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The vaginal microbiome and an emerging therapeutic option from Symbiomix for bacterial vaginosis

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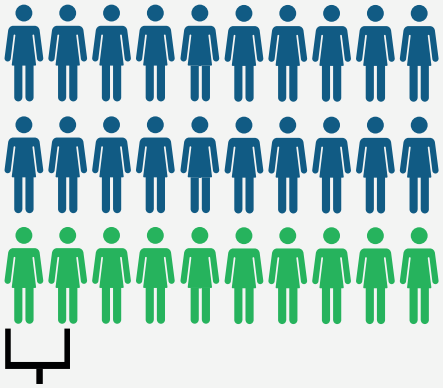
The vaginal microbiome is a complex environment that hinges on an appropriate balance of indigenous healthy and nonbeneficial bacterial species. The predominant healthy species, Gram-positive *Lactobacillus*, produces lactic acid, hydrogen peroxide, and other antimicrobial compounds[1]. These substances maintain the vaginal pH at between 3.5 and 4.5, which protects against infection in the vagina by mostly nonindigenous organisms. When the vaginal microbiota are disturbed, bacterial vaginosis (BV) occurs. Effectively treating BV is a key concern of Symbiomix Therapeutics, a biopharmaceutical company that is bringing innovative medicines to market for prevalent gynecological infections that may have serious health consequences.

Bacterial vaginosis

BV is a common gynecological infection (**Fig. 1**). Its prevalence in the United States is 29.2%, affecting 21.4 million women aged 14–49[2]. BV is characterized by the loss of normal vaginal microbiota, most notably the predominant *Lactobacillus* species, and an increase in the numbers and species of other Gram-negative and Gram-positive anaerobic bacteria in vaginal fluid (**Fig. 2**). Common bacteria associated with BV include *Gardnerella vaginalis, Mycoplasma, Ureaplasma*, and *Prevotella* and *Mobiluncus* species[1].



Only 16% of women with bacterial vaginosis report their symptoms.

Women with bacterial vaginosis are often misdiagnosed and undertreated.

Figure 1. Bacterial vaginosis in US women[2].

The etiology of BV is unknown and is likely to be multifactorial and polymicrobial, but risk factors include engaging in sex with multiple male or female partners or having a new partner, douching, not using condoms, and lacking the protective *Lactobacillus* species in the vagina[1]. Women who are not sexually active are infrequently affected.

BV symptoms include a vaginal discharge and fishy malodor. Vaginal symptoms of abnormal odor or discharge have been reported in 13.2% of all women, of whom 32–46% were found to have symptomatic BV[2,3].

If symptoms are present, they are similar to many other types of infections or vulvovaginal complaints, which can make confirming a BV diagnosis challenging[4]. Diagnosis requires the presence of at least three of the following: abnormal, gray vaginal discharge; vaginal pH > 4.5; positive amine test; and >20% clue cells (epithelial cells that are heavily coated with bacteria)[1]. A Nugent Gram stain test or molecular testing and PCR are also available for diagnosis of BV. Inconsistent clinical practices and lack of adherence to diagnostic criteria are associated with misdiagnosis.

BV is often thought to be a routine gynecological condition similar to a yeast infection, but it can have long-term consequences for reproductive health and fertility. The condition is known to increase the risk of sexually transmitted infections (STIs) such as chlamydia, gonorrhea, herpes simplex virus 2 and HIV, along with preterm birth, post-procedural gynecological infections, and pelvic inflammatory disease[1]. Recurrence affects up to 58% of patients, and it is due to the persistence of offending bacteria, reinfection, or continuing disturbances in the vaginal microbiota[1,3].

Limitations of current treatments

Treatment options for BV recommended by the Centers for Disease Control and Prevention (CDC) are metronidazole 500 mg orally twice daily for 7 days; metronidazole gel 0.75%, 5 g intravaginally once a day for 5 days; or clindamycin cream 2%, 5 g intravaginally once a day for 7 days[1].

Metronidazole is a first-generation nitroimidazole antibiotic, and clindamycin is a lincosamide antibiotic. Oral tinidazole or clindamycin, or intravaginal ovules of clindamycin, are alternative antimicrobial regimens recommended by the CDC. No single-dose oral therapy options for BV have been approved by the US Food and Drug Administration (FDA).

Treatment-regimen adherence is approximately 50% for oral metronidazole, presumably due to the week-long twice-daily dosing schedule[5]. Clindamycin is less effective than metronidazole for eradicating some BV-associated bacteria, and resistance to the drug has been documented[6]. Clindamycin cream, which is oil based, may weaken latex condoms and diaphragms for 5 days after use[1]. Oral metronidazole is associated with poor tolerability and adverse reactions to alcohol, and it can cause gastrointestinal irritation, nausea or vomiting, and a metallic taste in the mouth. Alcohol consumption should be avoided while taking nitroimidazoles, which means 5–7 days of abstaining from alcohol for metronidazole. Both clindamycin and metronidazole may deplete levels of healthy vaginal bacteria[7].

The majority of women with BV do not receive treatment for their infections, and current treatments do not meet patient expectations[2,3]. Bacterial resistance to current therapies has led to reduced efficacy, and recurrence rates after treatment are high.

A next-generation nitroimidazole antibiotic

Secnidazole (Solosec) 2-g oral granules, a next-generation nitroimidazole therapy by Symbiomix Therapeutics was approved under priority FDA review as a qualified infectious disease product (QIDP) to treat bacterial vaginosis in adult women.

It has demonstrated statistically significant efficacy and is well tolerated. *In vitro* drug–alcohol interaction studies showed no effect on ethanol metabolism by aldehyde dehydrogenase. The one-time dosing formulation is designed to enhance patient adherence and minimize the time of alcohol abstinence. If approved, it will be the only single-dose oral therapy for BV.

Other secnidazole formulations are used worldwide to treat many illnesses, including BV. It is a preferred treatment because of its long half-life, simple dosing regimen, and low side-effect profile[9]. It is considered an effective alternative to metronidazole, with comparable cure rates[8,10].

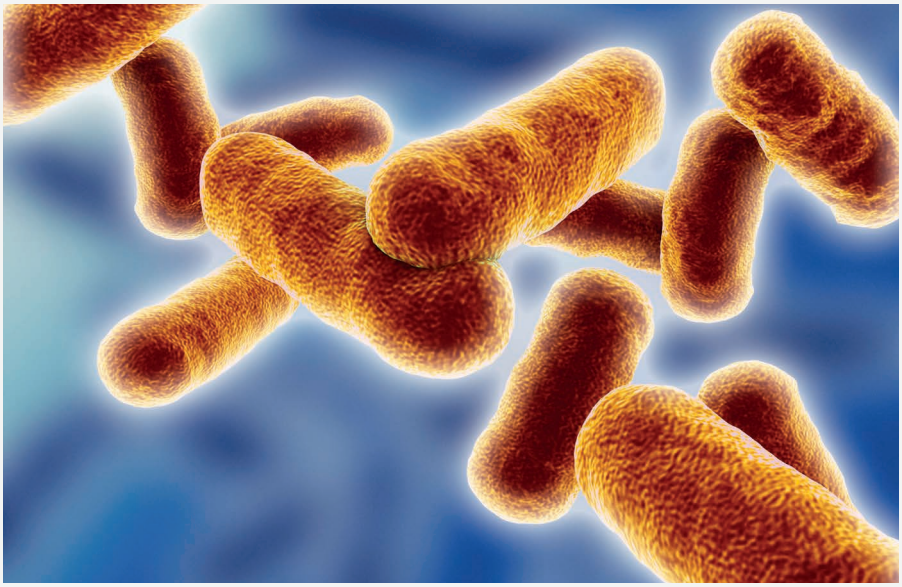


Figure 2. *Lactobacillus*. **Populations of these rod-shaped bacteria decline when bacterial vaginosis occurs.**

A phase 2 randomized, double-blind, placebo-controlled study of 215 women found that secnidazole at a single dose of 1 or 2 g was more effective than placebo for clinical, microbiological, and therapeutic cure rates of BV ($P < 0.05$ for all three)[8]. These findings were supported by a second study of 189 post-menarchal adolescent women who received a single dose of secnidazole 2-g granules, which determined that both clinical and microbiological cure rates were higher for secnidazole than placebo ($P < 0.001$).The most common adverse events in placebo-controlled studies were vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal itching (2.0%).

The future of BV treatment

New antimicrobial approaches are needed to counter the tide of BV infections in the United States, given that current treatment options for BV underperform against expectations and lead to high recurrence rates. The next-generation 5-nitroimidazole antibiotic secnidazole under development by Symbiomix has shown safety and superior efficacy in clinical trials, and antibiotic resistance to the drug occurs rarely if at all. The drug is listed as a qualified infectious disease product by the FDA for the treatment of BV, a designation that was created to encourage the development of new antibiotics to treat serious or life-threatening infections. Such medicines are urgently needed for BV, as serious health risks remain if BV is untreated or undertreated. Symbiomix is committed to innovative medicines for prevalent gynecological infections that may, if not treated, have serious health consequences.

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