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Bacterial vaginosis biofilms: a target for therapeutic innovation

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ABSTRACT

Bacterial vaginosis (BV) is one of the most common vaginal microbiome abnormalities worldwide and a risk factor for various obstetric and gynecological complications.

Despite years of exploration, existing and quickly emerging clinical, laboratory and instrumental diagnostic methods, and progressive development of science in general, the etiology and pathogenesis of BV remain poorly understood. This is evidenced by the high incidence of chronic and/or recurrent course. There are standard therapeutic approaches aimed to eradicating the causative agent, but the level of efficacy remains questionable due to recurrent episodes. Therefore, further studies of this problem are warranted. Actually, it is evident that *G. vaginalis* forms polymicrobial biofilms on urogenital tract mucosa.

Biofilms represent associations of microorganisms that are adhered to the surface of the epithelium and connected together in the polymer matrix. Biofilms change the properties of the microorganisms involved into their structural frame and provide beneficial conditions for their interactions. This results in the increase of the existing pathogenic properties of bacteria associated with BV, as well as in the appearance of new features. Thus, the microorganisms become less susceptible to previously effective antibiotics and to aggressive media. Finally, this contributes to the recurrent course of the disease.

In most cases, treatment of BV is based on the immediate effect on the microorganisms, but in patients with confirmed biofilm-associated BV this strategy is not effective and is associated with BV recurrences. Thus, currently relevant issues include exploration of the causes of recurrent BV, development of anti-biofilm agents able to disrupt their matrix and release bacteria from their carcass, and introduction of these agents into clinical practice. This will increase the effectiveness of treatment.

Keywords: bacterial vaginosis; etiology; biofilms; treatment.

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Биоплёнки бактериального вагиноза — мишень для терапевтического новаторства

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АННОТАЦИЯ

Бактериальный вагиноз — один из наиболее распространённых вариантов нарушения вагинального микробиома во всём мире. Он является фактором риска развития различных осложнений в акушерской и гинекологической практике.

Несмотря на многолетнее изучение этого синдрома, существующие и динамично совершенствующиеся клинико-лабораторные и инструментальные методы диагностики, прогрессивное развитие науки в целом, этиология и патогенез БВ до сих пор недостаточно изучены. Об этом свидетельствует высокая частота хронического и/или рецидивирующего течения. Существуют стандартные терапевтические подходы, направленные на эрадикацию этиологического агента, однако уровень эффективности остаётся сомнительным из-за повторяющихся эпизодов, что требует дальнейшего изучения данной проблемы. В настоящее время достоверно установлено, что *G. vaginalis* формирует на слизистой урогенитального тракта полимикробные биоплёнки.

Биоплёнка представляет собой кооперацию микроорганизмов, которые прикреплены к поверхности эпителия и связаны между собой полимерным матриксом. Биоплёнка оказывает влияние на свойства микроорганизмов, входящих в её структуру, обеспечивает условия для их взаимодействия. Это приводит не только к усилению уже имеющихся патогенных свойств бактерий, ассоциированных с бактериальным вагинозом, но и к формированию новых характеристик, благодаря которым микроорганизмы становятся в меньшей степени восприимчивы к ранее эффективным антибактериальным препаратам и агрессивным средам, что способствует рецидивированию.

В большинстве случаев лечение бактериального вагиноза осуществляется по прямому механизму воздействия на микроорганизмы, однако у пациенток с верифицированным биоплёночным бактериальным вагинозом такая стратегия нерезультативна, что приводит к рецидивам. Таким образом, на сегодняшний день остаются актуальными диагностика причин рецидивирующего бактериального вагиноза, разработка и внедрение в клиническую практику антибиоплёночных агентов, нацеленных на разрушение матрикса биоплёнки и освобождение из его структуры бактерий, что позволит повысить эффективность лечения.

Ключевые слова: бактериальный вагиноз; этиология; биоплёнки; лечение.

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细菌性阴道病生物膜：治疗创新的靶点

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摘要

细菌性阴道病（Bacterial Vaginosis, BV）是全球范围内最常见的阴道微生物群失调类型之一，同时是产科和妇科实践中各种并发症的重要风险因素。

尽管这一综合征已被研究多年，并且现有的临床实验室和仪器诊断方法不断完善，但BV的病因和发病机制仍未完全阐明。这可以从其高慢性化和高复发率的特点中看出。目前的标准治疗方法主要旨在根除病原体，但由于复发率高，治疗效果仍然有限，这需要进一步深入研究。研究表明，G. vaginalis 在尿生殖道黏膜上形成多菌种生物膜。

生物膜是微生物的集合体，其附着在上皮表面，并通过聚合物基质相互连接。生物膜改变了其内部微生物的特性，为其提供相互作用的条件。这不仅增强了与BV相关的细菌既有的致病特性，还赋予了它们新的特性，包括降低对以往有效抗菌药物和不利环境的敏感性，从而导致复发。

在大多数情况下，BV的治疗直接针对微生物，但对于被诊断为生物膜型BV的患者，这种治疗策略效果有限，往往导致复发。因此，目前的研究重点是明确复发性BV的原因，并开发针对生物膜基质破坏的抗生物膜药物。这些药物能够释放基质内的细菌，从而显著提高治疗效果。

关键词：细菌性阴道病；病因学；生物膜；治疗。

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BACKGROUND

Bacterial vaginosis (BV) is one of the most common gynecological conditions that does not directly affect a woman's health, but significantly impairs her quality of life [1]. Complications in patients with BV can be both gynecological (pelvic inflammatory disease, infertility of various origins, etc.) and obstetric (in women with BV, rates of miscarriage and preterm delivery are 3–5 and 2–7 fold higher, respectively, depending on gestational age) [2–4]. These complications can seriously affect women's reproductive health and therefore require attention of the medical community.

The global literature estimates the prevalence of BV in the female population to be approximately 29%, or more than 21 million diagnosed patients [5]. The prevalence of BV varies by geographic region and ethnicity. For example, a systematic review by Kenyon et al. [6] showed that the highest BV prevalence was reported in some parts of Africa (Botswana, Central African Republic, Gambia, Ghana, etc.), while most countries in Asia and Europe had low levels of the syndrome. A systematic review and meta-analysis by Peebles et al. found both regional and racial differences in the global prevalence of BV; rates of BV in African American and Hispanic women (33% and 31%, respectively) are significantly higher than in European (23%) and Asian (11%) women [7]. BV is a serious issue for women of childbearing age (23%–29%), which may affect the overall demographics, as the health of this population is directly related to the birth rate and the health of future generations [8]. In addition, the incidence of chronic and/or recurrent BV is increasing and the cost of diagnosis and treatment is a significant burden on the global economy [4]. For example, a meta-analysis by Peebles et al. [9] showed that annual cost burden of BV treatment is high, at an estimated US $4.8 billion.

BV can present in various clinical forms; one in four patients is asymptomatic, while symptomatic BV is often accompanied by a homogeneous gray or grayish-white foul-smelling (fishy odor) vaginal discharge, itching, burning, and other vaginal discomfort [5, 10]. Diagnosis of BV includes conventional modalities: vaginal pH, which is usually elevated in BV; the amine test (addition of 10% potassium hydroxide to vaginal discharge will produce a characteristic fishy odor); microscopy to detect key cells relevant to BV; microbiology to determine the composition of the microflora. New modalities are also being used, such as polymerase chain reaction for qualitative and quantitative assessment of vaginal bacterial composition, biochemical or molecular biotyping, and high-throughput sequencing, which provide a more comprehensive picture of microbiome composition [11].

HISTORY OF BACTERIAL VAGINOSIS RESEARCH

In practice, BV is usually characterized as a polymicrobial non-inflammatory condition caused by the decreased proportion of *Lactobacilli* or their complete absence in the vaginal microbiome and increased counts of obligate and facultative anaerobic opportunistic pathogens [12]. The vaginal microbiome is a complex, dynamic ecosystem that fluctuates throughout a menstrual period and an entire woman's life. Some authors report the bacterial count in young women of childbearing age to be 10^{10}–10^{11} CFU/mL [13]. The vaginal microbiome of a healthy woman is maintained in homeostasis. However, exogenous and endogenous factors may affect this balance. Endogenous factors include alterations in hormone levels, a woman›s age, weight, pregnancy, immune status, etc. Exogenous factors include the use of antibacterial agents, genital/extragenital infections, and inflammation [14]. *Lactobacilli* are the main bacteria that maintain a stable and healthy vaginal microbiocenosis. Albert Döderlein [15] was the first who discovered rod-shaped bacilli in the vagina and cultured them in a nutrient broth. He also found that these microorganisms are capable of producing lactic acid in the vagina, making it acidic, and proposed the concept of "vaginal acidity."

The history of vaginal microbiome research dates back to the mid-19th century, when clinicians noticed increasing rates of obstetrical and gynecological conditions caused by non-compliance with aseptic and antiseptic practice. The clinical use of light microscopy allowed in-depth research into the vaginal microflora composition and the search for causes of infectious complications in women. The identification of an etiologic agent and the development of a taxonomic classification of microbes associated with BV have been a challenge for many years due to the high selectivity of *Gardnerella vaginalis* to growth media, its unique physical and chemical structure and molecular architecture of the cell wall, genome diversity, and unclear pathogenic factors. For example, in 1953, Leopold published a study evaluating cervical discharge and urine in women with cervicitis and men with prostatitis, respectively. He detected a rod-shaped bacterium, which he described as small, gram-negative, non-motile, unencapsulated. Leopold could not identify the species of this bacterium, but based on its morphological characteristics, he proposed that it belonged to *Haemophilus* [16]. The microorganism previously described by Leopold was later discovered in 1955 by Gardner and Dukes [17] in women with non-specific vaginitis. Due to its tropism for blood-containing media, this rod-shaped bacterium was also classified as a member of the genus *Haemophilus* and named *Haemophilus vaginalis* due to its location. Since then, the condition associated with this pathogen has been classified as *Haemophilus vaginalis vaginitis*.

The species identification for the microorganism described by Leopold, Gardner, and Dukes has been the focus of research for many scientists since the 1960s, as subsequent studies provided conflicting results. In 1963, Zinnemann and Turnerg proposed to classify *Haemophilus vaginalis* as a member of the genus Corynebacterium and named it

Corynebacterium vaginale [18]. The taxonomic classification did not include the microorganism in Corynebacteria. *Gardnerella vaginalis*, formerly known as Corynebacterium vaginale and *Haemophilus vaginalis*, was named after Hermann L. Gardner, who discovered and classified it as the only member of the genus *Gardnerella* [19, 20]. Later, some features of *Gardnerella vaginalis* were identified: it was a gram-variable, pleomorphic, non-motile, non-sporeforming, acapsular, aflagellar bacterium ranging from 0.4–1.5 μm to 2–3 μm [21]. In addition, the size and morphology of the cells vary significantly depending on growth conditions and physiological status [22]. Due to the unique structure, *Gardnerella vaginalis* has attracted not only clinicians but also basic scientists, driving ongoing research in the field. Electron microscopy revealed fimbriae on the *Gardnerella vaginalis* surface. The fimbriae mediate adhesion to vaginal epithelium *in vivo* and to desquamated epithelium, which are the key cells [23]. Microscopy and cultivation of *Gardnerella vaginalis* often found that its cells were often linked together, which was explained by the production of exopolysaccharide with bacteria binding its filaments together [24]. It is now recognized that this is a biofilm consisting of microorganisms bound by a polymer matrix [25].

BIOFILMS: PATHOGENESIS OF BACTERIAL VAGINOSIS

Currently, biofilm-associated BV is detected in 90% of patients [8]. Of note that this term, as well as the term "biofilm-associated gardnerellosis" does not exist officially, but it is proposed by some authors to clarify the etiopathogenesis of the disease. Biofilms are a structured community of one or more species embedded in a polymer matrix consisting of proteins, carbohydrates, and nucleic acids [26, 27]. The biofilm concentration of some microbes can reach 10^{11} CFU/mL [28]. The American researcher John William Costerton described this phenomenon and introduced the term "biofilm" [29]. The formation of biofilms is a complex, stepwise, and dynamic process, as well as an effective survival strategy of microorganisms under unfavorable conditions [30]. Biofilm microorganisms are capable of regulating the production of virulence factors through an identified type of communication called quorum sensing. The biofilm cycle includes three stages: adhesion to the surface of the vaginal epithelium, secretion of the polymer matrix, and aggregation of microbes on the surface of the mature biofilm [27]. Biofilms have a higher tolerance to the aggressive factors compared to free-living microorganisms in the vaginal tract. This is possible due to the unique multi-component biofilm structure and the layered organization of microorganisms within the biofilm [31]. This structure contributes to the impaired diffusion of antimicrobial agents through the biofilm, reduced metabolic activity of the cells, and the emergence of antibiotic-resistant bacteria [32, 33].

For a long time, the role of Gardnerella in the biofilm formation was unclear: does *Gardnerella vaginalis* trigger this process or does it support the matrix of the biofilm formed by the association of bacteria? However, current literature suggests that *G. vaginalis* is a major colonizer that can provide a matrix for attachment of other BV-associated microorganisms, thereby enabling the formation of polymicrobial biofilms [27]. Some researchers, such as Bonnardel et al. [34], linked the mechanism of biofilm formation to bacterial lectins of Gardnerella, which are tropic to glycosylated components of the mucosa, thus forming a vaginal cell–Gardnerella complex. A study by Martin reported a role of a collagen-binding protein produced by Gardnerella, which may also contribute to the biofilm formation and possibly immune evasion through interaction with complement proteins [35]. In addition, regarding the microbiological features of Gardnerella, its significant adhesion to vaginal cells and ability to form biofilms confirm the trigger role of Gardnerella in the colonization of the vaginal epithelium, acting as a frame for the adherence of other species. Modern molecular diagnostic modalities show that *G. vaginalis* constitutes 60–90% of the biofilm. Other common biofilm members include *Sneathia sanguinegens*, *Porphyromonas assaccharolytica*, *Megasphera* spp. and the difficult-to-culture *Atopobium vaginae*, which may comprise up to 40% of the biofilm [5]. Their role in vaginal biofilm formation and pathogenicity of *G. vaginalis* has not been adequately evaluated [36]. Some studies reported that some, but not all, types of vaginal microflora can participate in biofilm formation and enhance *G. vaginalis* virulence [37]. Other studies found that microorganisms other than *G. vaginalis* may increase total biofilm biovolume [38]. Therefore, biofilm formation and development depend on both the triggering effect of Gardnerella and other vaginal microorganisms that form a kind of social network and thereby regulate the pathogenetic process of biofilm-associated BV. As a result, BV involves a complex interaction between opportunistic pathogens, endogenous vaginal microbiota, and the vaginal epithelium [39].

The main biofilm component is an extracellular polysaccharide matrix (exopolysaccharide), which constitutes 85% of its volume [25]. The matrix is produced by, and is composed of, the bacteria associated with BV, and it organizes the biofilm structurally and protects it from physical, chemical, and immune factors [40–42]. Nowadays, biofilms are thought to contribute to recurrent BV, although the term "recurrent BV" does not currently have a generally accepted definition [41]. There is no classification of BV in the relevant clinical guidelines published in 2022. The literature describes recurrent BV in a variety of ways. For example, Marshall et al. [43] considered this diagnosis in patients who "recur one or more times after completion of an episodic regimen," Letyaeva [1] diagnosed recurrent BV in patients with more than four episodes per year, and Pestrikova et al. used the criterion of 3–4 episodes per year [28].

CONCLUSION

There is an increasing research focus on biofilm as a pathogenetic factor of BV. Most treatment options focus on the etiologic agent of a disease, i.e. the direct mechanism of action. However, the ability of microorganisms to adapt to the effects of aggressive agents makes many treatment regimens ineffective, as evidenced by increased recurrence rates. The data on the structure of the biofilm confirmed the importance of the development and clinical use of agents that disrupt the polysaccharide matrix of the biofilm and release the bacteria present in this matrix (dispersants), and this is the focus of our research. This will both improve treatment outcomes and enable the practical use of previously effective and established treatment options.

ADDITIONAL INFO

Authors' contributions. K.A. Rossolovskaya performed literature review, collected and analyzed literature sources, prepared, wrote and edited the manuscript; N.S. Trifonova reviewed and edited the manuscript; I.V. Gadaeva reviewed and edited the manuscript; L.G. Spivak reviewed and edited the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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