

The State of the Vaginal Microbiocenosis, Bacterial Vaginosis and its Treatment Options

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Abstract: Bacterial vaginosis (BV) is a common pathological condition occurring in women of reproductive age, which includes a complex of changes in the vaginal biotope, characterized by a decrease in the amount of normal microflora and an increase in the concentration of other microorganisms, especially gram-negative anaerobes such as *Prevotella Porphyromonas spp.*, *Peptostreptococcus spp.*, *Fusobacterium spp.*, *Mobiluncus spp.*

Keywords: Bacterial vaginosis, microaerophilic rods, amine test, eubiotics probiotics.

It is known that the vaginal microflora of healthy women of reproductive age is represented by a wide range of microaerophiles, as well as facultative and obligate anaerobes [4], the presence of which does not disrupt the normal state, does not cause the development of an inflammatory reaction and pathological symptoms characteristic of vulvovaginitis or BV. Basically, the normal microflora is represented by microorganisms of the genus *Lactobacillus spp.* – microaerophilic rods producing hydrogen peroxide (71–100%), less often – anaerobic gram-positive rods (5–30%).

In addition to lactobacilli, the microaerophilic flora of the vagina of healthy women is represented by *Gardnerella vaginalis* (according to different authors, in 6–60% of cases), and also includes obligate anaerobes *Peptostreptococcus spp.* (30–90%), gram-positive anaerobic cocci, gram-positive rods – strict anaerobes *Bifidobacterium spp.* (in healthy women in about 12% of cases), *Clostridium spp.* (10–25%), *Propionibacterium spp.* – *P. acnes* (up to 25%), *Mobiluncus* are detected much less frequently *spp.* (0–5%). All these microorganisms are typical representatives of the normal microflora of the genital tract.

In a normal biotope, gram-negative, strictly anaerobic rod-shaped bacteria, bacteroides, can also be found. *spp.*: *B. urealyticum*, *B. fragilis*, *B. vulgatus*, *B. ovatus*, *B. distasonis*, *B. uniformis*, *B. coccae*, *B. multiacidus* (9–13%), *Fusobacterium spp.* (14–40%), *Porphyromonas spp.* (31%), *Prevotella spp.* (60%) and genital mycoplasmas *M. hominis*, *U. urealyticum* (in 2–15% of sexually active women).

Catalase-positive and coagulase-negative are often isolated. *Staphylococcus epidermidis*, novobiocin-resistant *Staphylococcus saprophyticus*, streptococcus spp. These are viridans group streptococci - "green" (a or g), hemolytic, serological group B streptococci (*Streptococcus agalactiae*), serogroup D streptococci (enterococci); nonpathogenic corynebacteria – *Corynebacterium minutissimum*, *C. equi* (new name – *Rhodococcus equi*), *C. aquaticum*, *C. xerosis*; *Escherichia coli*.

Other enterobacteria (*Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp.) are found in less than 10% of healthy women. Yeast-like fungi of the genus *Candida* – *C. albicans*, *C. tropicalis* and *Torulopsis glabrata* (formerly *C. glabrata*) – are found in the vagina of healthy women in 15–20% of cases. That is, the vaginal microflora of a healthy woman is represented by a wide range of different microorganisms that are in a state of biological balance and do not cause pathological changes in the mucous membranes of the vulva and vagina.

The vaginal microbiocenosis in BV is characterized by a sharp decrease in the level of peroxide-producing lactobacilli, up to their complete disappearance, and their replacement by *Gardnerella*, which promotes the growth of colonies of aerobic and anaerobic microorganisms. In addition to *G. vaginalis*, typical representatives of the microflora in BV are *Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Mobiluncus* spp., as well as *Fusobacterium* spp. and *Atopobium vaginae*.

The concentration of microaerophilic bacteria (*G. vaginalis*) in BV can increase hundreds of times, and anaerobic microorganisms *Bacteroides* spp., *Peptococcus* spp. – Thousands of times or more [1, 9].

In some cases, against the background of an absolute predominance of microorganisms associated with BV, lactobacilli may also be present in low titers, but, as a rule, these are anaerobic lactobacilli that are incapable of producing hydrogen peroxide.

In the complex chain of pathogenesis of various diseases of the female genital organs, a significant role is given to the immune reactions of the body. A decrease in non-specific resistance in patients with BV [2], as well as the fact that up to 90% of *G. vaginalis* are on the surface of the vaginal epithelium in the form of biofilms [21], contribute to the growth of resistance of anaerobic vaginal flora [13] to modern drugs and a long-term recurrent course of the pathological process.

Clinic

The main clinical manifestations of BV are homogeneous vaginal discharge, foamy, slightly viscous, white or gray in color with a specific "fishy" odor. Other complaints, such as itching, dysuric disorders, dyspareunia, are less common, may be completely absent or appear periodically. Asymptomatic course of the infectious process is observed in more than 1/2 of all women with BV, and they may have no subjective complaints at all [16].

With a long-term process, the discharge acquires a yellowish-greenish color, becomes thicker, often resembles a curdled mass, and is evenly distributed along the walls of the vagina without pronounced inflammation [8].

The most dangerous complications of BV are those that occur during pregnancy, during delivery (premature rupture of membranes, chorioamnionitis, abnormal labor), in the postpartum or postoperative period in the case of operative delivery (postpartum endometritis). BV can have an adverse effect on the development of the fetus (hypotrophy) or the newborn (pneumonia), so it is extremely important to treat this disease during the planning period and during pregnancy [1].

Diagnostics

Since 1983 and up to the present time, the criteria proposed by R. Amsel et al. (1983) have been used to diagnose BV, which include the presence of abundant vaginal discharge with an unpleasant odor; the appearance of a "rotten fish" odor during the amine test; an increase in the pH of the vaginal contents to 4.5; the presence of "clue cells" in Gram-stained smears. A diagnosis of BV

can be made if 3 of the 4 specified criteria are detected.

Microscopy of a vaginal smear stained by Gram is the most informative, reliable and accessible method for diagnosing BV, which makes it possible to objectively assess the state of vaginal microecology, and allows one to evaluate not only the morphological features and the ratio of individual components of the vaginal microflora, but also to obtain information about the state of the vaginal mucosa and the presence of a leukocyte reaction [5]. Polymerase chain reaction allows not only typing, but also quantitative determination of microorganisms in real time and has been widely used in clinical practice in recent years.

Treatment

Successful treatment of BV, like any disease, depends on correct and timely diagnosis and pathogenetically justified effective therapy.

The goal of BV treatment is to restore normal vaginal microflora and inhibit the growth of microorganisms that are not typical for this microecology. As a rule, at the first stage of treatment, the patient is prescribed a therapy that provides a high concentration of the drug in the vagina, which ensures the effectiveness of using small doses of the antimicrobial drug and rapid relief of the symptoms of the disease. The second stage of treatment includes stimulation of normal vaginal lactoflora through the use of biological bacterial preparations - eubiotics and probiotics [6].

The main drugs for the treatment of BV are metronidazole, clindamycin and tinidazole. These drugs can be used in tablet form for oral administration, as well as in the form of vaginal tablets, gels, and suppositories. Although the oral route of administration is associated with a higher frequency of side effects, it is more acceptable for most patients.

Metronidazole is recommended to be administered at a dose of 500 mg 2 times a day for 7 days or 1 time at a dose of 2 g, but this regimen is considered less effective. When taking metronidazole, side effects from the gastrointestinal tract may occur in the form of a metallic taste in the mouth and nausea (up to 10%), as well as transient neutropenia (7.5%), peripheral neuropathy. Nausea and other gastrointestinal effects are less pronounced with the intravaginal route of administration of metronidazole. Vaginal gel at a dose of 5 g, administered daily for 5 days, is not inferior in effectiveness to the oral route of administration and can be successfully used to treat BV [17].

Tinidazole is a nitroimidazole drug, used in tablets of 1 g once a day for 5 days or 2 g for 2 days.

Comparable in effectiveness to metronidazole, but having fewer side effects is clindamycin (Clindacin®) - an antibiotic of the lincosamide group, which has a broad spectrum of action, exerting mainly a bacteriostatic effect. Clindamycin is active against *Staphylococcus* spp. (including *Staphylococcus epidermidis*, producing penicillinase), *Streptococcus* spp. (excluding *Enterococcus* spp.), *Streptococcus pneumoniae*, *Corynebacterium diphtheriae*, against spore- and non-spore-forming anaerobes and microaerophilic gram-positive cocci (including *Peptococcus* spp. and *Peptostreptococcus* spp.), *Clostridium perfringens*, *Clostridium tetani*, *Mycoplasma* spp., *Bacteroides* spp. (including *Bacteroides fragilis* and *Prevotella melaninogenica*), *Fusobacterium* spp., *Propionibacterium* spp., *Eubacteria* spp., *Actinomyces* spp., i.e. against most microorganisms that cause vaginal dysbiosis and BV.

The preferred regimen is topical application of the drug for 3-7 days. In this case, vaginal suppositories are administered 1 at night or 2% vaginal cream with an applicator (5 g) at night for 3-7 days. Oral clindamycin is prescribed 2 times a day at 300 mg for 7 days.

Topical clindamycin is more effective than metronidazole in the treatment of recurrent BV, especially associated with *A. vaginae*; clinical cure with its use occurs in 83.3% of cases (side effects (pseudomembranous colitis, nausea) with clindamycin are rare, which significantly increases compliance with therapy).

The use of clindamycin (Clindacin®), which is very important, is possible during pregnancy or in the preparatory period for childbirth (locally only) in normal therapeutic doses.

The effectiveness, rapid achievement of positive treatment results, and good tolerability of clindamycin in treatment, including pregnant women, have been proven in numerous randomized, placebo-controlled comparative clinical studies [1, 7, 14].

The second stage of treatment, as well as for the purpose of preventing relapses of BV, prescribes eubiotics, probiotics, which can be used in combination with antibacterial drugs or as the main treatment. In the first case, it is advisable to prescribe probiotics no earlier than 3 days after the end of antibacterial therapy for BV in the form of intravaginal suppositories; the duration of treatment should be less than 7-10 days [6, 12].

After treatment, approximately 1/3 of patients experience a relapse of the disease within the first 3 months, and more than 1/2 experience symptoms within 12 months [19, 20]. This is most likely due to the ineffectiveness of the treatment, since 65 to 80% [15] of pathogens are found in biofilms, the matrix of which can bind or not allow, and/or inactivate antibiotics [3, 10, 11] and lead to a decrease in the effectiveness of treatment. Another possible reason for frequent relapses is that the normal vaginal microflora is not completely restored, and against this background, pathogenic microflora is reactivated [12, 23].

The question of the advisability of prescribing treatment to partners of women receiving treatment for BV has not been resolved. A number of researchers believe that treatment of sexual partners does not affect the success of therapy, although the role of sexual contacts in the occurrence and recurrence of BV has been proven. In addition, the effectiveness of using condoms in reducing the frequency of BV recurrences has been shown [22]. However, since the evidence base for final conclusions remains insufficient, new studies are needed to solve this problem.

Conclusions: Thus, BV, which represents a dysbiotic the state of the vaginal ecosystem, is a fairly common pathology in the modern population, requiring timely diagnosis, comprehensive adequate therapy and prevention. A drug that has a rapid positive effect and is well tolerated, and is also approved for use during pregnancy, is clindamycin (Clindacin®). High efficiency, proven by clinical studies, allows the use of Clindacin® in clinical practice as one of the main drugs for the treatment of BV.

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