

# Antibacterial treatment of bacterial vaginosis: current and emerging therapies

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**Abstract:** Bacterial vaginosis is a common cause of malodorous vaginal discharge. It is also associated with sexually transmitted infections and adverse pregnancy outcomes. The magnitude of the gynecological and obstetrical consequences has stimulated therapeutic research and led to the testing of several therapies. The objective of this work is to present the currently available therapeutic strategies for the treatment of bacterial vaginosis and associated recommendations, and discuss the emerging therapies.

**Keywords:** bacterial vaginosis, treatment, emerging therapy

## Introduction

Bacterial vaginosis (BV) is a common cause of malodorous vaginal discharge in women of reproductive age.<sup>1</sup> Women's awareness of BV is low and often they self-medicate with antifungals before presenting very late when symptoms have become intolerable. However, many affected women are asymptomatic.<sup>1</sup> The exact etiology remains elusive, although some authors have proposed a complex interaction between the numerous components of the vaginal microbial ecosystem and their human host.<sup>2</sup> Multiple risk factors for BV infection have been hypothesized, including vaginal douching, African-American race, multiple or new sexual partners, and women who have sex with women.<sup>1,3</sup> Inversely, hormonal contraceptive use, male circumcision, and consistent condom use reduce the incidence of BV.<sup>1,4,5</sup>

BV was first described in 1955 by Gardner and Dukes who reported a strong correlation between BV and the presence of *Gardnerella vaginalis*.<sup>6</sup> However, progress in defining the composition of the vaginal microbiome had to await the development of new molecular techniques. These implicated not one bacterial species but numerous bacteria in BV and increased our understanding of the characteristic shift in the normal vaginal microbiota from a predominance of protective lactobacilli to pathogenic anaerobic bacteria.<sup>7</sup> The resident *Lactobacillus* species are replaced by an overgrowth of vaginal anaerobes or Gram-negative bacteria including *Gardnerella vaginalis*, *Atopobium vaginae*, bacterial vaginosis-associated bacteria, *Megasphaera* species, *Mycoplasma hominis*, *Mobiluncus* species, *Ureaplasma urealyticum*, *Prevotella*, and *Peptostreptococcus* species.<sup>8</sup> Moreover, BV-associated bacteria have been shown to form a prolific polymicrobial biofilm, the main component of which was found to be *G. vaginalis* and *A. vaginae*, that adheres to the vaginal epithelium.<sup>9</sup> These recent advances have facilitated the detection and the identification of bacteria without the need for cultivation. Some of these bacteria have not previously been described or

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well characterized and have led some authors to propose new diagnostic tools based on molecular biological techniques.<sup>7,10</sup> Nevertheless, the clinical Amsel criteria and the Gram stain-based Nugent score remain widely used. Clinical diagnosis is based on the combination of any three of the following four criteria: vaginal pH > 4.5, thin homogeneous vaginal discharge, clue cells on microscopic examination of vaginal fluid, and a “fishy” amine odor.<sup>11</sup> A subjective clinical diagnosis is of limited value in assessing women in the general population as most of women with BV are asymptomatic. Microbiological diagnosis is based on Gram staining graded according to the Nugent score that reflects the presence of normal (score of 0–3) or intermediate flora (score of 4–6), or BV (score of 7–10).<sup>12</sup> The artificial category intermediate flora has further complicated the diagnostic approach since a considerable percentage of women tested fall into this category, the precise clinical implications of which, either none or pathology inducing, remain largely uncharacterized.

Interest in BV has grown since it was found to associate with an increased susceptibility to sexually transmitted infections, herpes simplex viruses, human papillomavirus, and human immunodeficiency virus (HIV).<sup>13,14</sup> BV has also been associated with postoperative infection and adverse pregnancy outcomes including premature rupture of membranes, premature labor and delivery, intra-amniotic infection, and low-birth-weight infants.<sup>15,16</sup>

The magnitude of these gynecological and obstetrical consequences has stimulated a research effort towards therapeutic development from which several therapies have been tested. However, evaluation of BV therapeutic studies reveals a major problem in that most used some or all of the clinical Amsel criteria, the Gram stain results, or a combination of both to define the diagnosis and the proposed cure, whereas a few others used the criteria defined by the US Food and Drug Administration (FDA) to perform the examination to evaluate the therapeutic response based on a combination of both the clinical outcome and the Gram stain results.<sup>17</sup> Making comparisons between these studies is therefore problematic. The main aim here was to present the currently available therapeutic strategies for BV and their associated recommendations, as well as discuss the emerging therapies. For this review, I performed searches of MEDLINE (2000 to present) using the keywords “bacterial vaginosis”, “treatment”, “prevention”, and “recurrent bacterial vaginosis” to identify all English-language articles concerning current and emerging therapies for BV. I observed the current guidelines published by the US Centers for Disease Control.

## Antibiotic therapy

### Metronidazole

Metronidazole is a nitroimidazole antimicrobial agent used to manage protozoal infections such as trichomoniasis and anaerobic infections.<sup>18</sup> Since the early 1980s, metronidazole has been used widely in the treatment of BV with good clinical results. Various preparations allowing a vaginal or oral administration and different regimens have been studied.

### Metronidazole vs placebo

Local (single-dose 100 mg, 250 mg, and 500 mg vaginal metronidazole tablets; or 0.75% metronidazole gel once or twice daily for 5 days) and oral metronidazole (400 mg twice daily for 7 days; or 500 mg three times daily for 10 days) have lower rates of treatment failure compared with placebo.<sup>19,20</sup> The cure rates of women given antibiotics were higher (58%–100%) than the cure rates of women given placebo (5%–29%) when evaluated 4 weeks after treatment. The cure rates varied widely according to the diagnostic criteria for abnormal flora at inclusion, the definition of cure and treatment failure, and length of time post-therapy before the follow-up visit.

### Routes of administration

Two randomized controlled studies directly compared the efficacy of vaginal (0.75% metronidazole vaginal gel 5 g, twice daily for 5 days) vs oral regimens (500 mg twice daily for 7 days). The efficacy of vaginal and oral regimens was similar when evaluated 2 weeks and 5 weeks after treatment.<sup>21,22</sup> However, the vaginal regimen was associated with less gastrointestinal complaints (33% vs 52%).<sup>21</sup>

### Duration of oral regimens

In 1992, a meta-analysis was conducted on ten studies comparing different oral metronidazole regimens.<sup>23</sup> The women were categorized according to the duration of oral metronidazole treatment: (1) 2 g single dose, (2) 2 g single dose daily for 2 days, (3) 400 mg twice or three times daily for 5 days, (4) 500 mg twice daily for 7 days. The cure rates ranged from 85% to 87% with no significant difference among the groups. Furthermore, no difference was found in the recurrence rates 1 month following single-dose, 5-day or 7-day regimens. The results of this meta-analysis were however criticized and in 1999, Joesoef and collaborators performed another meta-analysis including only the four studies that compared the single dose (2 g) and the 7-day regimens. They demonstrated that the clinical efficacy of

the 7-day regimen is superior to the single-dose regimen with cumulative cure rates 3–4 weeks after completion of treatment of 82% for the 7-day regimen vs 62% for the single-dose regimen.<sup>24</sup> A more recent review also concluded that the 7-day regimen of metronidazole is superior to the single-dose regimen leading the authors to recommend it as the first-line regimen in the treatment of BV. More recently, a randomized trial examined whether extending the duration of metronidazole therapy to 14 days was superior to the 7-day regimen by enhancing the cure rates for BV. Cure rates were significantly improved with the 14-day regimen at the 7-day follow-up visit (45% vs 63%). However, the cure rates were equal at the 21-day follow-up visit, suggesting that relapse or reinfection had occurred.<sup>25</sup> Extending the duration of metronidazole therapy was not associated with an increase of vaginal candidiasis or of gastrointestinal adverse effects.<sup>25</sup>

### Adverse effects

Metronidazole therapy is associated with side effects including gastrointestinal effects (metallic taste in the mouth, nausea, vomiting) and candida infection. However a recent meta-analysis did conclude that when applied topically, metronidazole was not significantly associated with candidiasis.<sup>20</sup> Such side effects have been used to support single-dose therapy of oral metronidazole or topical metronidazole.<sup>26</sup> They may also be responsible for difficulties adhering to a 7-day course of treatment and subsequently result in treatment failure. Incomplete cure would be associated with an increased risk of recurrence or the development of metronidazole resistance. Since vaginal regimens have been associated with fewer gastrointestinal complaints (33% vs 52%),<sup>21</sup> vaginal metronidazole may be an alternative to oral metronidazole.

## Clindamycin

Clindamycin is a second antimicrobial agent for the treatment of BV. This lincosamide antibiotic, a subclass of the larger family of macrolide antibiotics, has various treatment preparations including vaginal (ovule and cream) and oral.

### Clindamycin vs placebo

In a recent meta-analysis, intravaginal treatment (0.1%, 1%, 2% clindamycin cream twice daily for 5 days; 2% clindamycin cream at bedtime for 7 days) showed benefits to BV treatment with lower treatment failure compared with placebo (relative risk: 0.25; 95% confidence interval: 0.16–0.37).<sup>20</sup>

## Routes of administration

Only one study has evaluated the use of oral clindamycin vs intravaginal administration. According to this study, oral administration of 450 mg clindamycin three times daily and 2% clindamycin in vaginal cream 5 g once daily, for 7 days had similar cure rates.<sup>27</sup>

### Ovules vs cream

One randomized study compared the efficacy of clindamycin vaginal ovules (100 mg daily for 3 days) with clindamycin vaginal cream (5 g at bedtime for 7 days) for the treatment of BV.<sup>28</sup> The cure rates were similar: 53.7% for the ovule group and 47.8% for the cream group. Similarly, a single dose of clindamycin vaginal cream was found to be equivalent in terms of safety and efficacy to a 7-dose regimen of vaginal cream.<sup>29</sup>

### Clindamycin vs metronidazole

In the recent Cochrane review, topical clindamycin (2% clindamycin cream 5 g at bedtime for 7 days; ovule 100 mg daily for 3 days) or oral clindamycin (500 mg twice daily for 7 days) appeared to be equivalent to oral (500 mg twice daily for 7 days) or topical metronidazole (0.75% gel 5 g daily for 7 days).<sup>20</sup> However, topical clindamycin tended to cause a lower rate of adverse effects (metallic taste in the mouth, nausea, vomiting) than oral metronidazole.<sup>19</sup> In addition, clindamycin cream and ovules which are oil-based might interfere with the safety of latex condoms and diaphragms.

## Tinidazole

Tinidazole is a nitroimidazole antibiotic and an antiprotozoal agent that was first reported in Europe, Asia, and Latin America for its use in BV treatment. Trials evaluating oral regimens of 1–2 g daily for 1–5 days have given favorable results.<sup>30</sup> Tinidazole was licensed recently in the US for the treatment of BV.<sup>31</sup>

### Tinidazole vs placebo

A randomized controlled trial assessed the effectiveness, at 21–30 days after treatment, of tinidazole administered orally at 1 g once daily for 5 days and 2 g once daily for 2 days, compared with placebo.<sup>32</sup> The authors demonstrated superior efficacy of both tinidazole regimens to placebo in the treatment of BV. The cure rates were 37% for the 1 g once daily for 5 days group, 27% for the 2 g once daily for 2 days group, and 5.1% in the placebo group. The FDA based its recent approval on these results.

### Tinidazole vs metronidazole

Based on its pharmacokinetic profile, tinidazole has the potential of being a highly efficacious drug for BV. Compared with metronidazole, it has a higher  $C_{max}$ , area under the curve, and steady-state serum concentration, and longer half-life.<sup>33</sup> The spectrum of activity against bacteria associated with BV is very similar for the two agents.<sup>33</sup> The efficacy of two regimens of tinidazole (500 mg twice daily or 1 g twice daily for 7 days) was compared with metronidazole 500 mg twice daily for 7 days in a randomized trial.<sup>34</sup> No significant difference was found in treatment failure rates (Nugent score  $\geq 7$ ) between tinidazole (27% for the 1 g regimen and 25% for the 500 mg regimen) and metronidazole (18%) at the 14-day follow-up visit. Similarly, short-term recurrence rates at the 2-month follow-up visit were not significantly different (40%, 20%, and 34% respectively).

### Tinidazole vs clindamycin

Only one study has evaluated the efficacy of a single oral 2 g dose of tinidazole compared with 2% clindamycin vaginal cream for 7 days.<sup>35</sup> At the end of the therapy, the women in the tinidazole group were treated with an acidic vaginal gel 2 g every 3 days for an additional 3 weeks. After 1 week of treatment, the clinical cure rate ( $< 2$  Amsel's criteria) was 84% in both groups with no statistical difference. At the 4-week follow-up the clinical cure rate was higher in the tinidazole and acidic vaginal gel group (94%) than that in the clindamycin group (78%) with no statistical difference. This result suggests that a single dose of oral tinidazole is as effective as topical clindamycin. No study has compared the efficacy of oral tinidazole with oral clindamycin.

### Adverse effects

Oral tinidazole therapy has been associated with adverse events (yeast infection, nausea, vomiting, and bad taste in the mouth) such as those observed with oral metronidazole therapy.<sup>32</sup>

### Secnidazole

Secnidazole is a nitroimidazole antibiotic with a broad spectrum of activity against anaerobic microorganisms and has a longer half-life than metronidazole.<sup>36</sup> Used as a single-dose oral regimen it appears effective in the treatment of amebiasis, giardiasis, trichomoniasis, and BV.<sup>36</sup> It represents an attractive therapeutic option particularly in women whose likely compliance is doubtful.

### Secnidazole vs metronidazole

No study has evaluated the efficacy of secnidazole compared with placebo. The efficacy of secnidazole was however compared with the mainstay of BV therapy, metronidazole. A randomized, double-blind, noninferiority study was conducted according to FDA guidance to compare the efficacy of a single 2 g oral dose of secnidazole compared with a 7-day course of 500 mg metronidazole administered orally twice daily.<sup>37</sup> The secnidazole regimen was shown to be at least as effective as the multiple-dose metronidazole regimen. The therapeutic cure at the 28-day follow up was 60% in the secnidazole group and 59% in the metronidazole group. Secnidazole was well tolerated and adverse events were similar in both groups (38% in the metronidazole group and 39% in the secnidazole group). Although headaches were rarely reported, they were more frequent in the secnidazole group (9% vs 4%).

### Duration of oral regimens

In an attempt to reduce adverse effects, one study was conducted to determine whether BV could be treated with a single 1 g oral dose of secnidazole with the same efficacy as that achieved with the conventional single 2 g oral dose. The women with symptomatic BV were randomized to receive one of the two regimens.<sup>38</sup> The clinical cure rate was evaluated after 1 week based on Amsel's criteria. The cure rate was 97% using a 2 g therapy and 95% in the 1 g dose group. Adverse effects were reported at equal rates in both groups (34% and 36% respectively).

### Other routes

Narayana and collaborators developed and evaluated in vitro vaginal gels based on ion-activated systems for the local release of secnidazole.<sup>39</sup> This new formulation showed promise for reducing the systemic side effects and improving the therapeutic effects and patient compliance.

## Nonantibiotic therapy

### Probiotics

According to FDA and World Health Organization definitions, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host".<sup>40</sup> The mechanism by which probiotics confer such a health benefit is not well understood. Several hypotheses concerning their mechanism of action have been proposed: (i) as an example, *Lactobacillus fermentum* RC-14 has been reported to produce a biosurfactant containing a large number

of collagen-binding proteins that could inhibit pathogen adhesion and induce a competitive exclusion of the pathogen on epithelial cells; (ii) probiotics may produce antimicrobial compounds such as hydrogen peroxide, lactic acid, or bacteriocin, which inhibit pathogen growth; (iii) probiotic therapy may cause a mucosal modulation that enhances the host immune system response.<sup>41–43</sup>

Microorganisms with probiotic properties are *L. rhamnosus* GR-1, *L. rhamnosus* Lcr 35, *L. reuteri* RC-14, and *L. crispatus* CTV-05.<sup>44–47</sup> Taken orally or vaginally these have been shown to improve vaginal flora without any side effects and are of potential clinical importance.<sup>44–47</sup> Intestinal passage of probiotic has the advantage of interfering with the natural process by which pathogens emerge from the intestine and ascend along the perineum to the vagina.<sup>45</sup>

The newly recognized strains *L. rhamnosus* L60 and *L. fermentum* L23<sup>48</sup> have been considered for probiotics development due to their in vitro performance concerning bacteriocin production, adherence to epithelial cells, and coaggregation with pathogenic bacteria.<sup>48</sup>

### Treatment of BV

Evidence of reduced levels of resident *Lactobacillus* species in BV has given rise to the concept of *Lactobacillus* strain replacement to restore the normal vaginal flora. Two recent reviews supported the use of probiotics,<sup>49,50</sup> but further randomized controlled trials are needed before definitive conclusions can be made on the effectiveness of probiotics for the treatment of BV. One randomized study compared the efficacy of vaginal probiotics with vaginal metronidazole.<sup>51</sup> The authors suggested that the cure rate of BV after two intravaginal capsules of probiotics containing  $10^9$  *L. rhamnosus* GR-1 and  $10^9$  *L. reuteri* RC-14 daily at bedtime for 5 days was more effective than 0.75 metronidazole vaginal gel applied twice daily for 5 days. Symptomatic BV was significantly reduced at the 15-day follow-up in 85% of women in the probiotic group vs 45% in the metronidazole group. However, another recent randomized controlled trial comparing vaginal administration of  $10^7$  *L. acidophilus* and 0.03 mg estriol with vaginal metronidazole suggested equivalent cure rates at 3–7 days of follow-up with slightly inferior results at 1-month follow-up.<sup>52</sup> Other studies have associated antibiotics with probiotics, the results of which vary depending on the types of probiotics and antibiotics used and also according to route of administration (oral or vaginal). Oral metronidazole therapy (500 mg twice daily for 7 days) plus oral probiotic twice daily for 30 days (1 capsule

containing  $10^9$  *L. rhamnosus* GR-1 and  $10^9$  *L. reuteri* RC-14) showed significantly increased efficacy compared with oral metronidazole alone.<sup>53</sup> At the 30-day follow-up, 88% had normal vaginal flora in the probiotic group compared with 40% in the placebo group. Martinez and collaborators confirmed that *L. rhamnosus* GR-1 and *L. reuteri* RC-14 might provide an adjunct to antimicrobial treatment and improve cure rates.<sup>54</sup> In a similar study design, a single dose of tinidazole (2 g) supplemented with two capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 every morning for the next 4 weeks showed significantly increased efficacy compared with tinidazole alone. At the 28-day follow-up, 88% had normal vaginal flora in the probiotic group compared with 50% in the placebo group. This finding was not confirmed among HIV-infected women.<sup>55</sup> Those with BV treated by metronidazole for 10 days (400 mg administered orally twice daily), were randomized to receive daily oral capsules of probiotics *L. rhamnosus* GR-1 and *L. reuteri* RC-14 ( $2 \times 10^9$  viable organisms) or placebo for 6 months. No significant difference in the cure rate was found at the 2-week follow-up and the prevalence of BV was similar in both groups at 25 weeks of follow-up. This study therefore showed that BV is more difficult to eradicate in HIV patients and oral probiotic alone administered daily did not sufficiently improve the microbiota.

### Prevention of recurrence

The second proposed use for probiotics is in preventing the recurrence of BV after an initial treatment. The hypothesis is that abnormalities of the vaginal flora often persist even in the absence of clinical symptoms after antimicrobial therapy.

One double-blind randomized placebo-controlled trial compared the efficacy of vaginal gelatin capsules ( $10^9$  *L. gasseri* Lba EB01-DSM 14869 and *L. rhamnosus* Lpb PB01-DSM 14870) administered for 10 days during three menstrual cycles with that of placebo adjunctive therapy after a 7-day course of daily 2% clindamycin vaginal cream.<sup>56</sup> At 1-month follow-up, the cure rate was 64% in the probiotic group and 78% in the placebo group; the difference was not significant. At the end of the study (6 months of follow-up) and for the women initially cured, 65% of the probiotic group had normal flora compared with 46% of the placebo group; the difference was significant. Vaginal probiotics inserted on 10 days per menstrual cycle over 3 months contributed significantly to the avoidance of relapse. The study showed that supplementary treatment of lactobacilli does not improve the efficacy of BV therapy during the

first month of treatment, but for women initially cured, the adjunct treatment significantly lengthens the time to relapse. These results were confirmed in another study reporting the long-term administration of a vaginal probiotic. Women with symptomatic BV were randomized: (1) to receive twice daily oral metronidazole 500 mg for 7 days; (2) to receive the same metronidazole regimen followed 8 days later by vaginal application of 40 mg of *L. rhamnosus* (>40,000 colony forming units) once a week for 6 months.<sup>57</sup> The follow-up over 12 months showed an increase in abnormal vaginal flora from 9% 1 month after metronidazole alone to 31% at 12 months. In the probiotic group, the rate of abnormal flora was similar at the beginning and at the end of the follow-up (4% and 9% respectively). According to the authors, this progressive divergence between the two groups resulted from the stabilization of a balanced vaginal flora in the probiotic group and the progressive increase in recurrence of BV in the group receiving metronidazole alone. The administration of the vaginal probiotic after oral metronidazole therapy may increase the cure rate during the follow-up period by stabilizing the vaginal ecosystem and thereby reducing the number of patients suffering BV recurrence.

Other authors have proposed the prophylactic use of probiotics in healthy women with a history of recurrent BV. A randomized, double-blind, placebo-controlled trial was conducted among healthy women who had suffered >2 BV episodes in the previous year.<sup>58</sup> The women were randomized to receive either one vaginal capsule of probiotics (8 billion colony forming units of *L. rhamnosus*, *L. acidophilus*, and *Streptococcus thermophilus*) or placebo on a 7 days on, 7 days off, 7 days on regimen. Lower rates of BV incidence were reported during the 2 months after probiotic prophylaxis (16% for the probiotic and 45% for the placebo group) according to Amsel's criteria. The 11-month follow-up consisting of a telephone interview suggested that women receiving probiotics had a lower incidence of BV symptoms than did those in the placebo group. Although this study was limited by the telephone follow-up interview that may have under-reported the frequency of BV symptoms, the results do suggest that local administration of *Lactobacillus* strain could therefore be a useful complementary tool in the management of recurrent BV. Other studies are now needed to validate further the efficacy of probiotics in the prevention of recurrent BV.

## Local acidification of vaginal fluid

BV is characterized by the alkalization of vaginal fluid (vaginal pH > 4.5) prompting some authors to propose correcting the vaginal pH in order to treat BV. The results have

been discordant. In two randomized double-blind clinical trials, vaginal acidification alone (5 mL acetic acid gel intravaginally twice daily for 7 days or 5 g acid-buffering formulation gel intravaginally once daily for 5 days) was an ineffective therapy for BV compared with placebo or metronidazole.<sup>59,60</sup> However, in another randomized study, the combination of oral metronidazole 500 mg twice daily and 5 g lactic acid vaginal gel at bedtime for 7 days was found to be better than metronidazole alone at promoting lactobacilli colonization and reducing malodorous vaginal discharge.<sup>61</sup> Moreover, not only was the lactic acid well tolerated but it also reduced recurrence of symptomatic BV.<sup>61</sup>

## Emerging therapies Antibiotics and novel vaginal delivery systems

Vaginal delivery of metronidazole or clindamycin is the most common therapy in the treatment of BV, but its efficacy is not optimal. Some authors are working towards improving existing formulations or creating new dosage forms. One group in Egypt working on pluronic polymers, has developed a hydrogel that swells in aqueous environments for use as a drug delivery system. This novel vaginal delivery system for metronidazole, improved the therapeutic efficacy compared with that achieved with conventional vaginal gel.<sup>62</sup> In a pilot randomized trial, while similar cure rates were reported after 1 week of treatment (85% in the new vaginal gel group and 71.4% in the conventional vaginal gel group;  $P = 0.294$ ), the cure rate was significantly higher after 4 weeks in the new gel group compared with the conventional gel group (80% and 47%, respectively). These results suggest a novel and efficient long-term treatment of BV. Elsewhere, a new dosage form, containing metronidazole, was developed based on vaginal mucoadhesive tablets realized by including bioadhesive polymers.<sup>63</sup> Similarly, new bioadhesive film formulations of clindamycin phosphate for vaginal delivery have also been developed.<sup>64</sup> The in vitro properties and antibacterial activity of these new formulations may offer an alternative to traditional dosage forms for vaginal topical administration. The success of such new dosage forms, and bioadhesive products designed to extend the residence time of the antibiotic in the vaginal cavity, will not only depend on their effectiveness but also on their potential toxicity for epithelial cells of the vaginal mucosa and for resident lactobacilli.

## Novel antimicrobial agents

Nifuratel, a furane-derivative, is an antiprotozoal and antifungal agent. Safe, well tolerated and with no known

teratogenic effects, it can be used in the treatment of many infections of the genito-urinary tract.<sup>65</sup> Togni and collaborators recently compared the antimicrobial activity of nifuratel against *G. vaginalis*, *A. vaginae*, and lactobacilli with that of the two currently used antibiotics. Results suggest that nifuratel has a more optimum spectrum of activity, being highly active against *G. vaginalis* and *A. vaginae* without affecting lactobacilli.<sup>66</sup> These data are promising and led the authors to propose nifuratel for the treatment of BV. Clinical studies should now be developed.

## Effect of antifungal therapy on BV

Self-treatment with antifungals is widely practiced and it may be useful in women with *Candida* who are co-infected with BV. The general consensus is that opposing vaginal pH are required for the growth of *C. albicans* and BV, but because candida vulvo-vaginitis requires low acidity and BV requires high vaginal pH levels, this notion is incorrect. Indeed, Donders and collaborators reported recently that nine out of 142 women (roughly 6%) with symptomatic candidosis also had BV.<sup>67</sup> Antifungal treatment cured the BV in 70% of women with simultaneous candida vaginitis. While antifungal treatment may have a beneficial effect on women with concurrent BV, it does not prevent BV from occurring in BV-negative women. A similar benefit of antifungal therapy has been reported previously in a randomized controlled trial,<sup>68</sup> in which women who received ovules containing metronidazole and nystatin for BV had a better cure rate at 2 weeks of treatment than those receiving metronidazole 0.75% gel alone (20% and 4%, respectively). Moreover, the benefits of combined therapy remained at 3 months of treatment (52% and 33%, respectively).

## Antiseptics

Essential oils from medicinal plants have strong antiseptic properties. Two recent studies have suggested the use of thymol and eugenol for BV therapy.<sup>69,70</sup> Thymol is a natural monoterpene phenol found in oil of thyme, with an in vitro activity on *G. vaginalis* biofilms; and eugenol is a phenylpropene extracted in particular from clove oil. Both were applied via vaginal douche once daily for 7 days and resulted in a similar significant reduction in symptoms as that obtained with vaginal metronidazole.<sup>70</sup> Beyond reducing symptoms, the effect of thymol on vaginal flora should however be analyzed.

Glycerol monolaurate, another antiseptic, is a safe mono-glyceride with bactericidal properties for Gram-positive organisms. It is microbicidal for *Candida* and *G. vaginalis*

in vitro and reduces both organisms without affecting vaginal lactobacilli in vivo when applied via vaginal gel.<sup>71</sup> Clinical trials are now needed to assess the effectiveness of glycerol monolaurate gel in treating BV.

A recent study evaluated the efficacy of octenidine hydrochloride/phenoxyethanol, a local antiseptic spray, applied for 7 or 14 days compared with 7 days of metronidazole vaginal tablets for BV therapy.<sup>72</sup> The local antiseptic spray was as effective as the standard therapy with cure rates of 58% and 71% at 7 days and 14 days, respectively, compared with 61% at 7 days with metronidazole.

A team from China has developed a temperature-sensitive gel containing silver nanoparticles and investigated its antibacterial properties in vitro. This optimized silver nanoparticle dosage form demonstrated great potential, encouraging further development for the clinical treatment of BV.<sup>73</sup>

## Prebiotics

Another alternative for treating BV is to induce a vaginal flora shift from a BV- to a *Lactobacillus*-dominated flora by promoting the growth of lactobacilli. The principle behind prebiotics is to provide nutriment that stimulate the growth of lactobacilli. Oligosaccharides can selectively promote the growth of lactobacilli that in turn generate lactic acid to lower the vaginal pH and secrete antibacterial substances that inhibit the adhesion and replication of the anaerobic bacteria.<sup>74</sup> Some authors have proposed the topical application of a gel containing sucrose, a disaccharide of glucose and fructose, to treat BV. A Phase III clinical trial was conducted including women with symptomatic BV who were randomly assigned into three groups for vaginal application of sucrose (5 g), metronidazole (0.75%), and placebo gels, twice daily for 5 consecutive days.<sup>75</sup> The therapeutic cure rates (according to FDA guidelines) evaluated 21–35 days after the start of treatment were 61%, 67%, and 7%, respectively, for sucrose, metronidazole, and placebo gel groups. These results suggest that sucrose has a therapeutic cure rate similar to the metronidazole gel. Interestingly, at the intermediate visit (7–10 days after the start of treatment), the therapeutic cure rate was statistically higher for the sucrose group (83%) than for the metronidazole group (71.3%) and the placebo group (0.9%). The evaluation of lactobacilli based on the Nugent score at the 5–7 days visit showed significantly higher levels of lactobacilli in the sucrose gel group compared with the metronidazole group. These results suggest that by promoting the growth of lactobacilli, sucrose gel restores normal vaginal flora more rapidly than does metronidazole. However, while the rate of adverse events after sucrose gel was found to be

similar with that found in the other groups, treatment with sucrose would be expected also to promote the development of candidosis.

## Current strategies

### Symptomatic BV

BV is the most prevalent cause of vaginal discharge or odor. The most recent recommendations for the treatment of symptomatic BV to relieve these vaginal symptoms were issued in 2010 by the US Centers for Disease Control.<sup>76</sup> The recommended regimens in pregnant and nonpregnant women are reported in Table 1. First-line treatment includes metronidazole or clindamycin. Alcohol consumption should be avoided throughout the 7-day treatment with systemic metronidazole and 1 day after. For women presenting side effects, the vaginal route may be recommended. Choice of treatment should be carefully considered among users of condoms and diaphragms, since weakening of the latex can occur for up to 5 days after applying the oil-based clindamycin cream. Of note is the recent introduction of tinidazole as an alternative to metronidazole and clindamycin. During treatment regimens, women should be advised to avoid unprotected sex. In addition, vaginal douching that promotes vaginal recurrences should be discouraged. Routine treatment of sex partners is not considered necessary.

### Asymptomatic BV

The benefits gained from screening asymptomatic BV in order to prevent adverse outcomes are doubtful. While the association between BV and preterm birth is well established, data are inconsistent on the screening and treatment of asymptomatic BV during pregnancy in order to prevent

preterm birth.<sup>77</sup> Despite this, since 2008, the US Preventive Services Task Force recommends against the routine screening for BV in asymptomatic pregnant women. For pregnant women at high risk for preterm birth, the evidence is insufficient to make any recommendation about screening.<sup>78</sup> The Centers for Disease Control and Prevention have made similar recommendations.<sup>76</sup>

Women with BV also have an elevated risk of postoperative infection, especially after surgical abortion in the first trimester. Additional prophylactic antibiotics given to women with asymptomatic BV have not been shown to reduce the risk. As such, evidence to support the usefulness of pre-procedure screening for BV is lacking.<sup>79</sup> The Society of Family Planning does not recommend routine screening for asymptomatic BV but recommends the routine use of antibiotic prophylaxis, preferably with doxycycline, before surgical abortion.

Current recommendations do not advocate treatment of asymptomatic BV in order to reduce the acquisition of sexually transmitted diseases or HIV. Few studies have investigated the benefit of treatment. The first two randomized studies yielded conflicting results on the impact of screening and treatment of sexually transmitted infections, including BV, to prevent HIV acquisition.<sup>80,81</sup> However, a pilot study demonstrated that treatment of asymptomatic BV with metronidazole among HIV-infected women had an impact on HIV-1 shedding in the genital tract.<sup>82</sup> Furthermore, a prospective randomized study suggested that twice-weekly prophylactic use of intravaginal metronidazole gel resulted in significantly fewer cases of chlamydial infection.<sup>83</sup> Based on these data, consideration should be given to routine treatment of women with asymptomatic BV; however, further studies are warranted to confirm these findings.

### Treatment failure

Unfortunately, relapse is frequent after antibiotic treatment. The recurrence rate has been estimated at 58% 12 months after oral metronidazole therapy.<sup>84</sup> There are several possible reasons for the treatment failure. Firstly, the strains of *A. vaginae* have a variable susceptibility for metronidazole with some even showing a high-level resistance.<sup>85</sup> Secondly, resistance to antimicrobial agent may be due to the survival of *A. vaginae* and *G. vaginalis* as a biofilm on the vaginal epithelium after therapy.<sup>9</sup> Lastly, possible reinfection may explain the high recurrence rate as suggested by the highest cure rate observed among women who abstained from having sex or consistently used condoms during treatment.<sup>86</sup>

No recommendations and limited data are available on optimal management strategies for women with recurring BV

**Table 1** Regimens for the treatment of bacterial vaginosis according to the US Centers for Disease Control<sup>76</sup>

Three recommended regimens
1. Metronidazole 500 mg orally twice daily for 7 days
2. Metronidazole gel 0.75%, 1 full application (5 g) intravaginally, once daily for 5 days
3. Clindamycin cream 2%, 1 full application (5 g) intravaginally at bedtime for 7 days
Three alternative regimens
1. Tinidazole 2 g orally once daily for 2 days
2. Tinidazole 1 g orally once daily for 5 days
3. Clindamycin 300 mg orally twice daily for 7 days
4. Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days
Three recommended regimens for pregnant women
1. Metronidazole 500 mg orally twice daily for 7 days
2. Metronidazole 250 mg orally 3 times daily for 7 days
3. Clindamycin 300 mg orally twice daily for 7 days



or in whom treatment failed. It appears as though treatment of recurrent BV may require a combination of modalities.<sup>87</sup> Providers should firstly counsel women with recurrent BV to minimize their number of male sex partners, although few data support recommending other behavioral changes.<sup>88</sup> Then, in the absence of curative therapy, practitioners should resort to retreating each individual episode of BV with a different treatment regimen or extending the duration of therapy from a single dose to a 7-day regimen if needed.<sup>25,89</sup> For women with high risk of recurrence of symptomatic BV, others have suggested suppressive therapy after an initial treatment of BV. Topical boric acid associated with suppressive metronidazole gel or the use of acetic acid vaginal gel has been recommended to keep the vaginal pH at  $\leq 4.5$ .<sup>90,91</sup> Similarly, the use of lactic acid gel after an initial metronidazole treatment should reduce the recurrence of symptomatic BV.<sup>92</sup> Long-term follow-up periods are needed to validate this therapeutic option.

Finally, several studies have evaluated the clinical and microbiological efficacy of probiotics to treat and to prevent the recurrence of BV. Despite the need for more clinical studies, probiotics should be considered as part of the approach to disease prevention, and as an adjunct to antimicrobial treatment.<sup>92</sup>

## Conclusion

Several antimicrobial agents have been used to treat symptomatic BV. Until recently, the mainstay therapy consisted of either metronidazole or clindamycin. A recent alternative has been the use of tinidazole. Probiotics should be seriously considered as part of the approach to disease prevention, and as an adjunct to antimicrobial treatment. Current recommendations do not advocate treatment of asymptomatic BV.

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