OPEN

A Narrative Review of Current Challenges in the Diagnosis and Management of Bacterial Vaginosis

Christina A. Muzny, MD, MSPH and Przemyslaw Kardas, MD, PhD†*

Abstract: Despite the availability of a number of oral and intravaginal antibiotic medications for the treatment of bacterial vaginosis (BV), management of this condition remains challenging. Recurrent BV occurs in >50% of patients receiving guideline-recommended treatments. This may be due to persistence or resurgence of the BV biofilm after treatment cessation, failure to reestablish an optimal vaginal microbiome after treatment, reinfection from an untreated sexual partner, or a combination of these factors. Nonadherence to multidose BV therapies may potentially contribute to recurrent BV, although there are no published data that directly assess the role of nonadherence to poor treatment outcomes and recurrent BV. There is a need for studies of BV treatment adherence in real-world settings as well as studies to explore the relationship between treatment adherence and recurrence. This review explores challenges associated with diagnosing and treating BV, current multidose antibiotic treatment options, newer single-dose treatment options, and ways to potentially maximize treatment success for this common vaginal infection.

Bacterial vaginosis (BV) is the most common cause of vaginal discharge and is characterized by a shift in the vaginal microbiota from lactobacilli to facultative and strict anaerobic bacteria[1]; however, its etiology is controversial. The overall prevalence of BV in North America in women of reproductive age is 27.4%, with a higher prevalence in black (33.2%) and Hispanic women (30.7%) than in white (22.7%) or Asian women (11.1%).[2] Other characteristics associated with an increased risk of BV include new or multiple male sexual partners, partner concurrency, a female sexual partner with BV symptoms, being herpes simplex virus type 2 seropositive, and smoking, whereas consistent condom use is associated with a decreased risk.[3–7]

Epidemiological data strongly suggest that BV is sexually transmitted.[8–10] However, there remains a critical need to determine whether BV results from acquisition of a keystone pathogen or a polymicrobial consortium of bacteria that are sexually transmitted.[11,12] A key factor in BV is the occurrence of a multispecies biofilm on vaginal epithelial cells containing abundant *Gardnerella vaginalis*, smaller amounts of *Atopobium vaginae*, and other undefined bacterial species.[13,14] The BV biofilm becomes metabolically inactive upon treatment, which leads to decreased susceptibility to antibiotics; this may contribute to high BV recurrence rates after therapy.[15] Nonadherence to antibiotic treatment may also contribute to recurrent BV, although there are no published data that directly assess the role of nonadherence to treatment and recurrent BV.[16] This review explores challenges associated with diagnosing and treating BV, current multidose antibiotic treatment regimens, newer single-dose treatment options, potential barriers to treatment adherence, and ways to potentially maximize treatment success.

DIAGNOSIS OF BV

Misdiagnosis is a major challenge to effective management and treatment for women with BV. Women with BV report being misdiagnosed with vulvovaginal candidiasis (VVC) or not being tested for BV when they present with vaginal symptoms.[17] Telephone diagnosis is not accurate for diagnosis of BV, and health care providers may require additional education on the diagnostic criteria for BV.[18] Incorrect self-diagnosis of BV as candidiasis is also a concern[18,19] and may lead to inappropriate self-treatment with over-the-counter antifungals or home remedies, which may select for more resistant *Candida* strains, exacerbate recurrences

From the *Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL; and †Department of Family Medicine, Medical University of Lodz, Lodz, Poland

Acknowledgments: 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. Editorial support in the preparation of this manuscript was provided by Phase Five Communications, funded by Symbiomix Therapeutics, LLC, a Lupin Pharmaceuticals company.

Conflict of Interest and Sources of Funding: C.A.M. has received research grant support from the National Institute of Allergy and Infectious Diseases, is a consultant for Lupin Pharmaceuticals and BioFire Diagnostics, and has received honoraria from Lupin Pharmaceuticals, Cepheid, Becton Dickinson, and Roche Diagnostics. P.K. reports no conflict of interest.

Editorial support in the preparation of this manuscript (i.e., providing PDF copies of manuscripts reviewed, formatting of the manuscript text and tables, and management of the references) was provided by Phase Five Communications, funded by Symbiomix Therapeutics, LLC, a Lupin Pharmaceuticals company. The findings and conclusions in this manuscript are those of the authors and do not represent the views of Symbiomix Therapeutics, LLC, or Lupin Pharmaceuticals.

Author contributions: Both authors contributed to the literature review, writing, and reviewing of all drafts of this manuscript and approved the final draft. They also contributed to revising the manuscript per the reviewers' suggestions.

Correspondence: Christina A. Muzny, MD, MSPH, Division of Infectious Diseases, University of Alabama at Birmingham, ZRB 242, 1720 2nd Avenue South, Birmingham, AL 35294-0007. E-mail: cmuzny@uabmc.edu.

Received for publication November 20, 2019, and accepted March 10, 2020.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (http://www.stdjournal.com).

DOI: 10.1097/OLQ.0000000000001178

and complications, lead to increased costs and office visits, and/or make it difficult to implement appropriate treatment.[17–21]

In clinical settings, at least 3 of 4 Amsel criteria are necessary for a diagnosis of BV: homogenous, thin, grayish white vaginal discharge; vaginal pH >4.5, positive whiff amine test result; and clue cells present on a wet mount of vaginal fluid.[10] Bacterial vaginosis is more rigorously defined by determining the Nugent score on a Gram stain of vaginal secretions. Scores of 0 to 3 are graded as *Lactobacillus* predominant vaginal microbiota, 4 to 6 as intermediate microbiota, and 7 to 10 as BV.[22] Compared with the Nugent score, the sensitivity and specificity of the Amsel criteria range from 37% to 70% and from 94% to 99%, respectively (Table 1).[23] In the United States, several commercially available molecular diagnostic assays are available for the diagnosis of BV in women.[23] One of these is the Becton Dickinson BD Affirm VP III assay, which is a DNA hybridization probe assay for the detection of *G. vaginalis*. Additional commercially available molecular diagnostic assays for BV diagnosis in symptomatic women include 5 nucleic acid amplification tests. These are the Becton Dickinson BD MAX Vaginal Panel, Hologic Aptima BV, LabCorp NuSwab VG, Medical Diagnostics Laboratory OneSwab BV Panel PCR with *Lactobacillus* Profiling by qPCR, and the Quest Diagnostics SureSwab BV Panel, all of which detect multiple bacterial species through multiplex PCR (Table 1).[23–25] Although these assays are associated with higher sensitivity and specificity than the Amsel criteria (Table 1), they are not point-of-care tests and are more costly.[23]

CURRENTLY AVAILABLE BV TREATMENT REGIMENS

Currently recommended and alternative regimens for BV according to the 2015 US Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines as well as the 2018 European guidelines on the management of vaginal discharge include multidose oral metronidazole, tinidazole, or clindamycin in addition to multidose intravaginal of metronidazole or clindamycin.[26,27] Newer single-dose treatment options include oral secnidazole, a 5-nitroimidazole Food and Drug Administration (FDA) approved in 2017 in the United States as a single-dose granule formulation,[28] and 2 intravaginal treatments: 2% extended-release clindamycin cream and 1.3% vaginal metronidazole gel (Table 2).[16,23,24,28–30,31s–41s] Supplementary Table 1 (http://links.lww.com/OLQ/A485) lists the mechanism of action of metronidazole, tinidazole, secnidazole, and clindamycin.[28–30,32s,36s,39s–41s]

In the past, studies evaluating treatments for BV have been inconsistent in their definition of cure, most only using 1 week for follow-up.[22,42s] The Amsel or Nugent criteria provide an objective assessment of cure, and 3- or 4-week follow-up periods may provide a better measure of efficacy than earlier follow-up.[22] The 2016 guidance by the US FDA on developing drugs for the treatment of BV recommends evaluating clinical cure at 7 to 14 days after the first day of treatment, with clinical cure defined as resolution of abnormal vaginal discharge, negative whiff test result, and clue cells <20% per high-power field on wet mount.[43s] In addition, the 2016 US FDA guidance recommends that only patients with a Nugent score of ≥7 should be enrolled in clinical trials evaluating BV treatments to increase the reliability of diagnosis.[43s]

EFFICACY AND SAFETY PROFILES OF CURRENT BV TREATMENT REGIMENS

Recommended and Alternative Regimens

In studies comparing 7-day oral metronidazole (500 mg twice daily) to 7-day intravaginal clindamycin cream (2%, 5 g once daily) and 5-day intravaginal metronidazole gel (0.75%, 5 g twice daily), 4-week cure rates were comparable at approximately 70% to 80% (Table 2).[31s] However, these studies varied in whether the 3 components of their cure definitions included resolution of symptoms, homogeneous vaginal discharge, pH, amine odor, and/or clue cells.[31s] Moreover, none of these studies used a Nugent score ≥7 in their inclusion criteria, as all were conducted before the 2016 US FDA guidance.[31s,43s] It should also be noted that the prescribing information for the 5-day intravaginal metronidazole gel reported a lower 4-week cure rate: 53% for daily dosing and 57% for twice-daily dosing.[32s] In nonpregnant women, clindamycin (oral, cream, or ovule) and metronidazole (oral) had similar rates of treatment failure, but metronidazole had a higher rate of adverse events, including metallic taste, nausea, and vomiting.[44s] A randomized, double-blind study comparing oral metronidazole 500 mg and tinidazole 500 mg and 1 g, each twice daily for 7 days, showed similar cure rates among the 3 treatment groups (64.1%, 67.5%, and 61.9% at 1 month, respectively).[45s] There was a higher incidence of bad taste with tinidazole 1 g (41.8%) than with metronidazole 500 mg (11.0%) or tinidazole 500 mg (15.2%).[45s] The incidence of vaginal yeast infection was similar among the 3 treatment arms (24.5%–29.3%).[45s]

Single-Dose Oral and Intravaginal Regimens

Secnidazole is a recently approved single-dose oral treatment option for BV. The convenience of a single oral dose is a potential benefit of secnidazole compared with other oral regimens.[46s] A randomized, double-blind, phase 3, noninferiority study conducted in Europe showed that a single 2-g oral dose of secnidazole (in a sachet formulation) was as effective as 7 days of metronidazole 500 mg twice daily for treatment for women with

TABLE 1. Commercially Available Molecular Assays for the Diagnosis of Bacterial Vaginosis in Women in the United States[23–25]

Assay	Sensitivity, %*	Specificity, %*	FDA Approved
BD Affirm VP III	90 vs. clue cell detection 94 vs. Nugent score	97 vs. clue cell detection 81 vs. Nugent score	Yes
BD MAX Vaginal Panel	90.5	85.8	Yes
Hologic Aptima BV Assay	95.0	89.6	Yes
LabCorp NuSwab VP	96.7	92.2	LDT
MDL OneSwab BV Panel PCR with *Lactobacillus* Profiling by qPCR	99	94	LDT
Quest Diagnostics SureSwab BV Panel†			LDT

*Versus a combination of the Amsel criteria and Nugent score unless otherwise noted.

†No published test characteristics found in the literature.

BD indicates Becton Dickinson; BV, bacterial vaginosis; FDA, US Food and Drug Administration; LDT, laboratory-developed test; MDL, Medical Diagnostics Laboratory.

TABLE 2. Approved Treatment Regimens for Bacterial Vaginosis[16,28–30,31s–41s]

Drug Formulation, Dose, Frequency, and Duration	Mode of Administration	Clinical Cure Rates (From Prescribing Information Where Available)	Most Common Adverse Events (≥2% From Prescribing Information)
Recommended by CDC[27]			
Metronidazole, 500 mg, twice daily for 7 d	Oral	78% at 4 wk (n = 640; summary of 4 randomized trials)[31s]	Not available in prescribing information[36s]
Metronidazole gel 0.75%, 5 g (1 full applicator), once daily or twice daily for 5 d	Intravaginal	71% twice daily at 4 wk (n = 112; 1 randomized trial)[31s] Prescribing information: 53% once daily (98/185) and 57% twice daily (109/190) at 4 wk[32s]	Vaginal discharge (12%), symptomatic *Candida* cervicitis/vaginitis (10%), vulva/vaginal irritative symptoms (9%), gastrointestinal discomfort (7%), headache (5%), nausea and/or vomiting (4%), pelvic discomfort (3%), dizziness (2%), unusual taste (2%)[32s]
Clindamycin cream 2%, 5 g (1 full applicator), once daily (at bedtime) for 3 or 7 d	Intravaginal	82% for 7-d regimen at 4 wk (n = 528; summary of 3 randomized trials)[31s] Prescribing information: 72–81% for 3-day regimen; 84–86% for 7-day regimen at 1 month (N = 674)[40s]	Vaginal moniliasis (3-d: 7.7%; 7-d: 10.4%) Vulvovaginitis (3-d: 6.0%; 7-d: 4.4%) Vulvovaginal disorder (3-d: 3.2%; 7-d: 5.3%)[40s]
Alternatives recommended by CDC[27]			
Tinidazole, 2 g, once daily for 2 d	Oral	Prescribing information: 35.6%* (n = 227)[37s]	2-g single dose: metallic/bitter taste (3.7%), nausea (3.2%), weakness/fatigue/malaise (2.1%)[37s]
Tinidazole, 1 g, once daily for 5 d	Oral	Prescribing information: 51.3%* (n = 227)[37s]	Multiday dose: metallic/bitter taste (6.3%), nausea (4.5%), anorexia (2.5%)[37s]
Clindamycin, 300 mg, twice daily for 7 d	Oral	94% at 7–10 d (n = 99)[31s,38s]	Not available in prescribing information[39s]
Newer agents and regimens			
Secnidazole, 2 g, single dose	Oral	Prescribing information: 53.3% (n = 124) and 67.7% (n = 164) at 21–30 d[28]	Vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), diarrhea (2.5%), abdominal pain (2.0%), vulvovaginal pruritus (2.0%)[28]
Metronidazole, 2 g, single dose	Oral	62% at 3–4 wk[31s]	Not available in prescribing information[36s]
Metronidazole gel 1.3%, 5 g (1 full applicator), single dose at bedtime	Intravaginal	Prescribing information: 37% (n = 577) at 21–30 d[30]	Vulvovaginal candidiasis (5.6%), headache (2.2%)[30]
Clindamycin cream 2%, 5 g (1 full applicator), single dose	Intravaginal	Prescribing information: 41% at 21–30 d (n = 144)[29]	Vaginosis fungal (14%), headache (7%), back pain (5%), constipation (2%), urinary tract infection (2%)[29]
Clindamycin ovule, 100 mg, once daily (at bedtime) for 3 d	Oral	59.7% at 35 d (n = 384)[41s]	

*Time point for clinical cure was not provided in prescribing information.

CDC indicates Centers for Disease Control and Prevention.

BV, with cure rates at day 28 of 60.1% and 59.5%, respectively.[46s] In that study, BV cure was defined as both clinical and microbiological cure.[46s] In a randomized, double-blind, placebo-controlled phase 3 study in the United States, clinical outcome responder rates at 21 to 30 days were 53.3% with 2 g oral secnidazole (in a granule formulation) versus 19.3% with placebo ($P < 0.001$); clinical cure rates were 64.0% and 26.4%, respectively, based on the 2016 US FDA guidance, with resolution of abnormal vaginal discharge, normal whiff test result, and clue cells <20% at days 7 to 14. Assessment was limited to patients with Nugent scores of ≥7 at baseline.[28,47s] Another randomized, double-blind, placebo-controlled study reported clinical responder rates at 21 to 30 days of 67.7% with secnidazole versus 17.7% with placebo ($P < 0.001$).[28] Vaginal yeast infections were the most common treatment-related adverse events in randomized clinical trials of secnidazole (2.8%–4.8% with 2 g secnidazole, 1.4%–3.1% with placebo)[47s,48s] and in an open-label, single-arm phase 3 study evaluating the safety of 2 g secnidazole in women or adolescents with BV (5.3%).[49s] The safety profile of secnidazole is well established based on clinical practice experience during more than 30 years of use globally and is consistent with the safety profile for the 5-nitroimidazole class.[50s]

Single-dose intravaginal treatments may provide an alternative for patients who desire greater convenience than multidose regimens. The 2 US FDA-approved single-dose intravaginal treatments are 2% extended-release clindamycin cream and single-dose 1.3% vaginal metronidazole gel. Extended-release clindamycin cream (2%) and 7-day clindamycin cream were compared in a randomized, single-blind, active-controlled study.[51s] At the test-of-cure visit (21–30 days after treatment), clinical and microbiological BV cure rates were 64.3% and 56.5%, respectively, with the single-dose cream versus 63.2% and 57.7%, respectively, with the 7-day regimen.[51s] However, these results were based on a per-protocol and not intent-to-treat analysis, using data collected from only 46% of enrolled participants with evaluable data.[51s] In another randomized, double-blind, placebo-controlled study, lower clinical and microbiological cure rates at 21 to 30 days after treatment with the single-dose clindamycin cream (41.0% and 44.9%, respectively) were obtained.[29] The most common adverse events were VVC and vulvovaginal pruritus (14.4% and 4.2% with 2% extended-release clindamycin cream vs. 10.2% and 3.0% with the 7-day regimen, respectively).[51s] The other approved single-dose intravaginal treatment, 1.3% metronidazole gel, was compared with vehicle control in a randomized, double-blind

study.[52s,53s] Clinical and microbiological cure rates were 37.0% and 19.5%, respectively, with single-dose 1.3% metronidazole gel at the test-of-cure visit (days 21–30) versus 26.7% and 7.7%, respectively, with the vehicle control.[30,53s] The most common adverse event was VVC (5.6% vs. 3.2% with the control).[53s] With the exception of secnidazole, it is important to note that the efficacy of the 2 single-dose intravaginal creams has not been directly compared with multidose BV treatments.

RECURRENT BV

Although short-term cure rates are generally comparable with currently recommended treatments for BV, studies with longer follow-up indicate high rates of recurrence.[54s] The consequences of unresolved BV include adverse obstetric outcomes including premature rupture of membranes and preterm labor/delivery, increased risk of acquisition of HIV and other sexually transmitted infections, and development of precancerous cervical lesions, which may be related to its role in the persistence of human papillomavirus.[55s–58s] Recurrent BV can also have a significant psychosocial impact on women, affecting sexual relationships and quality of life.[59s,60s] More than half of patients treated with oral metronidazole for BV experience recurrence: 58% reported recurrence by 1 year in a prospective study of oral metronidazole 400 mg twice daily for 7 days, and 52% reported recurrence at a mean follow-up of 6.9 years in a long-term observational study following oral metronidazole 500 mg 3 times daily for 10 days.[33s,61s] Clindamycin cream seems to have relapse rates comparable to oral metronidazole, but long-term studies are lacking.[33s,44s] Short-term recurrence rates (at 1 and 2 months) were 30% to 40% with tinidazole 500 mg twice daily for 7 days and approximately 20% with 1 mg tinidazole twice daily for 7 days.[45s] In a dose-ranging study of intravaginal metronidazole gel, the rate of symptom recurrence ranged from 21.4% (with 1.3% gel for 5 days) to ≥50% (with 0.75% gel for 5 days or 1.3% gel for 1 or 3 days).[52s] The similar recurrence rates of intravaginal formulations of clindamycin and metronidazole administered as a single dose compared with a multidose course of metronidazole indicate that patient preference for mode and frequency of treatment administration could play a role in treatment selection.

The most significant risk factor for recurrent BV is a regular sexual partner.[33s] Recurrence may also be due to persistence or resurgence of BV-associated bacteria in the BV biofilm, or failure to reestablish an optimal vaginal microbiome dominated by *Lactobacillus* species after treatment.[54s,62s,63s] Vaginal colonization and extravaginal reservoirs of BV-associated bacteria are also risk factors for persistent and recurrent BV.[34s,64s] Patient nonadherence to multidose therapy could also potentially contribute to recurrent BV, although there are no published data that directly assess the role of nonadherence to treatment and recurrent BV. This role for adherence has been identified in treatment of other bacterial infections.[65s,66s]

CHALLENGES IN BV MANAGEMENT

Restoring Normal Vaginal Microbiota

The need to restore normal vaginal microbiota is a major challenge associated with BV treatment.[62s] Although up to 300 bacterial species may be present in BV, the most common microorganisms associated with BV include *G. vaginalis*, *A. vaginae*, *Mobiluncus* species, *Prevotella* species, *Leptotrichia*/*Sneathia* species, *Megasphaera* species, and bacteria in the *Clostridiales* order.[54s,67s–69s] Although *G. vaginalis* was previously believed to be the sole cause of BV, this has not been definitively established.[67s] An additional hypothesis for the pathogenesis of BV is that it is caused by a polymicrobial consortium of microorganisms that are sexually transmitted.[12] In the original study on the BV biofilm, *G. vaginalis* was found to constitute 60% to 95% of biofilm mass, in addition to smaller amounts of *Atopobium* (1%–40% of biofilm mass) and *Lactobacillus* species (0.01%–5% of biofilm mass).[14] The increased rate of BV in African American women may be related to differences in their vaginal microbiome compared with that of women of European ancestry.[70s] Healthy, reproductive-aged African American women are more likely to have a vaginal microbiome dominated by *G. vaginalis* and other BV-associated bacteria.[71s]

An optimal vaginal microbiome includes *Lactobacillus* species, which produce lactic acid and hydrogen peroxide and prevent the growth of BV-associated bacteria.[42s,63s] Beneficial *Lactobacillus* species in the vagina also produce bacteriocins, which inhibit the growth of other bacteria.[22,42s] *L. crispatus* is the vaginal lactobacilli most strongly associated with optimal vaginal microbiota.[63s,72s] Probiotics have been studied as adjuncts to traditional antibiotic therapy for BV in an attempt to reestablish optimal vaginal microbiota[67s,73s] and to prevent recurrent BV, with marginal results.[74s–77s] Several of the probiotics studied include a yogurt drink containing *L. crispatus*, *L. gasseri*, *L. jensenii*, and *L. rhamnosus*[73s]; a vaginal capsule containing *L. rhamnosus*, *L. acidophilus*, and *Streptococcus thermophilus*[74s]; a vaginal pessary containing *L. acidophilus*[75s]; and a vaginal capsule or applicator containing *L. crispatus*.[76s,77s] Overall, results from probiotic studies have been mixed and additional studies are needed to determine the efficacy of probiotics in preventing or treating BV.

Sustained cure and effectiveness against BV-associated sequelae and the high rate of recurrence without antibiotic-associated adverse events may be obtained through approaches combining antimicrobials with biofilm-disrupting agents. One such investigational agent, TOL-463, is a boric acid–based vaginal anti-infective enhanced with ethylenediaminetetraacetic acid that specifically targets vaginal bacterial and fungal biofilms.[78s] It has been designed as a dual-indication treatment of both BV and VVC. In a phase 2, investigator-blinded study of TOL-463 inserts and gel, clinical cure rates of BV at test of cure were 59% (95% confidence interval [CI], 41%–75%) for TOL-463 insert and 50% (95% CI, 31%–69%) for TOL-463 gel. For VVC, clinical cure rates were 92% (95% CI, 67%–99%) for TOL-463 insert and 81% (95% CI, 57%–93%) for TOL-463 gel. Both products were safe and well tolerated with no secondary cases of VVC; vulvovaginal burning was the most common adverse event (9.6%).[78s]

Another potential newcomer to the anti-BV armamentarium is astodrimer 1% gel, a microbicidal vaginal gel that may hold promise for the prevention of recurrent BV.[79s] Although not an antibiotic, astodrimer belongs to a group of topical microbicides known as polyanion-based entry inhibitors. In 2 phase 3, double-blind, multicenter trials, astodrimer sodium gel was associated with a lower rate of BV recurrence than placebo. Clinical cure rates at days 9 to 12 were 50.4% (59/117) versus 16.5% (19/115; $P < 0.001$) in study 1 and 56.7% (68/120) versus. 21.4% (25/117; $P < 0.001$) for study 2 of astodrimer versus placebo. Adverse events were generally mild and self-limiting.[79s]

Treatment Adherence and BV

Adherence rates from studies with BV treatments are not available for all drugs and formulations.[16,33s–35s] For metronidazole (500 mg twice daily for 7 days), adherence rates were 50% using a personal digital assistant and 68.3% using a paper diary.[16] At least 80% were self-reported.[33s,35s] For metronidazole gel 75%, 5 g once or twice daily for 5 days, adherence rates were 77.6%

using a personal digital assistant and 88.5% using a paper diary[16]; 93% were self-reported.[34s] As with other conditions treated by antibiotics, nonadherence to antibiotics for BV could potentially lead to drug resistance among BV-associated bacteria, which can adversely affect patient outcomes and result in a reduction in the number of effective antibiotics.[65s] Many of the currently recommended oral and intravaginal treatments for BV are associated with a number of drawbacks. Women with recurrent BV have reported frustration with rapid recurrence after initially effective 7-day regimens with side effects that may be difficult to tolerate; as a result, they may self-treat unless the episode is symptomatic or severe.[17] Potential barriers to adherence to oral treatments for BV may include gastrointestinal complaints, including nausea, stomach cramps, and diarrhea; bad (metallic) taste; and difficulty swallowing tablets.[17,80s,81s] For intravaginal treatments, barriers to adherence include product properties such as messiness, leakage, the need to reuse applicators, and lifestyle restrictions, such as refraining from intercourse while on therapy.[80s,82s] For intravaginal treatments that contain mineral oil (i.e., clindamycin ovule or cream), the use of condoms or diaphragms is not recommended for 3 or 5 days.[27,80s] Duration of therapy is another potential barrier to adherence for both oral and intravaginal treatments for BV,[80s] with most of the guideline-recommended and alternative treatments requiring up to 5 or 7 days of treatment.[26,27] In a survey of women with a history of BV that compared the use of a 3-day clindamycin ovule with that of a 5-day metronidazole intravaginal gel, the 3-day duration was cited as the most important feature of the ovule, due in part to better adherence.[80s] Although a shorter course of therapy may correspond with improved adherence, it is important to note that there are no published studies that directly assess the role of nonadherence in BV treatment failure and recurrence.

The fact that most BV clinical studies rely on self-report likely underestimates the rate of nonadherence to multidose regimens.[16] Patient self-report is a subjective method of measuring adherence and is considered less accurate than other methods, such as directly measuring medication taking or using electronic devices to indirectly measure medication taking; it is common for patients to overestimate their adherence level.[83s] Electronic devices, such as Medication Events Monitoring System (MEMS), are an accurate method for measuring adherence in clinical trials.[83s–85s] However, the high cost of MEMS limits its use in larger clinical trials or routine clinical practice.[83s] For practical reasons, it is also more difficult to use it for nonplanned, short-term therapies, which is a typical case of antibiotic treatment of BV. In a review of 117 studies comparing methods of measuring adherence, nonelectronic methods overestimated mean adherence compared with MEMS: 17% for self-report, 8% for pill count, and 6% for rating by a health care provider, caregiver, or parent.[84s]

Studies that use electronic devices to monitor adherence should be performed to assess adherence to treatment in women with BV. Moreover, it should be recognized that adherence is likely to be higher for patients enrolled in clinical trials compared with patients who take antibiotic courses for BV on their own. There is also a need for more studies of adherence in the general population of women with BV, namely, women who are not enrolled in clinical trials, for a real-world perspective on adherence. In addition, there is a need for well-designed studies to assess the role of treatment nonadherence in BV treatment failure and recurrence.

MAXIMIZING CLINICAL SUCCESS IN THE TREATMENT OF BV

Patient preference and tolerability, along with efficacy, should be considered when prescribing treatments for BV.[19] Given its high recurrence rates, further steps should be taken to improve the diagnosis, treatment, and management of patients with BV. The main barrier to improvements in diagnosis and treatment is that the exact etiology of BV remains controversial. Until this is determined, these issues will continue to be a challenge. Treatment rates and the prevention of recurrent BV may be enhanced by results of studies using both antibiotics, biofilm-disrupting agents, and/or probiotics to treat BV as well as to restore normal vaginal microbiota and prevent recurrent infections. Recently available single-dose oral and intravaginal therapies may provide more convenient alternatives for patients not wanting to take multidose regimens. However, there are no studies to date that demonstrate superior efficacy of single-dose therapies to multidose regimens for BV. Nevertheless, health care providers should consider the patient's perspective when prescribing a treatment regimen for BV to optimize adherence as well as clinical outcomes.

REFERENCES

1. Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001–2004 National Health and Nutrition Examination Survey data. Obstet Gynecol 2007; 109:114–120.
2. Peebles K, Velloza J, Balkus JE, et al. High global burden and costs of bacterial vaginosis: A systematic review and meta-analysis. Sex Transm Dis 2019; 46:304–311.
3. Fethers KA, Fairley CK, Hocking JS, et al. Sexual risk factors and bacterial vaginosis: A systematic review and meta-analysis. Clin Infect Dis 2008; 47:1426–1435.
4. Kenyon CR, Buyze J, Klebanoff M, et al. Association between bacterial vaginosis and partner concurrency: A longitudinal study. Sex Transm Infect 2018; 94:75–77.
5. 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: 1562–1572.
6. Vodstrcil LA, Walker SM, Hocking JS, et al. Incident bacterial vaginosis (BV) in women who have sex with women is associated with behaviors that suggest sexual transmission of BV. Clin Infect Dis 2015; 60:1042–1053.
7. Abbai NS, Nyirenda M, Naidoo S, et al. Prevalent herpes simplex virus-2 increases the risk of incident bacterial vaginosis in women from South Africa. AIDS Behav 2018; 22:2172–2180.
8. Forcey DS, Vodstrcil LA, Hocking JS, et al. Factors associated with bacterial vaginosis among women who have sex with women: A systematic review. PLoS One 2015; 10:e0141905.
9. Muzny CA, Schwebke JR. *Gardnerella vaginalis:* Still a prime suspect in the pathogenesis of bacterial vaginosis. Curr Infect Dis Rep 2013; 15:130–135.
10. Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis: Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983; 74:14–22.
11. Schwebke JR, Muzny CA, Josey WE. Role of *Gardnerella vaginalis* in the pathogenesis of bacterial vaginosis: A conceptual model. J Infect Dis 2014; 210:338–343.
12. Srinivasan S, Fredricks DN. The human vaginal bacterial biota and bacterial vaginosis. Interdiscip Perspect Infect Dis 2008; 2008:750479.
13. Machado A, Cerca N. Influence of biofilm formation by *Gardnerella vaginalis* and other anaerobes on bacterial vaginosis. J Infect Dis 2015; 212:1856–1861.
14. Swidsinski A, Mendling W, Loening-Baucke V, et al. Adherent biofilms in bacterial vaginosis. Obstet Gynecol 2005; 106(5 Pt 1): 1013–1023.
15. Swidsinski A, Mendling W, Loening-Baucke V, et al. An adherent *Gardnerella vaginalis* biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. Am J Obstet Gynecol 2008; 198:97.e91–97.e96.
16. Bartley JB, Ferris DG, Allmond LM, et al. Personal digital assistants used to document compliance of bacterial vaginosis treatment. Sex Transm Dis 2004; 31:488–491.

17. 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:e0151794.
18. Allen-Davis JT, Beck A, Parker R, et al. Assessment of vulvovaginal complaints: Accuracy of telephone triage and in-office diagnosis. Obstet Gynecol 2002; 99:18–22.
19. Chavoustie SE, Eder SE, Koltun WD, et al. Experts explore the state of bacterial vaginosis and the unmet needs facing women and providers. Int J Gynaecol Obstet 2017; 137:107–109.
20. Mania-Pramanik J, Kerkar SC, Salvi VS. Bacterial vaginosis: A cause of infertility? Int J STD AIDS 2009; 20:778–781.
21. Salah RM, Allam AM, Magdy AM, et al. Bacterial vaginosis and infertility: Cause or association? Eur J Obstet Gynecol Reprod Biol 2013; 167:59–63.
22. Verstraelen H, Verhelst R. Bacterial vaginosis: An update on diagnosis and treatment. Expert Rev Anti Infect Ther 2009; 7:1109–1124.
23. Coleman JS, Gaydos CA. Molecular diagnosis of bacterial vaginosis: An update. J Clin Microbiol 2018; 56:e00342–e00318.
24. Aptima BV. Assay Package Insert. San Diego, CA: Hologic, Inc.; 2019.
25. FDA clearance of Aptima BV and Aptima CV/TV molecular assays ushers in new era of comprehensive and objective diagnostic testing for vaginitis [press release]. 2019. Available at: https://investors.hologic.com/press-releases/press-release-details/2019/FDA-Clearance-of-Aptima-BV-and-Aptima-CVTV-Molecular-Assays-Ushers-in-New-Era-of-Comprehensive-and-Objective-Diagnostic-Testing-for-Vaginitis/default.aspx. Published 2019. Accessed October 24, 2019.
26. Sherrard J, Wilson J, Donders G, et al. 2018 European (IUSTI/WHO) International Union against sexually transmitted infections (IUSTI) World Health Organisation (WHO) guideline on the management of vaginal discharge. Int J STD AIDS 2018; 29:1258–1272.
27. 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.
28. Solosec (Secnidazole) Oral Granules Prescribing Information. Baltimore, MD: Symbiomix Therapeutics LLC (a Lupin company), 2017.
29. Clindesse (Clindamycin Phosphate) Vaginal Cream, 2% Prescribing Information. Allegan, MI: Perrigo, 2014.
30. Nuvessa (Metronidazole Vaginal Gel 1.3%) Prescribing Information. Florham Park, NJ: Exeltis USA, Inc., 2018.

For further references, please see "Supplemental References," http://links.lww.com/OLQ/A485.