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Bacterial vaginosis: a review of approaches to treatment and prevention

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Bacterial vaginosis (BV) is a common cause of vaginitis worldwide and is associated with serious reproductive health outcomes, including increased risk of preterm birth, sexually transmitted infections, and pelvic inflammatory disease. The current and only FDA-approved treatment regimens for BV are antibiotics, such as metronidazole and clindamycin. Antibiotics provide a short-term cure for bacterial vaginosis; however, fail to provide a consistent long-term cure for many women. Fifty to eighty percent of women experience a BV recurrence within a year of completing antibiotic treatment. This may be because after antibiotic treatment, beneficial strains of *Lactobacillus*, such as *L. crispatus,* do not recolonize the vagina. In the absence of an effective long-term cure, patients, providers, and researchers are exploring different approaches to treatment and prevention, resulting in a rapid evolution of perspectives on BV pathogenesis and approaches to management. Current areas of investigation for BV management include probiotics, vaginal microbiome transplantation, pH modulation, and biofilm disruption. Behavioral modifications that may help include smoking cessation, condom use and hormonal contraception. Additional strategies considered by many people include dietary modification, non-medical vaginally applied products, choice of lubricant, and treatments from medical practices outside of allopathic medicine. This review aims to provide a comprehensive and up to date outline of the landscape of ongoing and potential treatment and prevention strategies for BV.

KEYWORDS

bacterial vaginosis, vaginitis, gardnerella vaginalis, emerging therapies, vaginal microbiome

1. Introduction

Bacterial vaginosis (BV) is the most common cause of vaginitis among reproductive aged women, commonly presenting with vaginal discharge and odor (1). BV is characterized by a decline in abundance of *Lactobacillus,* a healthy vaginal bacteria (2, 3), and a simultaneous overgrowth of pathogenic bacteria, such as *Gardnerella vaginalis, Atopobium vaginae, Megasphaera spp., Prevotella spp. and Sneathia spp*. Point-of-care diagnosis of BV can be made by noting at least three of four Amsel criteria, which include thin, white discharge, clue cells on microscopy, a vaginal pH > 4.5, and a fishy odor with application of potassium hydroxide (4). Laboratory based molecular tests, which identify DNA from a subset of BV-associated species, have recently been FDA approved (5). Research studies often use the Nugent score of bacterial morphotypes on vaginal fluid Gram stain for diagnosis (6).

In the United States, the estimated prevalence of BV is 29%–49% (7, 8). Despite this high prevalence, an effective long-term cure for BV remains elusive for many women. There is a high recurrence rate of BV following antibiotics (9–11), the only approved therapeutic

regimen, and many women struggle with recurrent BV [defined as ≥3 episodes in a 12 month period (11)]. Such high recurrence may be due to persistence of the infection, re-exposure to BV-associated organisms, or a failure of lactobacilli to recolonize the vagina. Lack of adequate treatment for BV is a significant public health issue both because of the impact of symptoms on quality of life, and because women with BV are at increased risk for preterm birth (12, 13), sexually transmitted infections (STIs) including HIV(14, 15), and pelvic inflammatory disease(16). Additionally, women with BV are at increased risk for post-operative complications such as vaginal cuff cellulitis (17).

Various studies have found racial differences in BV prevalence (18). It is important to highlight that race is not a biologic factor, suggesting that there are environmental or situational factors linked to the lived experience of a racial or ethnic group, including racism (19), that may contribute to differences in BV prevalence. While differences in BV prevalence may exist across race or ethnicity (20), there is no known difference in treatment efficacy.

The failure of antibiotics to provide a long-term cure for BV has led many women and clinicians to consider alternative therapies. The focus of this review is to discuss the evidence for potential non-antibiotic therapeutic and preventive options for BV, including those currently under investigation and those more informally used (**Table 1**).

2. The current treatment paradigm

Antibiotics are the first line treatment for BV. The recommended therapeutic regimens include oral or intravaginal metronidazole and intravaginal clindamycin. These treatments have similar efficacy and are effective for short-term resolution of the infection (22). Recurrent bacterial vaginosis is a common drawback to current treatment options. Within 6–12 months of finishing antibiotic therapy, 50%–80% of women will experience a bacterial vaginosis recurrence (9–11). Proposed reasons for this treatment failure include reinfection via sexual partners, antimicrobial resistance, biofilm, and failure to reestablish a health-optimal vaginal microbiota. A more comprehensive review of the nuances of current antibiotic treatment regimens can be found in two review papers by Muzny et al. (42, 43).

There is a debate in the field as to whether BV can be transmitted sexually via male or female partners; however, studies have shown that treating male partners with antibiotics does not affect bacterial vaginosis reoccurrence in female partners (44–46). No studies have evaluated treatment of female partners in female-female partnerships.

Antibiotic resistance and biofilm persistence are other proposed reasons for long-term treatment failure. One study found that out of 50 strains of *Gardnerella vaginalis,* the majority were resistant to both metronidazole and clindamycin (47). Another study found increased antimicrobial resistance to clindamycin among anaerobic isolates following previous treatment (48). Although there is a paucity of data, a recent review discusses the studies that have attempted to examine antibiotic resistance in BV (49). In an analysis of available *in vivo* data, they indicate there is increasingly convincing evidence of antimicrobial resistance in BV and a need to address this in clinical management (49). Persistent polymicrobial biofilm, which has been more often identified in people with recurrent BV compared to healthy people or those with a single episode, may play a part in antimicrobial resistance (50). Bacterial biofilm reduces antimicrobial penetrance and even after clinically successful bacterial vaginosis antibiotic therapy, biofilm persists (51).

TABLE 1 Overview of interventions for treatment and/or prevention of bacterial vaginosis.

Intervention	Proposed mechanism of action	Example	Clinical evidence
Antibiotics	Antibacterial agents that act via inhibition of bacterial protein synthesis	Metronidazole, Clindamycin (22)	High quality evidence of benefit
Vaginal microbiome transplant (VMT)	Introduction of an exogenous bacterial microbiome to help restore eubiosis	Vaginal microbiome transplantation (23)	Low quality evidence for benefit
pH modulation	Modulation of vaginal pH to become more acidic, promoting an environment in which BV associated bacteria grow poorly	Lactic acid (24) Vitamin C (25)	Moderate quality evidence for no effect
Biofilm disruption	Disruption of the biofilms that may exist on BV associate bacteria, increasing the bacteria's susceptibility to antibacterial mechanisms	Boric acid (26) Astodrimer vaginal gel (27)	Moderate quality evidence for benefit
Probiotics	Recolonization of the vagina with health-promoting *Lactobacillus* species	Oral (28) and vaginally administered probiotics (25, 29–32), such as *L. crispatus* (33, 34).	Low to Moderate quality evidence for benefit
Diet	Modulation of the body's immune response to bacterial pathogenesis and/or interplay between the gastrointestinal and vaginal microbiomes	Avoidance of sugar (35, 36) and fat (37) Intake of Vitamins A, C, E, D (38)	Low to Moderate quality evidence for benefit
Barrier Contraception	Preventing the introduction of bacteria to the vaginal environment	Condom use (39)	Moderate quality evidence for benefit
Hormonal contraception	Immunoregulation by estrogen and progesterone and/or decreased menses	Oral contraceptive pill, hormonal IUD (40)	Moderate quality evidence for benefit
Smoking Cessation	Alteration of vaginal microbiota and potential increase in biogenic amines	Cessation of smoking (41)	Low to moderate quality evidence for benefit

Strength of clinical evidence determined through use of GRADE criteria (21), with specific factors driving classification of a body of evidence outlined in Supplementary Table S1.

Failure of antimicrobial *Lactobacillus* to recolonize the vagina following antibiotic therapy may be another reason for high BV recurrence. Among the *Lactobacillus* species most commonly found in the vagina, *Lactobacillus crispatus* is most correlated with a stable, lactobacilli-rich vaginal microbiome, while *Lactobacillus iners* correlates with vaginal microbiome instability (52, 53). Although antibiotic therapy reduces the quantity of *Gardnerella vaginalis* and other BV-associated species, the post-antibiotic treatment microbiota are usually dominated by *L. iners* rather than the species considered more beneficial (*L. crispatus, L. jensenii)* (54, 55). The failure to restore a non-*iners Lactobacillus* rich microbial community is a possible reason that antibiotics have failed to provide a long-term cure to recurrent BV.

3. Probiotics

Probiotics are live microorganisms that can be ingested through diet or supplements, or can be administered vaginally. Probiotics containing *Lactobacillus* are often used and marketed for the management of BV and may be beneficial in preventing recurrent BV through recolonization of the vaginal microbiota. *Lactobacillus* species have been shown to have antimicrobial effects against BV-associated species (53, 56, 57). Their use has been studied as both a treatment for BV as well as to prevent recurrence of BV after antibiotic therapy.

Studies of probiotics vary widely in species included in the product, study methodology, and final outcomes. The majority of studies used species of *Lactobacillus* that are prominent in the gut, not vagina (58). A wide variety of *Lactobacillus* strains exist, and their abundance differs between the gut and vagina (59, 60). *Lactobacillus crispatus, L. iners, L. gasseri* and *L. jensenii* are the species most commonly found in the vaginal tract (60, 61). Even among these strains, there is variability, with *L. crispatus* associated with a protective effect on vaginal health while *L. iners* is associated with a more unstable vaginal microbiome (52, 53). Despite this wide variability in environmental abundance and effect of strains, the majority of oral probiotics marketed for vaginal health contain *Lactobacillus* strains that are more commonly found in the gut than vagina (58), and very few contain *L. crispatus*.

The mechanism of action of oral probiotics, which are more commonly used, is unknown. It is possible that oral probiotics may reach the vaginal microbiome through the gastrointestinal tract. Two studies have demonstrated that bacterial species may be shared between intestinal and vaginal tracts (62, 63) and a cross-sectional study found that co-colonization of the rectum and vagina by hydrogen peroxide-producing lactobacilli was associated with lower prevalence of BV (63). A randomized controlled trial ($N = 544$) found that people with BV taking oral probiotics experienced a higher rate of restitution to *Lactobacillus*-rich vaginal microbiota at six weeks than in the placebo group (61.5% vs. 26.9%) (28). This research did not compare the effect of oral probiotics to existing antibiotic therapies. A comprehensive systemic review assessed randomized control trials using oral and vaginal probiotics for BV treatment (64). They identified four trials meeting their inclusion criteria and found no conclusive evidence that probiotics are comparable to or enhance the effectiveness of antibiotics. They did report a suggestible beneficial outcome of combined use of probiotics and antibiotics. Three out of the four identified studies used vaginal, rather than oral, probiotics.

Unlike oral probiotics, vaginal probiotics have the advantage of direct administration. Many trials are underpowered to determine whether probiotics are equivalent to existing therapies. Even among five randomized controlled trials that include more than 80 participants (and thus, approach reasonable power), results vary. Two placebo-controlled studies comparing antibiotic therapy and antibiotics plus vaginal probiotics found comparable cure rates (29) and recurrence (30) of BV between the two arms. Another study ($N = 100$) found that, when administered following antibiotic therapy, vaginal probiotics did not significantly impact BV cure rate, but they did prolong time without BV recurrence (64.9% vs. 46.2%) (31). Similar results were found in a study ($N = 115$) examining the effect of probiotics vs. antibiotic treatment; the probiotic arm had a higher 30-day cure rate than the antibiotic arm (96% vs. 70%), and among clinically cured participants, the probiotic arm had a lower BV recurrence rate (32). Finally, a randomized controlled trial ($N = 190$) demonstrated that vaginal probiotics significantly improved vaginal microbiota restoration following antibiotic treatment (25)—an outcome associated with decreased risk for BV recurrence. Even among these large-scale randomized controlled trials, the effectiveness of probiotics remains inconclusive. This is likely due to the variability of *Lactobacillus* species used across studies.

Two randomized studies have examined the effect of *L. crispatus* on BV recurrence after antibiotic treatment. In a phase III randomized clinical trial ($N = 98$), women with recurrent BV previously treated with metronidazole were given two treatments of vaginally administered *L. crispatus,* also known as Physioflor (34). The administration of *L. crispatus* significantly reduced the incidence of BV recurrence (20%) compared to those in the placebo group (41%). Of note, this study had a considerable amount of missing data, with only 78 participants' data included in their analysis, which introduces significant bias. A more robust, phase IIb randomized, placebo-controlled study examined the role of an intravaginally applied *L. crispatus* live biotherapeutic product, also known as Lactin-V, in managing recurrent BV among 228 women (33). Lactin-V was administered to women within 48 h of finishing a course of metronidazole, daily for 5 days and then twice weekly for 10 weeks. They found that at 12 weeks, women administered Lactin-V had a significantly lower incidence of BV recurrence (30%) than those who received placebo (45%). A secondary outcome demonstrated that at 24 weeks after antibiotic treatment, *L. crispatus* was detected in 48% of women who had received Lactin-V and 2% of women who received placebo. This well conducted study demonstrated that among women with recurrent BV, the vaginal administration of *L. crispatus* significantly reduces BV recurrence (33).

There is insufficient evidence to recommend commercially available probiotics at this time.

4. Vaginal microbiome transplantation

Vaginal microbiome transplantation (VMT) is a novel therapeutic option currently under investigation for prevention of recurrent BV. In VMT, women receive vaginal fluid collected from healthy donors. Similar to fecal microbiome transplantation, which can successfully treat recurrent *C. difficile* infections (65), VMT introduces an exogenous bacterial community to help restore eubiosis. Unlike probiotics, which introduce isolated species of bacteria into the vaginal microbiota, VMT transfers a whole microbiome.

A 2019 case series was the first to assess the effectiveness of VMT (23). The study enrolled five women with recurrent BV who had previously undergone multiple antibiotic regimens. Following an intravaginal antibiotic treatment, the women received transplanted vaginal fluids from donors. Two out of the five women had full remission of BV after one transplant, and two more after multiple transplants, for the duration of follow up (5–21 months) with no adverse effects. The fifth woman had partial remission. This study demonstrated that VMT can change the composition of vaginal microbiota. The four women for whom VMT was successful had vaginal microbiota dominated by *L. crispatus* for the duration of follow up. *L. gasseri* dominated the microbiota of the patient with unsuccessful VMT. This finding supports the hypothesis that *L. crispatus* may be the most beneficial species of *Lactobacillus* for restoring healthy vaginal microbiota.

This is a promising outcome, suggestive that VMT has potential to restore healthy vaginal microbiota and treat recurrent BV. However, there was no control group and some of the women required multiple VMTs to achieve full remission. Additionally, donors must be screened appropriately and thoroughly to minimize potential risks to recipients. Further research is needed before this approach can be adopted clinically. At the time of this review, per clinicaltrials.gov there are two ongoing randomized trials of VMT, one in Israel and one in the United States. This procedure should not be performed outside of clinical trials.

5. pH modulation

Lactobacilli produce lactic acid, which helps maintain a low, acidic, vaginal pH (66). BV-associated anaerobic bacteria grow poorly in acidic environments, which has led many to hypothesize that lactic acid could provide protective effects against vaginal infections (67). BV is characterized by loss of lactobacilli and the lactic acid they produce, leading to an increase in vaginal pH, which may allow the anaerobic overgrowth that is the hallmark of this syndrome (68, 69). The administration of lactic acid, and other pH modulators, therefore, may hold potential in the management of BV (2).

Studies of pH modulating agents including lactic acid, mucoadhesive vaginal gel, and acetic acid in women with BV have mostly been small, with sample sizes of less than 100. Results from these studies have varied: effects range from no benefit (70, 71) to providing a clinical cure (72, 73). A literature review concluded that lactic-acid containing agents do not significantly affect vaginal microbiota (74). A randomized controlled trial ($N = 409$) which compared lactic acid gel to oral metronidazole for clinical cure of BV found that lactic acid was less effective than metronidazole at resolving BV symptoms (47% vs. 70%) in a two-week span. For those in the study whose symptoms cleared in the initial 2 weeks, both lactic acid and metronidazole had correspondingly high recurrence rates at 70% and 71% (24).

Vaginally administered vitamin C has also been demonstrated to decrease vaginal pH (75–77). When used after antibiotic treatment, vitamin C helps maintain an acidic vaginal environment, allowing more time for restoration of healthy vaginal microbiota (75). A randomized controlled trial ($N = 277$) demonstrated that vitamin C, applied for 6 days intravaginally, had a higher clinical cure rate for BV than placebo (44% vs. 22%) (78). A subsequent randomized controlled trial ($N = 142$) found that intravaginal vitamin C significantly decreased BV recurrence rate for up to 6 months compared to placebo (16% vs. 32%) (79). However, in this trial, there was no difference in vaginal pH between people who did vs. did not receive vaginal Vitamin C during treatment, suggesting that any mechanism of effect was not related to lowering of pH. Of note, the formulation used in these studies is a silicone-coated tablet that slowly releases the ascorbic acid, which is not available in the United States.

There is no reliable evidence that pH modulators alone are effective at treating BV or that they are more effective than existing antibiotic treatments. In vitro experiments continue to provide biologic plausibility for elevated pH as a permissive mechanism to allow growth of BV-associated organisms, but it is not yet clear whether a pH altering product can counter that *in vivo*. Thus, pH modulating products should not be recommended at this time.

6. Biofilm disruptors

One hypothesized reason for high rates of recurrence of BV is the presence of a polymicrobial biofilm (80–85). Biofilms are composed of microbial cells and an extracellular matrix that can provide bacterial protection, and are generally associated with decreased efficacy of antimicrobial agents (86). Fluorescence in-situ hybridization (FISH) studies using vaginal biopsies demonstrate an adherent layer of bacteria in many people with BV (84). However, there is still some debate about whether this is a true biofilm, as no studies have yet demonstrated the presence of an extracellular matrix.

There are a variety of agents that are purported to target biofilms. *Thymbra capitata,* an essential oil, has antimicrobial effects on *Gardnerella* spp. (87) and BV-associated polymicrobial biofilms *in vitro* (88). Although not yet studied *in vivo*, it may

hold promise in BV management. Dequalinium chloride (DQC) is a quaternary ammonium compound that has antimicrobial activity against vaginal pathogens such as *Gardnerella* (89, 90) and it can partially disrupt *in vitro Gardnerella* biofilms on plastic culture plates (91). A randomized non-inferiority trial ($N = 321$) demonstrated DQC can also successfully treat BV clinically, with cure rates similar to vaginally administered clindamycin 25 days after treatment (74.8%vs. 74.8%) (92), however it is not available commercially in the United States.

PM-477, a genetically engineered endolysin, is asserted to destroy *Gardnerella* biofilms *in vitro*. Preclinical data demonstrates that PM-477 effectively inhibits *Gardnerella* biofilm growth and that it is not prone to resistance development, unlike metronidazole and clindamycin (93). PM-477 may also be effective at disrupting polymicrobial biofilms which include organisms other than *Gardnerella* (94). This agent has not yet been studied *in vivo*.

Boric acid is a chemical that, while not FDA-approved, is commonly used by women attempting to manage persistent BV (26). In vitro it inhibits biofilm formation by *Staphylococcus aureus* and *Pseudomonas auruginosa* (95). However, it did not decrease the viability of S. aureus in an existing biofilm (96). A retrospective chart review examined clinical use of boric acid for recurrent vulvovaginal candidiasis and BV in 272 patients. They found that long term use of boric acid was well tolerated, had high reported satisfaction by patients, and few adverse effects (97). A recent study ($N = 105$) found that boric acid, used in conjunction with antibiotic therapies, resulted in a 69% six month cure for women with recurrent BV (98). A randomized trial of two formulations of TOL-463, a boric-acid based therapy, in 106 participants demonstrated 50%–59% efficacy in early clinical cure (9–12 days) of BV (99). These results are promising and, if studied in the setting of recurrent BV, may have potential in clinical management. Despite its relatively widespread use in BV management, there is limited research on boric acid in the treatment of vaginitis and no studies have examined boric acid alone in the setting of recurrent BV. Additionally, boric acid is used as a pesticide, and although the EPA has found that it is not a carcinogen, the long-term safety of its topical use in humans is unexplored (100).

Astodrimer Sodium, also referred to as Astodrimer 1% Vaginal gel, is a polyanionic dendrimer that prevents formation of bacterial biofilms through blocking bacterial adhesion (27). Randomized, placebo-controlled studies have demonstrated greater clinical cure rates for BV compared to placebo (46.2% vs. 11.5%) (101) and comparable to current antibiotic treatments (102). A recent randomized control trial ($N = 864$) demonstrated that Astodrimer, when applied every other day for 16 weeks following antibiotic therapy, was associated with a 20% reduction in recurrent BV compared to placebo during 16-week follow up (27). This product is not commercially available in the United States, but is sold over the counter in the United Kingdom (Betafem), Europe (Betadine BV) and also in Australia, New Zealand, Southeast Asia and South Africa.

Of the products discussed, Astodrimer and dequalinium chloride have the most evidence of benefit in BV, however neither are available in the United States.

7. Smoking

It is well known that smoking has adverse effects on the body, including increased risk for infections (103). A cohort study of 956 women found smoking to be a significant risk factor for BV (adjusted odds ratio of 3.0) (41) and various other studies have found smoking to be an independent factor related to BV incidence (7, 104, 105). A small cross sectional study ($N = 20$) found that vaginal microbial communities of smokers were more likely to be *Lactobacillus* depleted while nonsmokers were more likely to have *L. crispatus* dominated microbiota (106). Another study identified that women who smoke have higher concentrations of biogenic amines, which may promote non-*Lactobacillus* species and increase vaginal pH (107). Smoking is a modifiable risk factor of BV and is an important lifestyle change to consider in its management (**Figure 1**).

8. Contraception

Both hormonal and non-hormonal contraceptives may play a role in BV occurrence. A large scale cross sectional study ($N = 16,314$) found that BV is more common in women using the non-hormonal copper intrauterine device (IUD) (14.8%) than women with hormonal IUDs (9.7%) and women who are not IUD users (11.1%) (109). Another large study ($N = 2,585$), as a secondary analysis, found that copper IUDs increased women's risk of BV 1.28 fold compared to other non-hormonal methods (110). A well-powered systematic review and meta-analysis found that hormonal contraceptive use, regardless of type, is associated with reduced prevalence, incidence, and recurrence of BV (40).

Various studies have examined condom use in relation to BV occurrence and prevalence. A systematic review and meta-analysis found that condom use was protective against BV, with an estimated relative risk of 0.8 (39). A case-crossover study among 871 women found that consistent condom use was protective against BV (111). Existing research suggests that copper IUDs may increase risk of BV, while condoms and hormonal forms of contraception may decrease risk of BV (**Figure 1**).

Contraceptive choice is very individual, however if a person with recurrent BV is interested in a hormonal contraceptive method rather than a copper IUD, this may reduce the risk for BV. Additionally, using condoms—at least during antibiotic therapy for BV—may be beneficial.

9. Complementary and alternative options

In today's health care climate, many now turn to the internet for answers to their medical questions. Online forums and articles describe several "home remedies" to cure BV. In the following section we discuss several remedies often mentioned

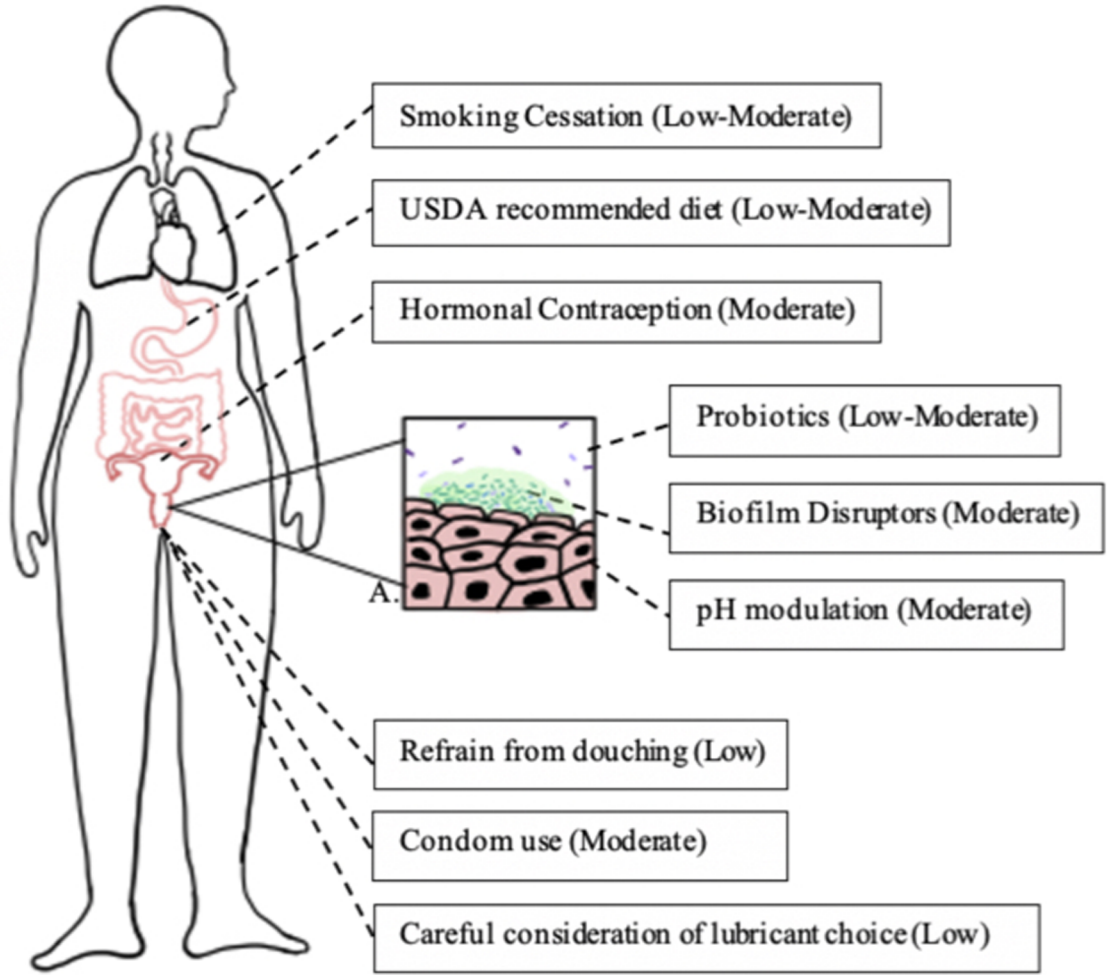

FIGURE 1
Lifestyle changes associated with reduced risk of bacterial vaginosis. Each box represents a lifestyle modification that may affect vaginal epithelium and bacterial vaginosis risk and the modification's quality of evidence, as determined by the GRADE criteria (108). Box A represents a bacterial vaginosis-pathogen dominated vaginal epithelium (dark green rods), with development of biofilm (light green) and reduction of lactobacilli (purple rods).

online (Table 2). Unfortunately, there are few rigorous studies on these therapies, making it difficult to draw conclusions about their potential efficacy.

9.1. Diet

While diet is a significant predictor of gut microbiota composition, it is not yet understood what role diet plays in determining vaginal microbial communities. It is possible that changes in diet may affect the vaginal microbiota through modulating the body's immune response to bacterial pathogenesis and/or through the interplay between the gastrointestinal and vaginal microbiomes (62, 63). A handful of cross-sectional and case control studies conducted mostly in the United States have examined how diet impacts the vaginal microbiome and vaginitis. These studies demonstrate correlations between BV and high glycemic load (35, 36), high dietary fat (37), low dietary fiber (36, 112), and poor intake of Vitamins (A, C, E, D) (38) and micronutrients (38, 124).

A large longitudinal study across over 1500 women in Alabama found that high total fat intake was a significant predictor of BV (37). They also found that high intake of folate, vitamin E and calcium were significantly associated with decreased risk of severe BV (Nugent score ≥9 and vaginal pH ≥5), with adjusted odds ratios of 0.40, 0.41, and 0.40, respectively (37). A separate study among 553 women in the United States found a significant correlation between deficiency in the micronutrient β-carotene and increased risk of BV, with an adjusted odds ratios of 9.2 (38). β-carotene is a micronutrient commonly found in fruits and vegetables and is a precursor to Vitamin A. Deficiencies in the micronutrient betaine, found in seafood and spinach, may also correlate with incident BV (124). Two recent studies also demonstrated that diets rich in fiber are significantly correlated with decreased risk of BV, with odds ratios of 0.22 (36) and 0.49 (112).

The oral intake of garlic, which has known antimicrobial properties, has also been explored as an antibacterial agent for

TABLE 2 Overview of complementary and alternative options for the management and prevention of bacterial vaginosis.

Intervention	Study type and population	Outcome
Diet		
Fat intake	Longitudinal study, $N = 1,521$ (37)	Increased total fat intake is associated with increased risk of BV; OR = 1.4–2.3
Folate	Longitudinal study, $N = 1,521$ (37)	Increased folate is associated with decreased risk of BV; OR = 0.40
Vitamin E	Longitudinal study, $N = 1,521$ (37)	Increased vitamin E is associated with decreased risk of BV; OR = 0.41
Calcium	Longitudinal study, $N = 1,521$ (37)	Increased calcium is associated with decreased risk of BV; OR = 0.40
Glycemic load	Case control study, $N = 144$ (36) Cohort study, $N = 1,735$ (35)	Dietary glycemic index and glycemic load are associated with increased risk and prevalence of BV; OR = 1.04–4.01
Fiber	Case control study, $N = 144$ (36) Cross sectional study, $N = 104$ (112)	Diets rich in fiber correlate with decreased risk of BV; OR = 0.22; 0.49
Beta-carotene	Cross sectional analysis, $N = 553$ (38)	Higher levels beta-carotene correlate with decreased risk of BV; OR = 9.2
Vitamin D	RCT, $N = 118$ (113)	Vitamin D intake does not affect risk of BV
Yogurt & other fermented foods	No *in vivo* studies.	No *in vivo* studies
Apple cider vinegar	No *in vivo* studies.	No *in vivo* studies
Garlic	Single-blinded RCT (without adherence to CONSORT guidelines), $N = 120$ (114)	Garlic and metronidazole have similar effectiveness in BV treatment
Lubricant	Cohort, $N = 44$ (115)	Lubricant use is correlated with few differences in vaginal inflammation, with a trend toward decreased *L. crispatus*
Essential Oils		
Thymbra capita	In vitro study (88) No *in vivo* studies.	Thymbra capita oil has antimicrobial effects on BV biofilm
Tea Tree	In vitro study (116) No *in vivo* studies.	BV pathogens have susceptibility to tea tree oil
Traditional Chinese Medicine	Case study, $N = 180$ (117)	*Cortex Phellodendri Chinesis* was associated with improvement of BV symptoms and Nugent score
Douching		
	Large cross sectional study, $N = 1,200$ (118)	Vaginal douching is associated with BV and BV-related microbiota; OR = 2.1.
	Cross sectional study, $N = 609$ (119)	Vaginal douching is associated with lactobacilli-depleted microbiomes; OR = 2.24
	Cross sectional study, $N = 272$ (120)	Vaginal douching is associated with reduction of beneficial lactobacilli; prevalence ratio = 0.57
	Cross sectional study, $N = 234$ (121)	Association between vaginal washing and BV-associated bacteria is variable geographically
	Longitudinal Observational study, $N = 100$ (122)	Douching is associated with reduced clearance of BV; OR = 0.45
	Pilot study, $N = 38$ (123)	Cessation of vaginal douching may reduce risk of BV; OR = 0.76

The adjusted odds ratio (aOR) reported by each study is included when available.

BV management. Allicin, a compound from garlic, has previously been demonstrated to have antifungal properties (125); however, these antifungal properties do not directly translate to antibacterial properties that might target BV. Garlic's antibacterial properties have been sparsely studied in the context of BV. One single-blinded study ($n = 120$) found that oral garlic tablets and oral metronidazole have similar effectiveness in treating BV (114); however, the study was underpowered and did not adhere to CONSORT guidelines for reporting. No other studies have examined garlic intake in the context of BV.

Many fermented foods are rich in *Lactobacillus* strains. The ingestion of fermented foods, such as yogurt or kimchi, function similarly to oral probiotics via the introduction of live bacteria to the gastrointestinal system. The effect of oral probiotic consumption on the management of BV is still not well understood but may have potential, as discussed in the probiotics section. Whether it is more effective to deliver live bacteria in food vs. as a capsule has not been evaluated.

Vitamin D, which is acquired from both dietary sources and UV-B, may play a role in BV occurrence. Researchers have examined its effects with conflicting results. Multiple studies among pregnant women have found that Vitamin D deficiency correlates with increased BV risk (126–128); however, a large scale longitudinal study ($N = 2,337$) did not find a significant relationship between Vitamin D deficiency and BV among non-pregnant women (129). Additionally, a randomized trial of Vitamin D supplementation, which demonstrated a significant increase in serum vitamin D in treated participants, did not demonstrate a significant reduction in BV incidence vs. placebo (65% vs. 48%) (113).

Dietary carbohydrate indices, such as glycemic load, can be useful indicators for carbohydrate rich diets that result in increased postprandial serum glucose. Women with diabetes are at greater risk of vaginal dysbiosis (130) and vaginal infections (131). A case control study among Iranian women ($N = 295$) found that high dietary glycemic index and glycemic load were significantly associated with increased risk of BV, with adjusted odds ratios of 2.99 and 4.01 (36). A cohort study of 1735 women found glycemic load to be associated with slightly greater incidence and persistence of BV, with odds ratios of 1.03 and 1.02 (35).

Available research seems to suggest that a diet which follows the USDA recommendations reduces risk of BV. Many studied

micronutrients interact with one another in the body, making it difficult to confidently separate their effects. The extent to which diet could play a part in the clinical management of BV is not known, although current data provide a foundation upon which future research could build.

9.2. Apple cider vinegar

Online articles discuss apple cider vinegar baths, douches, and oral consumption in the context of BV management. A 2018 *in vitro* study demonstrated that apple cider vinegar has antimicrobial effect on pathogens such as *S. aureus* and *E. coli* (132), but its effects on BV-associated bacteria have not been studied. Apple cider vinegar contains acetic acid and lactic acid, both of which have been studied in the context of BV management. One proposed mechanism of action of these properties is through acidification of the vaginal pH, making it less hospitable to BV-associated species that thrive at a higher pH. As we discuss in the pH modulation section, simply modifying the vaginal pH may not be sufficient to prevent BV. Oral consumption of apple cider vinegar would likely not have a direct effect on the vagina but may influence gut microbiota.

9.3. Lubricants

The World Health Organization (WHO) recommends that lubricants do not exceed an 1,200 mOsm/kg osmolality, which may be associated with vaginal cytotoxicity (133, 134), and recommends that vaginal lubricants have a pH near 4.5 (135). These guidelines are based on promoting vaginal epithelial integrity and decreasing risk for sexually transmitted infections. Otherwise, little is known regarding the effect of lubricant on BV. Various online forums discuss how the use of lubricant during intercourse may help prevent BV recurrence.

A recent *in vitro* study found that different vaginal products have varying effects on growth of beneficial *L. crispatus*. They found that two vaginal lubricants inhibited growth of *L. crispatus,* while another stimulated its growth (136). An *in vivo* study ($N = 44$) examining vaginal microbiota after lubricant use and non-use found few significant changes in vaginal inflammatory markers between the groups, as well as a trend towards decreased *L. crispatus* in the women who used lubricant (115); however, this study did not control for type of lubricant used. Depending on the product, lubricant may increase vaginal epithelial inflammation and dysbiosis (137, 138), affect vaginal microbiota through antimicrobial preservatives such as parabens or glycerine (139), and/or alter microbiota through pH and osmolality (139). The effect lubricants have on vaginal microbiome and BV are likely product specific. Further, products that induce mucosal inflammation, even if they have beneficial effects for prevention of BV, may increase the risk for acquisition of other STIs.

9.4. Douching

Vaginal douching is a method of flushing a product through the vagina, often as an attempt to address vaginal discomfort or discharge. An *in vitro* 2021 study found that the contents of common commercial douching products (vinegar, iodine and baking soda) all may be associated with epithelial inflammation and disruption of the anti-inflammatory effects of lactobacilli (140). It is hypothesized that increased inflammation may inhibit recolonization of beneficial lactobacilli. Douching has been associated with reduction of *L. crispatus*, with no reduction of *L. iners* or *L. jensenii* (120). An early pilot study among 39 women found that cessation of vaginal douching may reduce BV risk (123). A recent longitudinal observational study ($N = 100$) found that among women with *L. iners* dominated vaginal microbiota, douching was related with reduced clearance of BV (122). A cross sectional study among 1,200 women found that douching is associated with BV and BV-related pathogens (118). An international cross-sectional study ($N = 234$) found an associated between douching and BV-associated bacteria in American women but not among Kenyan women (121). Finally, a cross-sectional study of 609 women found that vaginal douching, regardless of product, is associated with lactobacilli-depleted microbiomes (119). However, most *in vivo* douching studies have been cross-sectional, limiting the ability to draw causal inference. Additionally, many people douche because of symptoms of BV, thus associations between douching and lower counts of lactobacilli may not be causally related. However, because of the possible association with decreased vaginal lactobacilli, and its association with pelvic inflammatory disease, douching should be discouraged (141).

9.5. Traditional Chinese medicine

Traditional Chinese medicine (TCM) uses therapeutic herbs in the prevention and treatment of disease, including mediation of microbiota (142). There are various approaches to treating BV with TCM (143), which include utilizing the immunity-enhancing and antimicrobial properties of medicinal herbs. Much of the clinical research on TCM in the context of BV have small sample sizes, and many of the research publications, completed in China, are not widely available on U.S. research databases. One available study examines berberine, the active ingredient of the herbal medicine *Cortex Phellodendri Chinesis*. A study of 240 Chinese women found that clinical symptoms of women in the BV arm ($N = 180$) significantly improved following topical treatment with berberine and the Nugent score improved in 92.78% (117). There was no control BV group, which makes these results difficult to analyze. Much of the clinical research on TCM in BV and vaginal health management has been done in the last few years and has recently been compiled into a published review (143). More clinical research is needed to better understand its potential effect on BV management.

9.6. Essential oils

In the 1990s, early research indicated that tea tree oil may have potential to manage BV symptoms (116, 144). A 1999 *in vitro* study, found that BV-associated bacteria are susceptible to tea tree oil while lactobacilli are more resistant (116). While these publications are referenced online, they are not peer reviewed nor do they have large sample sizes. Anecdotally, many providers report that patients have vaginal irritation with the use of tea tree oil.

Thymbra capita essential oil has also been studied in the context of BV management. Thymbra capita, a type of thyme, has well-established antimicrobial properties (108, 145, 146). Recently, a study on *in vitro* and ex vivo vaginal tissue models demonstrated that the oil's antimicrobial properties extend to *Gardnerella,* while sparing healthy *Lactobacillus* species (87). A subsequent study examining BV biofilm *in vitro* found that the biofilm model, containing six BV-associated species, was susceptible to the antibacterial effects of thymbra capita oil (117), suggesting that it may be effective against a variety of BV-associated pathogens. In this study, thymbra capita significantly reduced the total mass of the polymicrobial biofilm and posed no harm to vaginal epithelial cells. Notably, bacterial species present in this study were resistant to metronidazole, suggesting this essential oil could be a viable option for recurrent BV resistant to antibiotics. However, no data are available on how well tolerated this product would be, nor the impact on vaginal epithelium.

Additional BV management methods that are widely discussed online, such as vitamin C, boric acid, and oral probiotics, are discussed in previous sections of this article.

10. Conclusion

Bacterial vaginosis is a common medical diagnosis that significantly impacts women's quality of life and reproductive health. Antibiotics, the only approved treatment for BV, have high recurrence rates, negative side effects, and after antibiotic treatment, there is limited recolonization of the vaginal microbiota with beneficial *Lactobacillus* species. Despite high prevalence of BV worldwide and the inability of antibiotics to provide a long-term cure, few effective alternative treatment options exist. There are various studies underway attempting to identify novel approaches, with possible solutions ranging from diet and lifestyle changes to biofilm disruption, pH modulation and vaginal microbiome transplantation. Still, much of this research is either underpowered or concentrated on *in vitro* models. Considering the lack of science-based answers, clinicians and patients alike are attempting to find solutions on their own. It is important that medical research continues to prioritize BV management and that both clinicians and patients have the resources to be informed on the safety and efficacy of the products that many are already using.

Author contributions

CA provided the first draft of the manuscript and the tables and figure. CA and CMM defined the content of the article. Both authors critically reviewed multiple drafts of the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

CMM has served as a consultant for Ferring Pharmaceuticals, and receives royalties from Up to Date.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1100029/full#supplementary-material.

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