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Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Nuno Cerca (2022): Addressing the challenges with bacterial vaginosis pharmacotherapy, Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2022.2082285

To link to this article: https://doi.org/10.1080/14656566.2022.2082285

Published online: 30 May 2022.

EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2022.2082285

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EDITORIAL

Addressing the challenges with bacterial vaginosis pharmacotherapy

Nuno Cerca [a,b]

[a]Laboratory of Research in Biofilms Rosário Oliveira (LIBRO), Centre of Biological Engineering (CEB), University of Minho, Campus de Gualtar, Braga, Portugal; [b]LABBELS –Associate Laboratory, Braga, Portugal

ARTICLE HISTORY Integra30052022Integra30052022080320222305 2022Received 8 March 2022; Accepted 23 May 2022

KEYWORDS Bacterial vaginosis; recurrent infection; metronidazole; clindamycin; multi-species biofilm

1. Introduction

The healthy female vaginal environment is a dynamic ecosystem that is commonly colonized by several lactic acid-producing bacteria, most of the genus *Lactobacillus* [1]. It is believed that the normal human vaginal microbiota has an important role in maintaining health, with an impact on either baby delivery or increased risks in the acquisition of sexually transmitted infections [2]. The composition of the vaginal microbiota depends on ethnicity and can change over the menstrual cycle, during pregnancy, with age, and under external stresses, such as antimicrobial treatments [3]. For reasons not yet fully understood, the dominant healthy vagina lactic acid and hydrogen peroxide-producing lactobacilli can be replaced by a complex mixture of strictly and facultative anaerobic bacteria [4]. This significant shift in the composition of the vaginal microbiome is known as bacterial vaginosis (BV). Despite being the most common dysbiosis in women of childbearing age, BV etiology is not yet fully understood, with different controversial theories being raised over the years [3].

Although BV can be asymptomatic, approximately 50% of women experience a spectrum of symptoms, including vulvovaginal itching, burning, irritation, 'fishy' vaginal odor, and abnormal vaginal discharge [5]. BV has been associated with an enhanced risk of sexually transmitted infection acquisition as well as preterm labor, miscarriage, post-abortion, and postpartum infections [4].

Next-generation sequencing genomic analysis has identified more than 200 species associated with BV [6]. However, the role of these species in BV development is largely unknown and it has been suggested that the increased number of species colonizing the human vagina might be a consequence and not the cause of BV [7]. An important breakthrough in BV research was the recognition that BV is associated with a polymicrobial biofilm [8], wherein bacteria of the genus *Gardnerella* is thought to play a pivotal role [9]. Importantly, the presence of this biofilm is thought to be involved in treatment failure and leading to the high recurrence rates of BV [10].

2. Current approved therapeutic approaches against BV

Due to the lack of understanding of the mechanisms involved in BV development, current treatment is directed toward the alleviation of symptoms through reduction of BV-associated bacteria overgrowth and restoration of normal vaginal microbiota [5]. The first-line antibiotics used to treat BV are metronidazole (a DNA replication inhibitor) or clindamycin (a protein synthesis inhibitor) [11]. As recently reviewed, the recommended treatment regimens include 500 mg of metronidazole orally, twice a day for 7 days or in alternative an intravaginal application of 5 g of a gel containing 0.75% metronidazole, once a day, for 5 days. Because several side effects are associated with metronidazole therapy, such as nausea, vomiting, and gastrointestinal complaints, there is also the recommendation to use an intravaginal application of 5 g cream containing 2% of clindamycin, at bedtime, for 7 days. Alternative regimens include oral tinidazole and oral clindamycin [12]. Despite some evidence of sexual transmission and clinician recommendations to treat both the women with BV and her male partner [13], current antimicrobial treatment is only recommended for women with cases of symptomatic BV [14]. Furthermore, alternative regimens are being pursued, focused on either increasing treatment duration or drug concentration, as recently reviewed [12].

3. Challenges in bacterial vaginosis treatment

An important challenge for BV treatment derives from deficient diagnosis practices, as recently reviewed [15]. This is most likely the result of a poor understanding of BV etiology. With molecular diagnosis methods being developed, a better characterization of the BV microbiota could, potentially, increase BV treatment efficiency. Nevertheless, even when BV is properly diagnosed, clinicians face the high recurrence rate following antibiotic therapy [12]. Apart from BV persistence due to ineffective antibiotic therapy, BV recurrence rates are high, approximately 43–52% within 3–6 months after effective treatment [16]. One of the first studies addressing the impact of antimicrobial therapy failure in BV recurrence was performed by Bradshaw et al. They conducted a large cohort study of 139 women infected with BV that were also treated with metronidazole (400 mg, orally, twice daily for 7 days). Participants were scheduled for follow-up over 12 months. Interestingly, they showed that BV relapses were significantly more frequent in women co-colonized by both *Gardnerella*

CONTACT Nuno Cerca nunocerca@ceb.uminho.pt Centre of Biological Engineering, University of Minho, Campus de Gualtar, Rua da Universidade, Braga 4710-057, Portugal

spp. and *Atopobium* (*Fannyhessea) vaginae* and proposed that the association between these two bacteria enhanced the tolerance to metronidazole, with a direct impact on treatment failure [16]. On a follow-up study, while exploring the role of *Gardnerella* mediated polymicrobial biofilm in antimicrobial therapy failure, Swidsinski et al. found out that several women treated with metronidazole, despite not having further symptoms, had a significant number of *Gardnerella* spp. and *F. vaginae* present on the vaginal epithelial cells after completion of treatment [10]. More recently, by analyzing the microbiome prior and after treatment, Gustin et al. demonstrated that greater recurrence rates were observed in women colonized by a higher variety of bacterial species [17], further suggesting that microbial interactions play a role in BV recurrence.

In vitro evidence has been confirming the importance of biofilms in BV treatment failure. Similar to other biofilm-associated infections, Algburi et al. showed that the required concentration to completely eradicate an *in vitro* Gardnerella spp. biofilms was significantly higher than the concentration required to kill planktonic populations, with 2 mg/mL of metronidazole and 20 mg/mL of clindamycin required to eradicate the biofilm cells [18]. Importantly, the concentration of these antibiotics significantly exceeded their peak serum concentrations and, therefore, are not applicable for BV treatment. In fact, using clinically relevant concentrations of metronidazole, Gottschick et al. demonstrated that an in vitro Gardnerella biofilm could in fact not be eradicated [19].

4. Expert opinion

Despite somewhat currently successful BV treatment short-term cure rates, it is important to reduce the very high BV recurrence rates and antimicrobial therapy failure, especially because increased resistance to metronidazole and clindamycin has been reported [20], and resistance rates will likely increase in the upcoming years. Being BV associated with both biofilms and polymicrobial communities, and having in consideration that, alone, each of these traits can significantly contribute to antibiotic treatment failure, developing safe and lasting BV therapeutic options will be a challenging task.

Several new studies have been providing potential alternative therapeutic options, including antiseptic agents, probiotics and prebiotics, plant-derived compounds, natural antimicrobials, acidifying agents, and biofilm-disruption agents [21]. However, despite some promising results, most studies have not yet undergone clinical trials. A recent study involving a long-term regiment that started with oral nitroimidazole for 7 days and simultaneous boric acid for 30 days, followed by twice-weekly vaginal metronidazole gel for 5 months, was able to reduce recurrence in 20 out of 29 women that concluded the study regimen [22]. Furthermore, although an important focus has now being given to anti-biofilm agents [23], there are still many unanswered questions regarding how the polymicrobial community associated with BV is involved in the progression of BV. Recently, Rosca et al. demonstrated that synergistic interactions do occur in polymicrobial biofilms that directly lead to an enhanced antimicrobial tolerance [24], and this can explain the high recurrence rates observed. Current knowledge about BV etiology does not allow us to unequivocally determine that the multi-species biofilms are the cause of BV, but a better understanding of the biofilm-forming process and, even more important, on this polymicrobial biofilm involvement in antimicrobial tolerance, will most likely be pivotal for the development of long-lasting therapeutic options, wherein recurrence rates will be drastically reduced.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This manuscript was not funded.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

ORCID

Nuno Cerca http://orcid.org/0000-0003-3365-3537

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