Taylor & Francis
Taylor & Francis Group

Postgraduate Medicine

ISSN: 0032-5481 (Print) 1941-9260 (Online) Journal homepage: https://www.tandfonline.com/loi/ipgm20

Bacterial vaginosis: a primer for clinicians

Suzanne Reiter & Susan Kellogg Spadt

To cite this article: Suzanne Reiter & Susan Kellogg Spadt (2019) Bacterial vaginosis: a primer for clinicians, Postgraduate Medicine, 131:1, 8-18, DOI: 10.1080/00325481.2019.1546534

To link to this article: https://doi.org/10.1080/00325481.2019.1546534

Published online: 30 Nov 2018.

Submit your article to this journal

Article views: 629

View related articles

View Crossmark data

Citing articles: 5 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ipgm20

POSTGRADUATE MEDICINE
2019, VOL. 131, NO. 1, 8–18
https://doi.org/10.1080/00325481.2019.1546534

Taylor & Francis
Taylor & Francis Group

CLINICAL FEATURE
REVIEW

Bacterial vaginosis: a primer for clinicians

Suzanne Reiter[a] and Susan Kellogg Spadt[b]

[a]Mid-County Health Center, Largo, FL, USA; [b]Center for Pelvic Medicine, LLC, Rosemont, PA, USA

ABSTRACT

Bacterial vaginosis (BV) affects approximately one third of women in the United States. While often asymptomatic, BV infection may be accompanied by serious health consequences, such as preterm birth and pelvic inflammatory disease, and may facilitate acquisition of sexually transmitted infections. Identifying appropriate patients for screening, such as pregnant women, women planning pregnancy, and women with multiple and/or new sexual partners, is imperative for treatment. Diagnosis of BV has traditionally depended on the presence of vaginal discharge and odor, elevated pH, and clue cells as determined by microscopy, but newer diagnostic modalities that utilize molecular techniques allow for more convenient and accurate testing for BV. Approved treatment options consist of antibiotics administered as oral or intravaginal formulations. Patient counseling and education regarding treatment options, including adherence to prescribed treatments, appropriate hygienic practices, and treatment of symptomatic same-sex partners, are crucial to optimize patient outcomes and prevent recurrence.

ARTICLE HISTORY
Received 27 July 2018
Accepted 7 November 2018

KEYWORDS
Bacterial vaginosis; clindamycin; diagnosis; metronidazole; secnidazole; tinidazole

Introduction

Bacterial vaginosis (BV) is the most common cause of vaginal discharge in women of childbearing age, accounting for nearly half of all cases [1]. In the United States, approximately one third (29%) of women aged 14 to 49 years have either symptomatic or asymptomatic BV [2]. BV is associated with an altered vaginal environment, although at this time it is unclear whether the environment is the cause or the result of BV [3–5]. BV may also be referred to as dysbiosis, which is a general term that may refer to less severe changes in vaginal flora that are not fully classified as BV [6]. Unlike vaginitis, there is no clinical inflammation in BV patients; however, a pro-inflammatory response is observed at the molecular level [7,8]. BV is characterized by a shift from *Lactobacillus* bacterial species to a more diversified population of bacteria that may include a wide range of species, including Gram-negative rods and facultative anaerobes [4,9]. It is important to note that BV represents a general shift in vaginal homeostasis, rather than a one-size-fits-all definition of what constitutes a shift from a 'normal' vaginal microbiome [4,10].

Several risk factors are associated with increased BV prevalence, including sex with multiple partners, sex with women, ethnicity, tobacco use, age, and presence of sexually transmitted infections (Table 1) [11–14]. African-American women have a significantly different vaginal microbiome compared with those of European women [15], and the prevalence of BV has been reported as 50% [2]. Worldwide, the burden of BV is highest in sub-Saharan Africa and in women of sub-Saharan African descent [16]. As women age and estrogen levels decline, there may be a role for hormone levels on the natural history of BV, resulting in abnormal vaginal flora [17]. In one study, the mean estradiol level of women with BV was less than one quarter of that of women with normal flora [17]. Incidence and prevalence of BV is significantly decreased with any hormonal contraceptive use, and recurrence is halved when using estrogen-containing contraceptives [18,19]. Additionally, estrogen replacement therapy in postmenopausal women has been shown to increase colonization of the vaginal microbiome by *Lactobacillus* species in addition to decreasing rates of BV infection [10]. Although not statistically significant, an increase in BV-associated bacteria has been shown in women who smoke cigarettes, potentially due to lower estradiol levels [17], and in those with higher numbers of sexual partners [15].

Vaginal microbiome in women with BV

Recent, nonculture-based studies have demonstrated the diversity of the vaginal microbiome, especially its variability across race/ethnicity groups, leading researchers to reconsider the idea of a 'healthy' or 'normal' vaginal microbial community [20]. Clinical research on the human microbiome led to the inclusion of *Gardnerella, Atopobium, Prevotella, Peptostreptococcus, Mobiluncus, Sneathia, Leptotrichia, Mycoplasma*, and BV-associated bacterium 1 (BVAB1) to BVAB3 in BV pathology [4]. Four distinct clades of *Gardnerella* [21] have been identified, and studies are ongoing to differentiate pathogenic strains of *Gardnerella* from nonpathogenic strains, especially among strains that may be resistant to one of the primary antibiotic treatments for BV – metronidazole [22].

Unlike lactobacilli, which prevent the overgrowth of anaerobes [23], the predominant bacterial species associated with BV produce malodorous volatile amines [24] and are associated with increased vaginal transudation and squamous epithelial cell

CONTACT Suzanne Reiter srreit2@yahoo.com Mid-County Health Center, Largo, FL, USA
© 2018 Informa UK Limited, trading as Taylor & Francis Group

Table 1. Risk factors associated with bacterial vaginosis [11–14].

Risk Factors				
Increased Risk				
Sex with multiple new partners	Sex with women	Non-European ancestry (especially sub-Saharan ancestry)	Tobacco use	Herpes simplex virus or HIV infection
Douching	High-fat diets	Age 15–44 years	Alcohol intake	Stress
Decreased Risk				
European descent	Hormonal contraceptive use	Estrogen replacement therapy	Condom use	

exfoliation [25]. As vaginal epithelial cells are desquamated, they form the classic clue cells that are diagnostic for BV. Clue cells are desquamated epithelial cells that are covered by Gram-negative rods and other bacteria associated with BV [26], and are believed to develop due to exfoliation of the vaginal epithelium [27]. Typical vaginal pH ranges from 4.0 to 4.5, and increases to a level between 4.5 and 7 as BV progresses [28].

Biofilms

Emerging evidence suggests that the high recurrence rates of BV may be due to the inability of standard antibiotics, such as metronidazole, to eradicate the vaginal biofilm completely and/or the negative impacts of antibiotics on healthy vaginal microflora [29,30]. Researchers have demonstrated persistence and recovery of biofilm after antibiotic treatment [31]. Rather than adhering in loosely attached, unstructured accumulations within the vagina, *G. vaginalis* and other bacteria adhere to the vaginal epithelium, thereby contributing to an environment conducive to the development of a biofilm scaffolding that allows other species to adhere [5]. The polymicrobial nature of these biofilms allows for adaptation to many threats to the bacteria's survival, including antibiotic treatment. A study of 146 biopsies investigated the spatial organization of vaginal microbiota, and found that *G. vaginalis*-dominated biofilms do not grow in children, even from mothers with BV. This indicates that single organism exposure is not sufficient for transmission, further highlighting the important role of biofilms in BV [29].

Risk factors

A systematic review and meta-analysis involving 43 observational studies found that sexual contact with new and multiple male and female partners was associated with an increased risk of BV, while condom use was associated with a reduced risk [32]. Although many BV-associated bacterial species have been isolated from the male penile skin, semen, urethra, and urine [33], studies involving the treatment of male sexual partners have yielded mixed results. Furthermore, BV was diagnosed in one quarter to one half of women who have sex with women, particularly those female partners who have a symptomatic BV infection, and the risk of BV increases with a greater number of female sexual partners [34].

Despite these findings that suggest a direct relationship between BV incidence and sexual activity, BV is not classified as a sexually transmitted infection because there is no single causative agent and no clear disease counterpart has been established in men [32,35]. Current Centers for Disease Control and Prevention (CDC) recommendations do not recommend the treatment of sexual partners of women with BV based on these clinical trials; however, female partners would be treated if they were symptomatic or concerned that they also might have BV and sought diagnosis and treatment. With regard to BV and sexually transmitted infections, studies have shown that women who have herpes simplex virus and/or human immunodeficiency virus (HIV) are more likely to develop BV; conversely, BV may also increase the risk of HIV infection [12].

With regard to race and ethnicity, women of non-European ancestry are at a higher risk of developing BV, but it is unclear which genetic, socioeconomic, behavioral, or other differences are associated [2,15]. In a National Health and Nutrition Examination Survey (NHANES) conducted from 2001 to 2004, 51% of African-American women, 32% of Mexican-American women, and 23% of women of European ancestry had BV [2].

Finally, a number of other potential risk factors have been identified as associated with increased BV prevalence, include douching, cigarette smoking, and high-fat diets [36,37]. Women with fertility problems have also been found to have a higher prevalence of asymptomatic vaginosis compared with healthy women [38]. A potential protective role for folate, vitamin E, and calcium has been found against BV [39]. No association has been found between BV and chronic medical conditions such as diabetes or immunosuppressive states.

Symptoms of BV

Approximately 50%–75% of women with BV are asymptomatic [40]. When symptoms are present, the most common presenting symptoms include an off-white, thin, homogenous vaginal discharge and/or an unpleasant vaginal odor or 'fishy smell' that is particularly noticeable after sexual intercourse and around the time of menstruation [40,41]. BV does not cause dysuria, dyspareunia, pruritus, burning, or vaginal inflammation; if present, these symptoms suggest vaginitis due to a different pathogen [8,41,42]. Typically, BV does not involve the cervix, but it can be associated with an endocervical mucopurulent discharge or easily induced cervical bleeding on rare occasions [43].

Consequences of untreated BV infection

Several consequences of untreated BV infection have been identified, including a higher risk of preterm delivery in pregnant women [44,45]; the potential to cause endometrial bacterial colonization, plasma-cell endometritis, postpartum fever,

posthysterectomy vaginal cuff cellulitis, and postabortal infection [46,47]; a higher risk of HIV acquisition and transmission [48]; a higher risk of acquiring herpes simplex virus type 2, gonorrhea, chlamydia, and *Trichomonas* infection [49–51]; a higher association with pelvic inflammatory disease [52]; and a potential association with the development of precancerous cervical lesions, possibly by allowing human papillomavirus infection to persist [53]. Pelvic inflammatory disease, particularly in women aged 15–24 years, has also been associated with vaginal flora organisms that cause BV. However, it has not been definitively established whether the incidence of pelvic inflammatory disease can be reduced by treating women with BV [54].

Diagnosis and differential diagnosis of BV

The Nugent or Hay/Ison criteria to evaluate a Gram-stained vaginal discharge smear represent the gold standard of diagnosing BV. However, because this method requires more time, resources, and expertise than the Amsel criteria, it is usually not utilized in the clinical setting [55,56]. In routine clinical practice, health care providers use the Amsel criteria, which are simple and can be used in any office where microscopy is available [41,56]. Premenopausal women are diagnosed based on the presence of at least three of the four Amsel criteria: characteristic vaginal discharge, elevated pH, clue cells, and fishy odor (Table 2) [41,56,57]. Compared with the Nugent or Hay/Ison criteria, the Amsel criteria for BV diagnosis show a sensitivity of 90% and a specificity of 77% [58]. The Pap smear is not recommended for BV diagnosis as it has high specificity (93%) but low sensitivity (49%) for BV [59]. Vaginal culture is also not appropriate for BV diagnosis: although *G. vaginalis* is nearly always found in BV, it is also found in healthy, asymptomatic women.

Several commercial diagnostic tests are available for the diagnosis of BV. The BD Affirm VPIII microbial identification test (Becton Dickinson and Company, Sparks, Maryland) is a 1-hour multianalyte, nucleic acid probe-based assay system that can identify and differentiate *G. vaginalis, Candida* species, and *T. vaginalis* [60]. Sample preparation takes 10 min (3 min of hands-on time), and clear color results are available after the 33-min automated test [61]. In a study of women with or without BV based on Amsel and Nugent criteria, the BD Affirm VPIII test showed a sensitivity of 90.1% and specificity of 67.6% [60]. The 10-min OSOM BVBlue test (Sekisui Diagnostics, Lexington, Massachusetts) evaluates elevated activity of the enzyme sialidase produced by *Gardnerella, Bacteroides, Prevotella*, and *Mobiluncus* species in vaginal fluid [62]; in a study of 266 women with BV diagnosed based on Nugent criteria (score 7–10), the BVBlue test had a sensitivity of 38% and a specificity of 95% [63]. The recently approved diagnostic BD Max Vaginal Panel, a microbiome-based PCR assay, can detect BV, vulvovaginal candidiasis, and trichomoniasis [64]. These commercial tests play an increasingly important role in the diagnosis of BV, particularly in offices without microscopy, but would likely need to be used in conjunction with other diagnostic methods based on sensitivity and specificity.

For a differential diagnosis, many health care providers anecdotally maintain that a lack of fishy odor (negative whiff test) makes the diagnosis of BV unlikely. Additionally, practitioners note that although women with BV typically have a high vaginal pH (>4.5), trichomoniasis, atrophic vaginitis, and desquamative inflammatory vaginitis can also cause high vaginal pH. In these cases, clinical and microscopic features are used to distinguish whether symptoms are due to BV or other causes.

Treatment of incident BV by pregnancy and symptom status

The treatment of incident BV can be categorized by pregnancy status and whether or not symptoms are present.

Nonpregnant women with asymptomatic BV

For women with BV who are about to undergo a hysterectomy or pregnancy termination, treatment of asymptomatic BV may prevent postprocedure infection and reduce postoperative complications by 10%–75% [65–69]. Although evidence suggests that treatment of nonpregnant women with asymptomatic BV may reduce the risk of acquiring sexually transmitted infections [70], including *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium* [51,70], *T. vaginalis* [71], HIV [72], and herpes simplex type 2 [50], the overall potential benefits of treating women with asymptomatic BV to prevent the transmission of sexually transmitted diseases remains the subject of debate.

Pregnant women with asymptomatic BV

Approximately one third of pregnant women in the United States have BV [45,73]. The results of a large meta-analysis demonstrated that BV is associated with a two-fold increased risk of preterm birth potentially due to chorioamnionitis [74], a 2.5-fold higher risk of postpartum endometritis, and a 6.3-fold higher chance of miscarriage late in pregnancy [73]. Although treatment of pregnant women with asymptomatic BV has been shown to reduce the incidence of preterm

Table 2. Amsel criteria [41,56,57].

- Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls
- Vaginal pH >4.5
- Positive whiff-amine test, defined as the presence of a fishy odor when a drop of 10% potassium hydroxide (KOH) is added to a sample of vaginal discharge
- Clue cells on saline wet mount

- Clue cells are vaginal epithelial cells studded with adherent coccobacilli that are best appreciated at the edge of the cell
- For a positive result, at least 20% of the epithelial cells on wet mount should be clue cells
- The presence of clue cells diagnosed by an experienced microscopist is the single most reliable predictor of BV

Table 3. Treatment options for bacterial vaginosis [56,84–89].

Current CDC Guidelines		
Treatment Option	Common Adverse Effects	Clinical Pearls
Recommended Regimens		
Metronidazole 500 mg orally twice a day for 7 days	Abdominal discomfort, nausea, dizziness, vaginitis	Avoid alcohol until 24 h after completion
Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days	Abdominal discomfort, headache, dizziness, vaginitis	
Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days	*Candida* vaginitis, diarrhea, dry skin, nausea	May weaken latex condoms and diaphragms for 5 days after use
Alternative Regimens		
Tinidazole 1 or 2 g orally once daily for 2 days	Nausea, altered taste sense, *Candida* vaginitis	Avoid alcohol until 72 h after completion
Clindamycin 300 mg orally twice daily for 7 days	Morbilliform-like skin rashes, abdominal pain, diarrhea, nausea	
Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days	Dry skin, morbilliform eruption, nausea, *Candida* vaginitis, vaginal pain	Ovules may weaken latex or rubber condoms and diaphragms for 72 h after treatment
Additional Treatment Options Not Currently in CDC Guidelines		
Secnidazole 1 or 2 g orally once	Nausea, headache, *Candida* vaginitis	May be sprinkled into applesauce, yogurt, or pudding
Lactoferrin 100 or 200 mg vaginal pessaries once daily for 10 days	Mild nausea, diarrhea, and abdominal discomfort associated with oral lactoferrin	

labor or delivery, current American College of Obstetricians and Gynecologists (ACOG), US Preventive Services Task Force (USPSTF), CDC, and Society of Obstetricians and Gynecologists of Canada guidelines do not recommend routine screening and treatment of asymptomatic pregnant women [56,65,75,76]. When BV treatment is considered, selecting the optimal antibiotic can be challenging, as trials involving the use of metronidazole and clindamycin during pregnancy to reduce the risk of preterm birth in high-risk women have yielded conflicting results [77–80].

The results of a meta-analysis and UK guidelines recommend universal antibiotic prophylaxis of women prior to elective termination of a pregnancy [69,81]. However, in a randomized trial of 638 women who screened positive for BV prior to elective termination, no reduction in post-procedure complications was observed with prophylactic treatment with metronidazole plus doxycycline compared with placebo treatment (21% vs. 19%, respectively) [68].

Nonpregnant women with symptomatic BV

Prior to the approval of secnidazole for the treatment of BV in adult women in 2017, no new drugs had been approved for BV treatment in the past decade in the United States. For symptomatic women, the goal of BV treatment is to provide symptom relief. The 2015 CDC Sexually Transmitted Disease Treatment Guidelines recommend treatment of BV for all women with BV symptoms [56].

Pregnant women with symptomatic BV

Oral BV treatment is effective and should be given to all pregnant women with symptomatic BV, as it has not been associated with adverse fetal or obstetrical effects [82,83]. Therapeutic options to date include oral, systemic (rather than intravaginal) treatments, including metronidazole 500 mg twice daily for 7 days, metronidazole 250 mg three times daily for 7 days, or clindamycin 300 mg twice daily for 7 days. Importantly, according to the prescribing information, the use of metronidazole for the treatment of trichomoniasis and, by extrapolation, for BV during pregnancy should be restricted to patients for whom alternative treatment was inadequate.

Selecting BV treatment

Metronidazole and clindamycin

Approved treatments for BV include members of the nitroimidazole class of drugs, which includes metronidazole, tinidazole, and secnidazole, as well as clindamycin (Table 3) [56,84–89]. Nitroimidazoles are antimicrobial agents that are used to treat trichomoniasis, amebiasis, and anaerobic bacterial infections, and they act by interfering with DNA synthesis. Current CDC guidelines recommend multidose oral or intravaginal formulations of metronidazole and clindamycin, as well as oral tinidazole [56,90,91]. The cure rate for twice-daily oral 500 mg doses of metronidazole is 58% using the revised definition of clinical cure rate (resolution of 3 of 4 Amsel criteria and Nugent score <4) at 4 weeks [92]. A similar clinical cure rate (resolution of all 4 Amsel criteria or Nugent score <4) was observed with 7-day clindamycin cream treatment [90]. After 4 weeks, symptomatic treatment of nonpregnant women with oral or intravaginally administered metronidazole or clindamycin yields a clinical cure rate of 70%–80% using various definitions of cure [93]. Selection of metronidazole or clindamycin is made on the basis of availability, patient preference, side effects, and cost. Although the oral route of administration is more convenient than intravaginal administration, oral metronidazole and clindamycin are also associated with adverse effects such as headache, nausea, abdominal pain, and *Clostridium difficile* diarrhea due to systemic absorption. According to CDC guidelines and the metronidazole package insert, alcoholic beverages should not be consumed during metronidazole therapy and for at least 1 day afterward due to a possible disulfiram-like reaction, including abdominal cramps, nausea, vomiting, headaches, and flushing [56].

Single-dose intravaginal treatments are available for the treatment of BV, namely, clindamycin cream and metronidazole gel [90,91]. Single-dose clindamycin cream (2% clindamycin phosphate) yielded clinical and microbiologic cure rates of 64% and 57%, respectively [90], whereas single-dose 1.3% metronidazole gel yielded clinical and microbiologic cure rates of 37% and 18% at the 21-day visit [91]. It is unknown why microbiologic cure rates lag behind clinical cure rates and at which point lactobacilli species recover to reflect a healthy vaginal environment. Metronidazole gel 0.75% is indicated for the treatment of BV in nonpregnant women and is used intravaginally once or twice per day for 5 days. Clinical cure rates assessed 4 weeks after completion of therapy were 98/185 (53%) for the daily and 109/190 (57%) for twice-daily regimens [94]. Since clindamycin cream is oil-based, there is a potential to weaken latex condoms and diaphragms if used within 5 days of clindamycin treatment [56].

Tinidazole

Tinidazole is a second-generation nitroimidazole that is more expensive than metronidazole because there is no generic formulation available, but it also has a longer half-life than metronidazole (12–14 h vs. 6–7 h) and a better side-effect profile [95]. The efficacy of tinidazole is not inferior to that of metronidazole [96], and a single-dose regimen is at least as effective as vaginal clindamycin cream [97]. A randomized, controlled trial evaluated the efficacy of two regimens of oral tinidazole, 1 g/day for 5 days or 2 g for 2 days, compared with placebo. After 21–30 days of treatment using strict US Food and Drug Administration (FDA) criteria to define cure, the cure rates were 37% for 1 g/day for 5 days and 27% for 2 g/day for 2 days compared with 5% in placebo-treated patients [98]. In a recent comparison of tinidazole and oral metronidazole, lower-dose tinidazole (500 mg once daily for 5 days) yielded better efficacy than oral metronidazole (500 mg twice daily for 5 days) in terms of cure rates at 4 weeks (94% vs. 75%, $P = 0.0013$), and fewer patients presented with either relapse or reinfection with tinidazole (0 patients) than metronidazole (13 patients). Moreover, there were significantly fewer reports of gastrointestinal irritation in patients treated with tinidazole compared with metronidazole (2 vs. 28, $P = 0.03$) [99].

Secnidazole (SYM-1219)

Secnidazole (SYM-1219) is a novel granular formulation member of the family of 5-nitroimidazoles that was approved in the United States in 2017 for the treatment of BV [100]. This granular formulation is designed to be sprinkled into applesauce, yogurt, or pudding and consumed without chewing the granules. Prior to US approval, secnidazole was used in Europe and Asia to treat BV, trichomoniasis, and other conditions. *In vitro* studies with secnidazole demonstrated clinical and microbiologic evidence of activity against many anaerobic Gram-positive and Gram-negative bacteria implicated in BV [101] and limited activity against beneficial lactobacilli species [92,102,103]. Pharmacokinetic/pharmacodynamic studies of secnidazole have been favorable, showing rapid absorption, high bioavailability, low intersubject variability, longer half-life, high potency, and minimal potential for interactions with CYP450 substrates, inhibitors, or inducers, supporting its use as a single-dose treatment for BV [104,105]. Additionally, the results of a thorough QT/QTc evaluation of the cardiac safety of secnidazole at therapeutic and supratherapeutic doses in healthy individuals demonstrated that secnidazole does not have any clinically concerning effect on ECG parameters, including QT interval [106].

The safety profile of secnidazole is well established, given the long history of successful use of secnidazole outside the United States to treat BV and parasitic diseases [92,101,102]. Secnidazole has been shown to be safe and well tolerated in women with BV, including having no effect of single-dose secnidazole on either the estrogen or progestin components of combined oral contraceptives, ensuring maintenance of contraceptive efficacy [107]. Additionally, there is no contraindication for the use of secnidazole in the United States with alcohol, as there is for other BV drugs [56,100].

Results from a randomized, double-blind, noninferiority trial showed that a single 2 g dose of oral secnidazole was at least as effective as a 7-day course of metronidazole 500 mg administered twice per day [92]. In a randomized study of 76 women, a single 1 g oral dose of secnidazole also demonstrated efficacy compared with a single 2 g dose of oral secnidazole, with clinical cure rates of 95.5% and 97.4%, respectively [102]. Although no head-to-head comparisons have been performed, clinical and microbiologic cure rates for single-dose oral treatment with secnidazole granules (68% and 40%, respectively) are similar to those of single-dose clindamycin cream (53% and 46%) and 1.3% metronidazole gel (37% and 19%, respectively). Of note, the FDA requirements for BV clinical trials have changed since the secnidazole trials were conducted; these changes include a Nugent score ≥7 at enrollment (previously ≥4), a test-of-cure visit at 7–14 days after randomization (previously 21–30 days), and revising the definition of clinical responders to include the absence of abnormal discharge in addition to normal discharge [108].

All of the pivotal secnidazole trials included an ethnically diverse patient population of a large percentage of African-American women. It was observed that a single 1 g or 2 g dose of oral secnidazole was superior to placebo, with clinical outcome responder rates of 68% for 2 g secnidazole vs. 18% for placebo, even in patients with recurrent infection [109]. The second pivotal clinical trial designed to support licensure confirmed that a single dose of 2 g secnidazole yielded a clinical outcome responder rate of 53.3% (57/107) vs. 19.3% (11/57; $P < 0.001$) in placebo-treated patients [105]. Using an alternate definition of responder that accounted for resolution of abnormal discharge consistent with BV or normal discharge, similar results were reported with a clinical outcome responder rate of 58.9% versus 24.6% ($P < 0.001$) for single-dose secnidazole versus placebo [105].

Most currently available BV treatments require patients to take medication for 5–7 days [56]. As the length and complexity of the drug regimen increases, adherence decreases. Low adherence can contribute to treatment failure, recurrent and/or chronic disease, higher health care costs, and possibly more rapid development of resistance among vaginal bacteria [110]. Studies have shown that approximately half of patients do not comply with a 5- or 7-day antimicrobial regimen [111]. Thus,

the convenience of single-dose secnidazole treatment may improve patient adherence and overall outcomes.

Other agents

Pre- and probiotics

Several other treatments for BV have also been investigated. Probiotic formulations containing lactobacilli strains have been shown to reduce BV symptoms, disrupt, and eradicate vaginal pathogenic biofilms, and restore 'normal' microflora [112,113]. Probiotics are often used alone or with antibiotic therapy to treat and prevent relapse of BV. However, further studies are required to determine the optimal route of administration, bacterial strains, and dose and duration of use [114]. Low-quality evidence suggests that adjuvant probiotic therapy may increase the rate of short-term clinical or mycological cure compared with conventional pharmacotherapy [115]. In the 2015 Sexually Transmitted Diseases Treatment Guidelines, the CDC does not recommend the use of probiotics due to no conclusive studies supporting their use [84].

Lactoferrin

Lactoferrin, an iron-binding glycoprotein prebiotic with both bacteriostatic and bactericidal properties, has been shown in an open-label, prospective, randomized trial to be effective in shifting the vaginal microbiome away from *Gardnerella, Prevotella*, and *Lachnospira* and toward *Lactobacillus* species when administered as 100 or 200 mg vaginal pessaries [116]. Case studies have demonstrated that lactoferrin may play a role in preventing refractory vaginitis, cervical inflammation, and preterm delivery [117].

Biofilm disruptors

Given the increasing evidence that BV is a biofilm-mediated infection, a number of novel biofilm disrupting agents, such as DNases, retrocyclins, probiotics, antiseptics, natural antimicrobials, and plant-derived compounds are being investigated [118]. The antiseptic agent dequalinium chloride has recently demonstrated similar efficacy as clindamycin 2% cream for the treatment of BV [119].

Thymol, a molecule present in thyme essential oil, has demonstrated an inhibitory effect on biofilms *in vitro* [120]. Natural antimicrobials, primarily bacteriocins, may improve cure rates of antibiotic therapies when used in combination with conventional antibiotics, especially those in which bacterial resistance has developed [118]. Vaginal acidification through the application of acidifying agents, such as vitamin C or buffering agents (polycarbophil or boric acid), used in combination with a nitroimidazole antibiotic have been shown to reduce BV recurrence, potentially through the disruption of the vaginal biofilm [118]. Additional promising therapeutic agents for the treatment of BV include DNase agents that may disrupt vaginal biofilms by targeting the extracellular DNA that are essential to their structural integrity [121] and retrocyclin 101, a synthetic cyclic antimicrobial peptide that inhibited the growth and biofilm formation of *G. vaginalis in vitro* [122].

Recently, an amphoteric tenside (WO3191) pessary was found to disrupt biofilms after metronidazole treatment and promote growth of *Lactobacillus* species [123]. In other studies, two series of cationic amphiphiles (CAms) acted synergistically with metronidazole to disrupt and control biofilm formation by BV pathogens [124]. Given that currently approved BV treatments are insufficient to deal with this multispecies, biofilm-related vaginal disorder as evidenced by the high recurrence and relapse rates, future research should be conducted to identify and evaluate these novel, biofilm-disrupting treatment strategies.

Special considerations/challenges

Breastfeeding women

Vaginal metronidazole or clindamycin may be preferable over an orally administered medication in breastfeeding women because only approximately 30% of an intravaginally administered dose of either drug is systemically absorbed. When treating women with symptomatic BV who are breastfeeding with clindamycin, it is important for health care providers to monitor infants for diarrhea, candidiasis (thrush and/or diaper rash), and blood in the stool that may indicate possible antibiotic-associated colitis [125]. Breastfeeding women who are treated with a single, 2 g oral dose of metronidazole are advised to express and discard their breast milk for 12–24 h because infant drug exposure is higher with an oral than an intravaginal dose (29% vs. <2%) [125]. Similarly, breastfeeding women treated with tinidazole or secnidazole are advised to interrupt breastfeeding during treatment and for 3 days (tinidazole) or 4 days (secnidazole) after the last dose as a precautionary measure [56,100].

Relapses and recurrent infection with BV

Approximately 39% of women who initially respond to BV treatment experience symptom recurrence within 3 months, and more than half experience a recurrence within the subsequent 12 months [126]. Although the high rate of recurrence may be due to reinfection, it is more likely due to a failure to eradicate the pathogens responsible for the incident case of BV, or a failure to restore the protective vaginal *Lactobacillus* populations [127]. Specifically, BV infection within the vaginal biofilm may be particularly difficult to eradicate. Deep-sequencing techniques have shed light on the changes in the vaginal microbiome with treatment overtime [128]. Using multiplex PCR detection methods, a high frequency of infection with key BV-related pathogens was observed in childbearing women and correlated with the severity of infection as well as complicated and recurrent BV [129]. Treatment failure after oral metronidazole is not associated with higher loads of *G. vaginalis* and/or *A. vaginae* [130].

Limited data are available to guide health care providers in selecting the optimal treatment strategy for women who experience recurrent BV infection [56]. Many health care providers choose to repeat the same treatment regimen that was used with incident BV infection. In these cases, a 7-day course of oral metronidazole or clindamycin, or a single dose of oral secnidazole, vaginal metronidazole gel 1.3%, or vaginal clindamycin cream is generally appropriate. Women who exhibit more than three documented BV recurrences within the

previous year may benefit from a long-term maintenance regimen of metronidazole gel 0.75% or an oral nitroimidazole for 7–10 days followed by twice-weekly gel administration for 4–6 months [56]; neither oral nor intravaginal clindamycin regimens are advised for long-term or maintenance therapy [19]. Less well-studied treatment options for recurrent BV infections include combination therapy with metronidazole plus fluconazole or miconazole [131,132]. Use of condoms and abstinence have also been reported to prevent recurrence of BV [19,72,126].

Psychosexual sequelae of chronic bacterial vaginosis

There are significant psychosexual sequelae in women with chronic BV. Interviews conducted with 35 women with male and/or female partners about their experiences with recurrent BV found no significant differences between heterosexual and bisexual women [133]. Overall, women experienced between 2 and 35 distinct, recurrent episodes of BV that were primarily characterized by abnormal discharge and malodor. The majority of women in this study reported a moderate to severe impact of BV on their physical, emotional, sexual, and social lives. Women who experienced more frequent episodes (≥ 4) and more severe symptoms were most likely to experience moderate to severe impact. Physically, the most common impact was malodor followed by profuse discharge. Emotionally, women felt embarrassed, self-conscious, uncomfortable, disgusted, ashamed, dirty, annoyed, and distressed – especially due to a lack of control with regard to if or when recurrences occurred. Sexually, women were concerned that their partners would be offended by the smell and therefore avoided sexual activity. Overall, many of the women reported a decrease in self-esteem and self-confidence because of BV. Finally, although most women did not feel that recurrent/chronic BV affected their work or social lives, some limited their social interactions or took care to sit or stand away from their colleagues.

Role of clinicians in educating/counseling women about BV

Clinicians play a critical role in educating women regarding the risk factors that may predispose them to BV infection or reinfection. Topics of discussion include considering abstinence, limiting the number of sexual partners, avoiding douching, and presenting them with the latest evidence on how screening and/or treatment of female sex partners may help to improve patient outcomes. Women with BV and other vaginal complaints commonly self-medicate with intensive hygiene regimens and over-the-counter remedies that have little benefit and may actually increase the likelihood of recurrence [134,135]. Timely communication with patients to avoid these practices may help prevent BV recurrence.

Clinicians also play an important role in identifying BV and differentiating it from vulvovaginal candidiasis and trichomoniasis, and in assessing BV before and during pregnancy [136]. Although it is not current practice to screen for asymptomatic BV in pregnant women or those planning pregnancy, it is important to consider the consequences of untreated BV in this patient population. In assessing BV, clinicians must use resources such as laboratory tests and medications wisely, and some opt for pH testing as a fast and low-cost method to obtain a preliminary BV diagnosis. A recent study conducted in a primary care setting found that self-administered vaginal swabs were a valid alternative to clinician-administered high vaginal swabs for detecting BV [137].

With several FDA-approved treatment options for BV, a discussion between the clinician and patient to review the available treatments may improve treatment adherence and outcomes. Each treatment has a unique side-effect profile and frequency and/or mode of administration. For example, patients should refrain from consuming alcohol while using oral or vaginal metronidazole; if this recommendation cannot be adhered to, an alternate treatment option without an alcohol interaction should be considered. While some patients may prefer vaginal formulations for lower systemic absorption and correspondingly decreased incidence of adverse events, other patients may prefer the ease of administration associated with oral formulations. Timely and appropriate screening, diagnosis, and counseling regarding behaviors as well as treatment options are necessary to optimize outcomes of patients with BV.

Author contributions

The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this manuscript. Both authors contributed to the research, writing, and reviewing of all drafts of this manuscript and approved the final version.

Funding

Editorial support in preparation of this manuscript was provided by Phase Five Communications, funded by Symbiomix Therapeutics, LLC.

Declaration of interest

S. Kellogg Spadt has been a consultant for Deka Development and Research Corporation, Materna, AMAG Pharmaceuticals, Inc., Ipsen, Duchesnay, TherapeuticsMD, and Lupin Pharmaceuticals, Inc. S. Reiter has been a consultant for Hologic Inc. and Lupin Pharmaceuticals, Inc./Symbiomix Therapeutics, LLC. The authors have no other 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. Peer reviewers on this manuscript have no relevant financial relationships to disclose.

References

1. Morris M, Nicoll A, Simms I, et al. Bacterial vaginosis: a public health review. BJOG. 2001;108:439.
2. Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001–2004 National Health and Nutrition Examination Survey date. Obstet Gynecol. 2007;109:114–120.
3. Murphy K, Mitchell CM. The interplay of host immunity, environment and the risk of bacterial vaginosis and associated reproductive health outcomes. J Infect Dis. 2016;214(suppl 1):S29–S35.
4. Onderdonk AB, Delaney ML, Fichorova RN. The human microbiome during bacterial vaginosis. Clin Microbiol Rev. 2016;29(2):223–238.
5. Jung HS, Ehlers MM, Lombaard H, et al. Etiology of bacterial vaginosis and polymicrobial biofilm formation. Crit Rev Microbiol. 2017;43(6):651–667.

6. Campisciano G, Zanotta N, Licastro D, et al. In vivo microbiome and associated immune markers: new insights into the pathogenesis of vaginal dysbiosis. Sci Rep. 2018;8(1):2307.
7. Thurman AR, Kimble T, Herold B, et al. Bacterial vaginosis and subclinical markers of genital tract inflammation and mucosal immunity. AIDS Res Hum Retroviruses. 2015;31(11):1139–1152.
8. Sobel JD, Subramanian C, Foxman B, et al. Mixed vaginitis—more than coinfection and with therapeutic implications. Curr Infect Dis Rep. 2013;15(2):104–108.
9. Lamont RF, Sobel JD, Akins RA, et al. The vaginal microbiome: new information about genital tract flora using molecular based techniques. BJOG. 2011;118(5):533–549.
10. Muhleisen AL, Herbst-Kralovetz MM. Menopause and the vaginal microbiome. Maturitas. 2015;91:42–50.
11. Bagnall P, Rizzolo D. Bacterial vaginosis: a practical review. JAAPA. 2017;30(12):15–21.
12. Esber A, Vicetti Miguel RD, Cherpes TL, et al. Risk of bacterial vaginosis among women with herpes simplex virus type 2 infection: a systematic review and meta-analysis. J Infect Dis. 2015;212(1):8–17.
13. Centers for Disease Control and Prevention. Bacterial Vaginosis – CDC Fact Sheet. Atlanta, GA: CDC; 2017. [cited 2018 Oct 3] Available from: https://www.cdc.gov/std/bv/stdfact-bacterial-vaginosis.htm
14. Ranjit E, Raghubanshi BR, Maskey S, et al. Prevalence of bacterial vaginosis and its association with risk factors among nonpregnant women: a hospital based study. Int J Microbiol. 2018;2018:8349601.
15. Fettweis JM, Brooks JP, Serrano MG, et al. Differences in vaginal microbiome in African American women versus women of European ancestry. Microbiology. 2014;160(Pt 10):2272–2282.
16. Van de Wijgert JHHM, Jespers V. The global health impact of vaginal dysbiosis. Res Microbiol. 2017;168(9–10):859–864.
17. Wilson JD, Lee RA, Balen AH, et al. Bacterial vaginal flora in relation to changing oestrogen levels. Int J STD AIDS. 2007;18(5):308–311.
18. Vodstrcil LA, Hocking JS, Law M, et al. Hormonal contraception is associated with a reduced risk of bacterial vaginosis: a systematic review and meta-analysis. PLoS One. 2013;8(9):e73055.
19. Bradshaw CS, Vodstrcil LA, Hocking JS, et al. Recurrence of bacterial vaginosis is significantly associated with posttreatment sexual activities and hormonal contraceptive use. Clin Infect Dis. 2013;56(6):777–786.
20. Power ML, Quaglieri C, Schulkin J. Reproductive microbiomes: a new thread in the microbial network. Reprod Sci. 2017;24(11):1482–1492.
21. Schellenberg JJ, Patterson MH, Hill JE. *Gardnerella vaginalis* diversity and ecology in relation to vaginal symptoms. Res Microbiol. 2017;168(9–10):837–844.
22. Janulaitiene M, Paliulyte V, Grinceviciene S, et al. Prevalence and distribution of *Gardnerella vaginalis* subgroups in women with and without bacterial vaginosis. BMC Infect Dis. 2017;17(1):394.
23. Tachedjian G, O'Hanion DE, Ravel J. The implausible "in vivo" role of hydrogen peroxide as an antimicrobial factor produced by vaginal microbiota. Microbiome. 2018;6(1):29.
24. Wolrath H, Forsum U, Larsson PG, et al. Analysis of bacterial vaginosis-related amines in vaginal fluid by gas chromatography and mass spectrometry. J Clin Microbiol. 2001;39(11):4026–4031.
25. Hodiwala AB, Koli A. Bacterial vaginosis. Int J Curr Microbiol App Sci. 2015;4(6):530–538.
26. Cook RL, Reid G, Pond DG, et al. Clue cells in bacterial vaginosis: immunofluorescent identification of the adherent gram-negative bacteria as *Gardnerella vaginalis*. J Infect Dis. 1989;160(3):490–496.
27. Amegashie CP, Gilbert NM, Peipert JF, et al. Relationship between Nugent score and vaginal epithelial exfoliation. PLoS One. 2017;12(5):e0177797.
28. Brogden KA, Guthmiller JM, eds. Polymicrobial Diseases. Washington, DC: ASM Press; 2002.
29. Swidsinski A, Loening-Baucke V, Mendling W, et al. Infection through structured polymicrobial *Gardnerella* biofilms (StPM-GB). Histol Histopathol. 2014;29(5):567–587.
30. Castro J, Cerca N. BV and non-BV associated *Gardnerella vaginalis* establish similar synergistic interactions with other BV-associated microorganisms in dual-species biofilms. Anaerobe. 2015;36:56–59.
31. Hay P. Bacterial vaginosis. F1000Res. 2017;6:1761.
32. Fethers KA, Fairley CK, Hocking JS, et al. Sexual risk factors and bacterial vaginosis: a systematic review and meta-analysis. Clin Infect Dis. 2008;47(11):1426-1435.
33. Nelson DE, Dong Q, Van der Pol B, et al. Bacterial communities of the coronal sulcus and distal urethra of adolescent males. PLoS One. 2012;7(5):e36298.
34. Bradshaw CS, Walker SM, Vodstrcil LA, et al. The influence of behaviors and relationships on the vaginal microbiota of women and their female partners: the WOW Health Study. J Infect Dis. 2014;209(10):1562–1572.
35. Bradshaw CS, Morton AN, Garland SM, et al. Higher-risk behavioral practices associated with bacterial vaginosis compared with vaginal candidiasis. Obstet Gynecol. 2005;106(1):105–114.
36. Brotman RM, Klebanoff MA, Nansel TR, et al. A longitudinal study of vaginal douching and bacterial vaginosis—a marginal structural modeling analysis. Am J Epidemiol. 2008;168(2):188-196.
37. Klebanoff MA, Nansel TR, Brotman RM, et al. Personal hygienic behaviors and bacterial vaginosis. Sex Trans Dis. 2010;37(2):94–99.
38. Babu G, Singaravelu BG, Srikumar R, et al. Comparative study on the vaginal flora and incidence of asymptomatic vaginosis among healthy women and in women with infertility problems of reproductive age. J Clin Diagn Res. 2017;11(8):DC18–DC22.
39. Neggers YH, Nansel TR, Andrews WW, et al. Dietary intake of selected nutrients affects bacterial vaginosis in women. J Nutr. 2007;137(9):2128–2133.
40. Klebanoff MA, Schwebke JR, Zhang J, et al. Vulvovaginal symptoms in women with bacterial vaginosis. Obstet Gynecol. 2004;104(2):267–272.
41. Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74:14–22.
42. Klebanoff MA, Huath JC, MacPherson CA, et al. Time course of the regression of asymptomatic bacterial vaginosis in pregnancy with and without treatment. Am J Obstet Gynecol. 2004;190(2):363–370.
43. Marrazzo JM, Wiesenfeld HC, Murray PJ, et al. Risk factors for cervicitis among women with bacterial vaginosis. J Infect Dis. 2006;193(5):617–624.
44. Flynn CA, Helwig AL, Meureer LN. Bacterial vaginosis in pregnancy and the risk of prematurity: a meta-analysis. J Fam Pract. 1999;48(11):885–892.
45. Klebanoff MA, Hillier SL, Nugent RP, et al. Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation? Am J Obstet Gynecol. 2005;192(2):470–477.
46. Andrews WW, Klebanoff MA, Thom EA, et al. Midpregnancy genitourinary tract infection with *Chlamydia trachomatis*: association with subsequent preterm delivery in women with bacterial vaginosis and *Trichomonas vaginalis*. Am J Obstet Gynecol. 2006;194(2):493–500.
47. Oleen-Burkey MA, Hillier SL. Pregnancy complications associated with bacterial vaginosis and their estimated costs. Infect Dis Obstet Gynecol. 1995;3(4):149–157.
48. Cohen C, Lingappa JR, Baeten JM, et al. Bacterial vaginosis associated with increased risk of female-to-male HIV-1 transmission: a prospective cohort analysis among African couples. PLoS Med. 2012;9:e1001251.
49. Balkus JE, Richardson BA, Rabe LK, et al. Bacterial vaginosis and the risk of *Trichomonas vaginalis* acquisition among HIV-1-negative women. Sex Trans Dis. 2014;41(2):123–128.
50. Cherpes TL, Megyn LA, Krohn MA, et al. Association between acquisition of herpes simplex virus type 2 in women and bacterial vaginosis. Clin Infect Dis. 2003;37(3):319–325.
51. Wiesenfeld HC, Hillier SL, Krohn MA, et al. Bacterial vaginosis is a strong predictor of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection. Clin Infect Dis. 2003;36(5):663–668.
52. Ness RB, Hillier SL, Kip KE, et al. Bacterial vaginosis and risk of pelvic inflammatory disease. Obstet Gynecol. 2004;104(4):761–769.

53. Gillet E, Meys JF, Verstraelen H, et al. Association between bacterial vaginosis and cervical intraepithelial neoplasia: systematic review and meta-analysis. PLoS One. 2012;7(10):e45201.
54. Risser WL, Risser JM, Risser AL. Current perspectives in the USA on the diagnosis and treatment of pelvic inflammatory disease in adolescents. Adolesc Health Med Ther. 2017;8:87–94.
55. Tam MT, Yungbluth M, Myles T. Gram stain methods shows better sensitivity than clinical criteria for detection of bacterial vaginosis in surveillance of pregnant, low-income women in a clinical setting. Infect Dis Obstet Gynecol. 1998;6(5):204–208.
56. Workowski KA, Bolan GA. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(RR–03):1–137.
57. Eschenbach DA, Hillier S, Critchlow C, et al. Diagnosis and clinical manifestations of bacterial vaginosis. Am J Obstet Gynecol. 1988;158(4):819-828.
58. Landers DV, Wiesenfeld HC, Heine RP, et al. Predictive value of the clinical diagnosis of lower genital tract infection in women. Am J Obstet Gynecol. 2004;190(4):1004–1010.
59. Greene JF 3rd, Kuehl TJ, Allen SR. The papanicolaou smear: inadequate screening test for bacterial vaginosis during pregnancy. Am J Obstet Gynecol. 2000;182(5):1048–1049.
60. Cartwright CP, Lembke BD, Ramachandran K, et al. Comparison of nucleic acid amplification assays with BD Affirm VPIII for diagnosis in vaginitis in symptomatic women. J Clin Microbiol. 2013;5 (11):3694–3699.
61. Becton, Dickinson and Company. BD Diagnostics Affirm brochure; December 2010. Sparks, MD: BD Diagnostics. Available from https://www.bd.com/Documents/bd-legacy/brochures/molecular-diagnostics/BD_Affirm-VPIII-Brochure-PE_TR.pdf.
62. Bradshaw CS, Morton AN, Garland SM, et al. Evaluation of a point-of-care test, BVBlue, and clinical and laboratory criteria for diagnosis of bacterial vaginosis. J Clin Microbiol. 2005;43 (3):1304–1308.
63. Madhivanan P, Krupp K, Li T, et al. Performance of BVBlue rapid test in detecting bacterial vaginosis among women in Mysore, India. Infect Dis Obstet Gynecol. 2014;2014:908313.
64. Van Der Pol B. Profile of the triplex assay for detection of chlamydia, gonorrhea and trichomonas using the BD MAX™ System. Expert Rev Mol Diagn. 2017;17(6):539–547.
65. American College of Obstetricians and Gynecologists. Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012;120:964.
66. Crowley T, Low N, Turner A, et al. Antibiotic prophylaxis to prevent post-abortal upper genital tract infection in women with bacterial vaginosis: randomized controlled trial. BJOG. 2001;108(4):396–402.
67. Larsson PG, Carlsson B. Dose pre- and postoperative metronidazole treatment lower vaginal cuff infection rate after abdominal hysterectomy among women with bacterial vaginosis? Infect Dis Obstet Gynecol. 2002;10(3):133–140.
68. Miller L, Thomas K, Hughes JP, et al. Randomised treatment trial of bacterial vaginosis to prevent post-abortion complication. BJOG. 2004;111(9):982–988.
69. Penney GC, Ghomspon M, Norman J, et al. A randomized comparison of strategies for reducing infective complications of induced abortion. Br J Obstet Gynaecol. 1998;105(6):599–604.
70. Balkus JE, Manhart LE, Lee J, et al. Periodic presumptive treatment for vaginal infections may reduce the incidence of sexually transmitted bacterial infections. J Infect Dis. 2016;213 (12):1932–1937.
71. Brotman RM. Vaginal microbiome and sexually transmitted infections: an epidemiologic perspective. J Clin Invest. 2011;121 (12):4610–4617.
72. Schwebke JR, Desmond R. A randomized trial of metronidazole in asymptomatic bacterial vaginosis to prevent the acquisition of sexually transmitted diseases. Am J Obstet Gynecol. 2007;196 (6):517.e1-e6.
73. Leitich H, Kiss H. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. Best Pract Res Clin Obstet Gynaecol. 2007;21(3):375–390.
74. Hillier SL, Martius J, Krohn M, et al. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med. 1988;319(15):972–978.
75. Nygren P, Fu R, Freeman M, et al. Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: an updated review for the US Preventive Services Task Force. Ann Intern Med. 2008;148 (3):220–233.
76. Yudin MH, Money DM. No. 211—screening and management of bacterial vaginosis in pregnancy. J Obstet Gynaecol Can. 2017;39 (8):e184–e191.
77. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N Engl J Med. 1995;333(26):1732–1736.
78. McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (*Gardnerella vaginalis*): a randomized, placebo controlled trial. Br J Obstet Gynaecol. 1997;104(12):1391–1397.
79. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. Am J Obstet Gynecol. 1994;171(2):345–347.
80. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomized placebo-controlled double-blind trial. Br J Obstet Gynaecol. 1999;106(7):652–657.
81. Sawaya GF, Grady D, Kerlikowske K, et al. Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis. Obstet Gynecol. 1996;87(5):884–890.
82. Brocklehurst P, Gordon A, Heatley E, et al. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev. 2013 Jan 31;CD000262.
83. Leitich H, Brunbauer M, Bodner-Adler B, et al. Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis. Am J Obstet Gynecol. 2003;188(3):752–758.
84. Centers for Disease Control and Prevention. Bacterial Vaginosis. Atlanta, GA: CDC; 2015. [cited 2018 Oct 2] Available from https://www.cdc.gov/std/tg2015/bv.htm
85. Metronidazole. Micromedex Solutions. Ann Arbor, MI: Truven Health Analytics, Inc. [cited 2018 Oct 3] Available from: http://www.micromedexsolutions.com
86. Clindamycin Cream. Micromedex Solutions. Ann Arbor, MI: Truven Health Analytics, Inc. [cited 2018 Oct 3] Available from: http://www.micromedexsolutions.com
87. Tinidazole. Micromedex Solutions. Ann Arbor, MI: Truven Health Analytics, Inc. [cited 2018 Oct 3] Available from: http://www.micromedexsolutions.com
88. Secnidazole. Micromedex Solutions. Ann Arbor, MI: Truven Health Analytics, Inc. [cited 2018 Oct 3] Available from: http://www.micromedexsolutions.com
89. Rathe M, Müller K, Sangild PT, et al. Clinical applications of bovine colostrum therapy: a systematic review. Nutr Rev. 2014;72 (4):237–254.
90. Faro S, Skokos CK; Clindesse Investigators Group. The efficacy and safety of a single dose of Clindesse vaginal cream versus a seven-dose regimen of Cleocin vaginal cream in patients with bacterial vaginosis. Infect Dis Obstet Gynecol. 2005;13(3):155–160.
91. Schwebke JR, Marrazzo J, Beelen AP, et al. A phase 3, multicenter, randomized double-blind vehicle-controlled study evaluating the safety and efficacy of metronidazole vaginal gel 1.3% in the treatment of bacterial vaginosis. Sex Transm Dis. 2015;42 (7):376–381.
92. Bohbot JM, Vicaut E, Fagnen D, et al. Treatment of bacterial vaginosis: a multicenter, double-blind, double-dummy, randomized phase III study comparing secnidazole and metronidazole. Infect Dis Obstet Gynecol. 2010;2010:705692.
93. Oduyebo OO, Anorlu RI, Ogunsola FT. The effects of antimicrobial therapy on bacterial vaginosis in nonpregnant women. Cochrane Database Syst Rev. 2009 Jul8;(3):CD006055.

94. Metrogel Vaginal [prescribing information]. Northridge, CA: 3M Pharmaceuticals; 2006.
95. Tindamax [prescribing information]. San Antonio, TX: Mission Pharmacal Company; 2007.
96. Schwebke JR, Demond RA. Tinidazole vs metronidazole for the treatment of bacterial vaginosis. Am J Obstet Gynecol. 2011;204 (3):211.e1–e6.
97. Milani M, Barcellona E, Agnello A. Efficacy of the combination of 2 g oral tinidazole and acidic buffering vaginal gel in comparison with vaginal clindamycin alone in bacterial vaginosis: a randomized, investigator-blinded, controlled trial. Eur J Obstet Gynecol Reprod Biol. 2003;109(1):67–71.
98. Livengood CH, Ferris DG, Wiesenfeld HC, et al. Effectiveness of two tinidazole regimens in treatment of bacterial vaginosis. Obstet Gynecol. 2007;110(2):302–309.
99. Raja IM, Basavareddy A, Mukherjee D, et al. Randomized, double-blind, comparative study of oral metronidazole and tinidazole in treatment of bacterial vaginosis. Indian J Pharmacol. 2016;48(6):654–658.
100. Solosec [prescribing information]. Newark, NJ: Symbiomix Therapeutics, LLC; 2017.
101. Gillis JC, Wiseman LR. Secnidazole, a review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. Drugs. 1996;51(4):621–638.
102. Nunez JT, Gomez G. Low-dose secnidazole in the treatment of bacterial vaginosis. Int J Gynaecol Obstet. 2005;88(3):281–285.
103. Petrina MAB, Cosentino LA, Rabe LK, et al. Susceptibility of bacterial vaginosis (BV)-associated bacteria to secnidazole compared to metronidazole, tinidazole and clindamycin. Anaerobe. 2017;47:115–119.
104. Pentikis HS, Adetoro N. Two phase 1, open-label, single-dose, randomized, crossover studies to assess the pharmacokinetics, safety, and tolerability of orally administered granules of secnidazole (2 g) in healthy female volunteers under different administration conditions. Clin Pharmacol Drug Dev. 2018;7(5):543-553.
105. Schwebke JR, Morgan FG Jr, Koltun W, et al. A phase-3, double-blind, placebo-controlled study of the effectiveness and safety of single oral doses of secnidazole 2 g for the treatment of women with bacterial vaginosis. Am J Obstet Gynecol. 2017;217 (6):678e1-678e9.
106. Darpo B, Xue H, Adetoro N, et al. Thorough QT/QTc evaluation of the cardiac safety of secnidazole at therapeutic and supratherapeutic doses in healthy individuals. J Clin Pharmacol. 2018;58(3):286-293.
107. Pentikis HS, Adetor N, Braun CJ. Lack of a pharmacokinetic interaction between SYM-1219 granules containing 2 grams of secnidazole and a combined oral contraceptive in a phase 1, randomized, open-label study in healthy female volunteers. Adv Ther. 2017;33(12):2229–2241.
108. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER). In: Guidance for Industry: Bacterial Vaginosis: Developing Drugs for Treatment. Silver Spring, MD: FDA; 2016. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM510948.pdf
109. Hillier SL, Nyirjesy P, Waldbaum AS, et al. Secnidazole treatment of bacterial vaginosis: a randomized controlled trial. Obstet Gynecol. 2017;130(2):379–386.
110. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. J Antimicrob Chemother. 2002;49(6):897–903.
111. Bartley JB, Ferris DG, Allmond LM, et al. Personal digital assistants used to document compliance of bacterial vaginosis treatment. Sex Transm Dis. 2004;31(8):488–491.
112. Mur Pérez AM, Mateo Segura Z, Ramírez Domínguez N, Vela Condón P. Use of probiotics in bacterial vaginosis. Semergen. 2017;43(5):394–398. [Article in Spanish].
113. Homayouni A, Bastani P, Ziyadi S, et al. Effects of probiotics on the recurrence of bacterial vaginosis: a review. J Low Genit Tract Dis. 2014;18(1):79–86.
114. Senok AC, Verstraelen H, Temmerman M, et al. Probiotics for the treatment of bacterial vaginosis. Cochrane Database Syst Rev. 2009 Oct7;(4):CD006289.
115. Xie HY, Feng D, Wei DM, et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. Cochrane Database Syst Rev. 2017;11:CD010496.
116. Pino A, Giunta G, Randazzo CL, et al. Bacterial biota of women with bacterial vaginosis treated with lactoferrin: an open prospective randomized trial. Microb Ecol Health Dis. 2017;28(1):1357417.
117. Otsuki K, Imai N. Effects of lactoferrin in 6 patients with refractory bacterial vaginosis. Biochem Cell Biol. 2017;95(1):31–33.
118. Machado D, Castro J, Palmeira-de-Oliveira A, et al. Bacterial vaginosis biofilms: challenges to current therapies and emerging solutions. Front Microbiol. 2015;6:1528.
119. Weissenbacher ER, Donders G, Unzeitig V, et al. A comparison of dequalinium chloride vaginal tablets (Fluomizin®) and clindamycin vaginal cream in the treatment of bacterial vaginosis: a single-blind, randomized clinical trial of efficacy and safety. Gynecol Obstet Invest. 2012;73(1):8–15.
120. Braga PC, Dal Sasso M, Culici M, et al. Inhibitory activity of thymol on native and mature *Gardnerella vaginalis* biofilms: in vitro study. Arzneimittelforschung. 2010;60(11):675–681.
121. Hymes SR, Randis TM, Sun TY, et al. DNase inhibits *Gardnerella vaginalis* biofilms in vitro and in vivo. J Infect Dis. 2013;207 (10):1491–1497.
122. Hooven TA, Randis TM, Hymes SR, et al. Retrocyclin inhibits *Gardnerella vaginalis* biofilm formation and toxin activity. J Antimicrob Chemother. 2012;67(12):2870–2872.
123. Gottschick C, Deng ZL, Vital M, et al. Treatment of biofilms in bacterial vaginosis by an amphoteric tenside pessary—clinical study and microbiota analysis. Microbiome. 2017;5(1):119.
124. Algburi A, Zhang Y, Weeks R, et al. Gemini cationic amphiphiles control biofilm formation by bacterial vaginosis pathogens. Antimicrob Agents Chemother. 2017;61(12):e00650–17.
125. National Institutes of Health. US National Library of Medicine. LactMed: a TOXNET database. [cited 2018 Nov 9] Available from: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
126. Bradshaw CS, Morton AN, Hocking J, et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. J Infect Dis. 2006;193(11):1478–1486.
127. Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. Am J Obstet Gynecol. 2006;194:1283.
128. Xiao B, Niu X, Han N, et al. Predictive value of the composition of the vaginal microbiota in bacterial vaginosis, a dynamic study to identify recurrence-related flora. Sci Rep. 2015;6:26674.
129. Tosheva-Daskalova K, Strateva TV, Mitov IG, et al. Multiplex PCR detection of problematic pathogens of clinically heterogeneous bacterial vaginosis in Bulgarian women. Turk J Med Sci. 2017;47 (5):1492–1499.
130. Ferreira CST, Donders GG, Parada CMGL, et al. Treatment failure of bacterial vaginosis is not associated with higher loads of *Atopobium vaginae* and *Gardnerella vaginalis*. J Med Microbiol. 2017;66(8):1217–1224.
131. McClelland RS, Richardson BA, Hassan WM, et al. Improvement of vaginal health for Kenyan women at risk for acquisition of human immunodeficiency virus type 1: results of a randomized trial. J Infect Dis. 2008;197(10):1361–1368.
132. McClelland RS, Balkus JE, Lee J, et al. Randomized trial of periodic presumptive treatment with high-dose intravaginal metronidazole and miconazole to prevent vaginal infections in HIV-negative women. J Infect Dis. 2015;211(12):1875–1882.
133. Bilardi JE, Walker S, Temple-Smith M, et al. The burden of bacterial vaginosis: women's experience of the physical, emotional, sexual and social impact of living with recurrent bacterial vaginosis. PLoS One. 2013;8(9):e74378.

134. Payne SC, Cromer PR, Stanek MK, et al. Evidence of African-American women's frustrations with chronic recurrent bacterial vaginosis. J Am Acad Nurse Pract. 2010;22(2):101–108.
135. Bilardi J, Walker S, McNair R, et al. Women's management of recurrent bacterial vaginosis and experiences of clinical care: a qualitative study. PLoS One. 2016;11(3):e0151794.
136. Keane FE, Maw R, Pritchard C, et al. Methods employed by genitourinary medicine clinics in the United Kingdom to diagnose bacterial vaginosis. Sex Trans Infect. 2005;81(2):155–157.
137. Barnes P, Viera R, Harwood J, et al. Self-taken vaginal swabs versus clinician-taken for detection of candida and bacterial vaginosis: a case-control study in primary care. Br J Gen Pract. 2017;67(665):e824–e829.