimed to eliminate the increased number of anaerobic microorganisms. In stage II, BV treatment consisted of the restoration of a sufficient number of lactobacilli using probiotics [12, 20].

There is also an evidence base for the use of chlorhexidine, dequalinium chloride, and some other antiseptics as an alternative therapy for BV at stage I or in monotherapy [22–24]. The bactericidal action of chlorhexidine is based on the ability of its salts to dissociate with the release of cations that bind to the negatively charged bacterial membranes, thereby causing an osmotic imbalance and the loss of potassium and phosphorus by the bacterial cell. Clindamycin, metronidazole, and chlorhexidine were argued to have comparable efficacy in therapy, while chlorhexidine has fewer side effects, since it does not have a negative effect on lactobacilli during treatment of BV [25].

Evidence on the use of chlorhexidine during pregnancy is limited, but in Russia, it is approved for use in the first trimester of pregnancy and during breastfeeding, unlike metronidazole and clindamycin [12].

One of the main principles of BV therapy is the restoration of the normal biochemical and biophysical parameters of the vaginal microecosystem, that is, the restoration of the vaginal environment pH. In this regard, acid-containing preparations are of great importance [26]. A decrease in the vaginal fluid pH using acid-containing agents leads to a rapid restoration of the normal lactobacillary flora of the vagina [27].

Recent multicenter studies have demonstrated the efficacy of vaginal lactic acid suppositories in the treatment of BV, including during pregnancy. Lactic acid is a natural waste product of vaginal lactobacilli, and it contributes to the pH of vaginal secretions in the range of 3.5–4.5 and helps inhibit the growth of pathogenic and opportunistic flora [7, 26, 28].

Vaginal suppositories containing chlorhexidine and lactic acid, in addition to the main active ingredient, contain a water-soluble polyethylene oxide base that potentiates the therapeutic effect of the active substance by absorbing pathological secretions. This action contributes to the destruction of biofilms, creates favorable conditions, and exerts therapeutic effect on the vaginal mucosa [24, 28].

Currently, there are no universal recommendations for the treatment and prevention of relapses, because of the multifactorial nature of the causes and polymorphism of BV pathogens; therefore, alternative means and methods are still being sought [8].

At present, combinations of topical drugs, such as Klion-D, Neo-Penotran®, Terzhinan®, and Macmiror complex®, have been used more frequently for the treatment of BV at stage I, as well as monotherapy. As a rule, combinations of modern drugs contain agents that affect the anaerobic flora, have a pronounced clinical and laboratory efficacy in the treatment of BV, include broad-spectrum antibiotics, are effective against Gram-positive and Gram-negative bacteria, and have an antifungal component. Some drugs contain microdoses of a corticosteroid which has an anti-inflammatory and desensitizing effect, or a local anesthetic agent, e.g., lidocaine, which eliminates quickly itching, burning, and pain [29–32].

In 2016, a new drug Elzhina® (Vertex, Russia) for intravaginal use was developed and registered in Russia. It contains 500 mg of ornidazole + 65,000 IU of neomycin + 100 mg of econazole + 3 mg of prednisolone. Ornidazole is a modern drug of the 5-nitroimidazole group; it affects anaerobic flora, including BV pathogens and protozoa, represents an alternative to metronidazole, and has a pronounced clinical and laboratory efficiency [33]. Econazole acts by inhibiting the synthesis of ergosterol of the fungal cell membrane, characterized by both fungicidal and bactericidal properties. Prednisolone has anti-inflammatory and antipruritic actions.

In 2017, Professor Savicheva and colleagues demonstrated that this drug can be considered the drug of choice in the treatment of BV [34]. According to other data, the efficiency of ornidazole + neomycin + prednisolone + econazole was at least 95% in the women examined. This forms the basis for recommending this drug as a monotherapy for BV, including recurrent BV [34, 35].

The search for new approaches to the elimination of disorders related to the vaginal microflora is the subject of further research. According to some experiments, treatment of vaginal disorders using drug solutions cavitated by low-frequency ultrasound can be an effective way to destabilize bacterial films. The effect of ultrasound exposure is manifested in the destruction of biofilms, which enhances the influences of antibiotics and antiseptics [36]. According to Plotko et al., when a probiotic drug is used at the stage II of therapy, clinical recovery and restoration of vaginal normocenosis can be achieved in every second patient [37]. The microbiological efficacy and safety of this technique have been proven in the correction of dysbiotic disorders in the vagina in pregnant patients [38].

New, more advanced, safer, and more effective therapeutic options in the treatment of gynecological diseases, especially BV, are sought to reduce the risk of obstetric and gynecological complications, increase the reproductive potential of the female body, and improve the quality of life.

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