

Bacterial vaginosis and biofilms: Therapeutic challenges and innovations – A narrative review

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Abstract

Bacterial vaginosis (BV), characterised by an imbalance in vaginal microbiota, frequently leading to recurrent episodes, has garnered recent research attention due to the significance of biofilms in its pathogenesis. BV biofilms contribute to recurrence by providing a shelter for harmful bacteria, rendering them resistant to conventional treatment. Objectives of this review include characterising BV biofilms, evaluating the limitations of current antibiotic therapy, highlighting emerging solutions and emphasising multifaceted approaches. The review presents data from clinical studies and trials on biofilm-focused treatments which might reduce BV recurrence, with the ultimate goal of improving the quality of life of women with BV and reducing its burden on their reproductive health.

Key words: Antibiotics, probiotics, bacterial vaginosis, biofilm-disrupting agents, biofilms, patient education, recurrent BV, vaginal microbiota

Introduction

Bacterial Vaginosis (BV) is a common complex vaginal infection predominantly affecting women of reproductive age. It is characterised by a disturbance in the delicate balance of microbial communities within the vaginal tract. BV is hallmarked by the disruption of equilibrium between beneficial and harmful bacteria, often resulting in an overgrowth of the latter. The human vagina hosts a diverse ecosystem of microorganisms, primarily composed of bacteria. In a state of health, *Lactobacillus* species play a dominant role, working harmoniously to uphold an acidic pH level and inhibit the proliferation of harmful microorganisms. However, in the context of BV, this harmony is disrupted. Lactobacilli populations diminish, while anaerobic bacteria such as *Gardnerella vaginalis*, *Prevotella* and *Mobiluncus* species thrive. Consequently, the vaginal environment becomes less acidic, rendering it more susceptible to infection. The characteristic symptoms of BV often encompass

unusual vaginal discharge, typically greyish-white in colour and accompanied by a fishy odour, which becomes particularly noticeable after sexual intercourse. Additional symptoms include vaginal itching, burning sensation and discomfort during urination. Some women with BV remain asymptomatic, making it challenging to diagnose.¹

The Center for Disease Control and Prevention (CDC) identifies it as the most common vaginal infection among women of reproductive age in the United States. Globally, the prevalence varies based on region and demographic factors, with some studies suggesting that up to 30% of women may experience BV at some point in their lives. Numerous risk factors have been associated with an increased susceptibility to BV, including sexual activity (although it is not classified as a sexually transmitted infection), douching and the absence of vaginal lactobacilli. While BV itself may not inevitably lead to severe complications, it is linked to adverse outcomes such as a heightened risk of contracting sexually transmitted

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infections, including HIV. Moreover, during pregnancy, BV is linked to complications like preterm birth and low birth weight, emphasising the need for effective management. The diagnosis of BV is typically based on clinical criteria, including the Amsel criteria, and microscopic examination of vaginal fluid.² Treatment typically involves antibiotics, with metronidazole and clindamycin being the most commonly prescribed options. Unfortunately, even after effective treatment, BV often recurs. Given the prevalence and complexities of BV, there is a pressing need for increased awareness and a deeper understanding of its impact on women's reproductive health.

Recent research has unveiled the existence and significance of biofilms formed by BV-associated bacteria, particularly *Gardnerella vaginalis*, within the vaginal environment.² These biofilms pose challenges to treatment and may contribute to the recurrent nature of BV. Investigating the role of biofilms in BV could lead to more effective treatment strategies to bring relief to the many women affected by this condition.³ The aim of this review is to investigate the challenges posed by current BV therapies when biofilms are present within the vaginal environment. We also present emerging strategies that hold promise in overcoming these challenges.

Literature Search

The search for relevant articles was conducted across three key databases: PubMed, ScienceDirect, and Google Scholar.

We concentrated on articles published between 2010 and 2023, in order to maintain relevance to the contemporary research on BV and biofilms. Only articles in English language were included. Diverse study designs encompassing clinical trials, observational studies, experimental research, and systematic reviews were included.

Keywords used included “Bacterial Vaginosis”, “Biofilms”, “Therapeutic Challenges” and “Innovations”. Boolean operators were applied to refine search queries. “Bacterial Vaginosis” and “Biofilms”, “Therapeutic Challenges” or “Innovations”, “Bacterial Vaginosis” or BV and “Biofilms” or “Microbial communities”, “Treatment options” and “Antibiotics” or “Probiotics”, “Biofilm Formation” or “Biofilm Disruption” and “Pathogenesis” or “Treatment Strategies”.

A total of 187 articles were identified based on the initial search criteria. After applying the inclusion criteria, 30 articles were selected for detailed review.

Bacterial Vaginosis and Biofilms

Biofilms are structured communities of microorganisms that adhere to surfaces and are encased in a self-produced matrix of extracellular polymeric substances. They play a role in various bacterial infections, including dental plaque, chronic wounds, device-associated infections, lung infections and implant-related infections. In the context of BV, biofilms are primarily formed by BV-associated bacteria, notably

Gardnerella vaginalis.⁴ These biofilms involve attachment to vaginal epithelial cells, matrix formation composed of polysaccharides, proteins and DNA, and microbial communities of various bacterial species. Understanding these biofilms is crucial for developing strategies to disrupt them and improving BV treatment outcome.⁵

Challenges Posed by BV Biofilms: One of the most concerning aspects of BV biofilms is their ability to hinder the effectiveness of antibiotics. The biofilm's protective matrix shields BV-associated bacteria from antibiotics, making it difficult for these drugs to reach and kill them, resulting in treatment resistance and recurrent BV. This is not merely a theoretical concern; Clinical study conducted by Machado *D et al.* included a detailed exploration on the impact of biofilms on recurrence of BV and therapeutic failure due to resistance.³

Biofilm Formation in BV: BV biofilms are complex structures formed by bacterial species like *Gardnerella vaginalis*, *Atopobium vaginae*, and others on the vaginal epithelium. These biofilms consist of bacteria encased in an extracellular matrix, providing a protective environment that shields them from host immune defenses and antibiotic treatments.³

Recurrence of BV: Studies have shown that BV biofilms contribute to the recurrence of BV episodes. Even after successful antibiotic treatment, biofilms can persist in the vaginal environment. Residual biofilms may contain bacteria that were not effectively eradicated by the initial treatment, leading to rapid re-establishment of the dysbiotic environment and recurrent BV episodes.³

Treatment Resistance: Biofilm-embedded bacteria exhibit increased resistance to antibiotics compared to planktonic bacteria. The extracellular matrix of biofilms acts as a physical barrier, preventing antibiotics from effectively reaching bacterial cells. Additionally, bacteria within biofilms may enter a dormant or slow-growing state, making them less susceptible to antibiotic action.³

Alteration of Vaginal Microenvironment: BV biofilms alter the local vaginal microenvironment, creating conditions favourable for dysbiosis. The disruption of the acidic environment maintained by beneficial *Lactobacillus* species promotes the growth of anaerobic bacteria, further perpetuating BV.³

Impact on Host Immune Response: BV biofilms can modulate the host immune response, leading to chronic inflammation and tissue damage. The presence of biofilms activates inflammatory pathways, contributing to symptoms associated with BV.³

Researchers have utilised advanced imaging techniques, molecular analyses, and patient samples to delve into the intricate nature of BV biofilms and their central role in the pathogenesis of BV, underscoring the need to address biofilms in its management.⁶

Current Therapies for BV: Antibiotics, including metronidazole and clindamycin, represent the primary treatments employed to combat BV. These antibiotics have demonstrated effectiveness in alleviating BV symptoms by reducing the overgrowth of harmful bacteria. However, the matrix in which biofilm bacteria are embedded acts as a physical shield, obstructing antibiotic penetration and rendering these medications less effective. The bacteria within biofilms are often more resistant to antibiotics due to their altered physiological state.⁷ While antibiotics can provide relief from BV symptoms, they come with potential side effects, including gastrointestinal disturbances and nausea. Moreover, they can disrupt the normal vaginal microbiota, potentially leading to a resurgence of BV. Additionally, the incomplete penetration of antibiotics may result in an insufficient eradication of BV-causing bacteria within biofilms, leaving behind a reservoir for potential recurrence. The protracted exposure of bacteria to antibiotics can also contribute to the development of antibiotic resistance, which is a global public health concern. Thus women with asymptomatic BV often experience high recurrence rates due to a lack of treatment.⁸ To address these challenges, researchers are actively exploring innovative therapeutic strategies, such as biofilm-disrupting agents and alternative antimicrobial agents, with the aim of improving treatment outcomes, reducing the recurrence rate, and mitigating the development of antibiotic resistance in the management of BV.⁹

Emerging Solutions for BV Biofilms: Probiotics and biofilm-disrupting agents offer promising approaches to address BV biofilms.

Probiotics: Probiotics are beneficial microorganisms that, when introduced into the vaginal ecosystem, are aimed to restore a healthy microbial balance. They work by promoting the growth of *Lactobacillus* species, which are essential for maintaining an acidic pH in the vagina and inhibiting harmful microorganisms. Probiotics can disrupt BV biofilms by competing with and displacing BV-associated bacteria. By doing so, they help create an environment less conducive to biofilm formation and reduce the risk of recurrence. Probiotics are being explored as an adjunct to standard BV treatment, with research focused on identifying the most effective probiotic strains and optimal delivery methods.¹⁰

Biofilm-Disrupting Agents: Biofilm-disrupting agents encompass a range of treatments designed to target and dismantle BV biofilms. This category includes enzymatic disruptors and antibiofilm agents.¹¹ Enzymatic disruptors work by degrading the extracellular polymeric substances that comprise the biofilm matrix, thus destabilising the biofilm structure. Antibiofilm agents are compounds that interfere with the adhesion and communication among bacteria within the biofilm, ultimately leading to its disruption. These agents are under investigation in clinical trials to assess their safety and efficacy in addressing biofilm-related challenges in BV therapy.¹²

Ongoing research and clinical trials aim to characterise BV biofilms, evaluate the effectiveness of biofilm-targeted therapies, study patient outcomes, and analyse the vaginal microbiome.¹³

Data from Clinical Trials on Emerging Solutions

A clinical trial conducted by Gawande *et al.* in 2014 examined the effectiveness of an enzymatic biofilm-disrupting agent, dispersin B. This trial investigated the impact of dispersin B when administered alongside standard antibiotic therapy for recurrent BV. The results revealed a significantly higher BV cure rate in the dispersin B group compared to the control group. While the composition of dispersin B was not specified in the report, this study provides evidence of the efficacy of this biofilm-disrupting agent. Ongoing research in this field may uncover additional agents with antibiofilm activity, offering more options in BV management.¹⁴

The study conducted by Heczko *et al.* was a double-blind, placebo-controlled trial involving women with recurrent bacterial vaginosis (BV) or aerobic vaginitis (AV). Participants received either a probiotic supplement or a placebo alongside standard metronidazole treatment. Results showed that the probiotic significantly delayed the recurrence of BV/AV symptoms compared to the placebo, by up to 51% for BV and 76% for AV. Additionally, probiotic use maintained lower vaginal pH and Nugent scores while increasing *Lactobacillus* counts after treatment. These findings suggest that oral probiotics can effectively prolong remission and improve clinical outcomes in women with recurrent BV/AV.¹⁵

Impact of Biofilm targeted therapy on BV

Biofilm-focused treatments, including biofilm-disrupting agents and probiotics, offer the potential to reduce BV recurrence substantially. By targeting the protective biofilm matrix, these treatments aim to enhance the efficacy of antibiotic therapy, making embedded bacteria more susceptible to eradication.¹⁶ In addition to addressing recurrent BV, these modalities may also have a preventive role by disrupting the initial formation of BV biofilms, potentially thwarting the onset of BV and recurrent episodes.³ This can lead to longer remission periods and a reduction in the frequency of recurrent BV episodes, ultimately improving patient outcomes and reducing the burden on healthcare systems.¹⁷

Treatment strategies for bacterial vaginosis (BV) encompass a range of interventions targeting the restoration of a healthy vaginal microbiota. Antibiotics such as metronidazole and clindamycin serve as frontline therapies, directly targeting the overgrowth of pathogenic bacteria. Emerging approaches include Vaginal Microbiome Transplantation (VMT), where a healthy microbiota is transferred from a donor to the recipient, offering potential relief for recurrent or refractory BV cases. Modulating vaginal pH with agents like lactic acid and Vitamin C creates an inhospitable environment for harmful bacteria while promoting the growth of beneficial

Lactobacillus species. Disruption of BV biofilms, notorious for treatment resistance, is achieved through agents like boric acid and Astodrim vaginal gel, enhancing susceptibility to antibiotics. Probiotics, particularly those containing *Lactobacillus crispatus*, play a pivotal role in restoring microbial balance when administered orally or vaginally, thereby reducing BV recurrence and promoting vaginal health. These multifaceted strategies collectively aim to alleviate symptoms, prevent recurrence, and restore the equilibrium of the vaginal microbiota for optimal health outcomes in BV management [Table 1].¹⁸

Table 1: Summary of strategies for the treatment of bacterial vaginosis

Intervention	Example
Antibiotics	Metronidazole, Clindamycin
Vaginal microbiome transplant (VMT)	Vaginal microbiome transplantation
pH modulation	Lactic acid, Vitamin C
Biofilm disruption	Boric acid, Astodrim vaginal gel ¹⁹
Probiotics	Oral and vaginally administered probiotics, for example, <i>L. crispatus</i> ¹⁴

The study conducted by Schwebke JR and colleagues aimed to evaluate the efficacy and safety of Astodrim 1% Gel in preventing the recurrence of bacterial vaginosis (BV) in women with a history of recurrent BV. Involving 864 women initially treated with oral metronidazole, those successfully treated were randomly assigned to receive either Astodrim 1% Gel or a placebo vaginally every second day for 16 weeks, followed by 12 weeks off-treatment. Results demonstrated that Astodrim was significantly more effective than placebo in preventing BV recurrence, with fewer women experiencing recurrence by Week 16 and a longer time to recurrence in the Astodrim group. Moreover, the Astodrim group reported fewer subject-reported symptoms such as vaginal odour and discharge. Adverse events were infrequent, though vulvovaginal candidiasis and urinary tract infection were slightly more common in the Astodrim group. In conclusion, Astodrim 1% Gel showed efficacy, superiority to placebo, and good tolerability in preventing recurrent BV in women with a history of the condition.¹⁹

The Need for Further Research

While there is a substantial body of existing research on the composition of bacterial biofilms, it is imperative that future investigations take a more granular approach.²⁰ More comprehensive characterisation of BV biofilms is needed, encompassing their structural properties, detailed composition, and the specific bacterial species that play a role within these complex microbial communities. This comprehensive understanding is vital for the development of targeted biofilm-disrupting strategies.²¹ Rigorous clinical trials are essential, incorporating diverse patient populations to account for variations in BV presentation and biofilm composition. Additionally, further research is needed

to explore the intricate interactions within the vaginal microbiome, with a focus on how alterations in microbial communities contribute to BV and biofilm formation.²² The advancement of metagenomic and metatranscriptomic techniques can provide valuable insights into these complex dynamics. Research should also strive to optimise the effectiveness and safety of biofilm-disrupting agents, ensuring that they are well tolerated and capable of disrupting biofilms without adverse effects. Exploring the long-term effects of these treatments is also important.²³

Patient Education and Prevention Strategies

Patient education and prevention strategies play a vital role in the holistic management of BV. Educating patients about BV, its symptoms, and the importance of seeking early medical attention is essential.²⁴ Early intervention can prevent BV from worsening and significantly improve treatment outcomes. Patients should also be informed about lifestyle modifications that support a healthy vaginal microbiota, such as avoiding scented feminine hygiene products, maintaining a balanced diet, and practicing safe sex.²⁵ These choices can influence the risk of BV. Scented feminine hygiene products can disrupt the natural balance of vaginal microflora and should be avoided. A balanced diet rich in probiotics and prebiotics can also positively impact the vaginal microbiota.²⁶ Dietary prebiotics, such as fibers, fuel beneficial bacteria in the gut, leading to the production of short-chain fatty acids that help maintain vaginal acidity. This discourages harmful bacteria growth. Probiotics, like certain *Lactobacillus* strains, when consumed, can colonise the vagina, competing with pathogens and bolstering immune defenses. A balanced diet rich in prebiotics and probiotics can thus promote a healthy vaginal microbiota, reducing infection risks. Probiotic-rich foods like yogurt and kefir can promote the growth of beneficial bacteria, while prebiotic foods like whole grains and certain fruits and vegetables provide nourishment for these beneficial microbes.^{27,28} Further, a proactive approach to women's health, including regular gynaecologic check-ups, is of utmost importance. Routine screening can detect BV even in asymptomatic cases, allowing timely intervention with better outcomes.^{29,30}

Conclusion

The presence of BV biofilms in the vaginal environment adds challenges to current therapeutic approaches due to their bacterial shielding, leading to incomplete eradication, antibiotic resistance, and recurrent infections. These limitations necessitate a paradigm shift in our approach to BV management. Patient education and awareness are pivotal in early intervention and lifestyle modifications, contributing to maintaining a healthy vaginal microbiota. Clinical evidence suggests that probiotics can promote a healthier vaginal microbiota, while biofilm-disrupting agents hold the potential in breaking down the protective matrix, reducing recurrence rates, and enhancing treatment outcomes for BV patients. More clinical trials focused on BV biofilms are vital

in optimising these treatments. In conclusion, addressing BV biofilms requires a holistic strategy that encompasses prevention, patient education, and innovative treatments, working towards improving the quality of life of women affected by BV and reducing the burden of this common condition.

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