BEST PRACTICES: In the Evolving Mystery of BV, an Innovative Oral Treatment Emerges

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Our understanding of bacterial vaginosis (BV) has evolved over many years, yet the condition remains mysterious. BV has been described as a complex microbial imbalance, with the native vaginal *Lactobacillus* species and increased anaerobic bacteria playing significant roles. Today, BV is understood as dysbiosis of the vaginal microbiome, whether symptomatic or asymptomatic. The condition is common, but despite years of study, the lack of an exact cause—and why some women get it and others do not—adds to its mystery. In 2017, however, an innovative single oral dose treatment emerged that may reduce incidence.

BV terminology and treatment over time

The German gynecologist Albert Döderlein first described the lactic-acid-producing lactobacilli from healthy vaginas in 1882. Progress in understanding what is now known as BV came slowly from there.

In 1921, Schröder published illustrations of vaginal smears with three grades of vaginal flora and changes in flora consistent with BV. The illustrations demonstrated the microbiologic diversity of the female reproductive tract.

In the late 1940s and early 1950s, BV was basically a syndrome in search of an etiology.[1] Symptoms consisted of a gray, homogenous, malodorous vaginal discharge. Because a single organism was not consistently isolated, the term nonspecific vaginitis (NSV) was used.

By mid-century, in 1955, Gardner and Dukes isolated a small gram-negative rod from 90% of women presenting with symptoms.[2] This newly discovered organism was coined *Haemophilus vaginalis* and assumed to be the etiological agent in NSV.

When "*Haemophilus vaginalis* vaginitis" was present, lactobacilli were noted as almost completely absent, and other organisms and "pus cells" were described as greatly reduced. "Clue cells" were ascribed to *Haemophilus*, described as a nonmotile, short gram-negative bacillus that agglutinates to the epithelial cells and forms the clue cells.[3] Patient complaints were described as an offensive discharge with little or no discomfort or itching. The condition was considered a venereal disease and so treatment included all patient sexual contacts.

By 1983 gardnerella became the term for what we now consider BV,[4] based on the presence of the facultative anaerobe *Gardnerella vaginalis*. Herman Gardner established its role as a common cause of vaginitis through studies that fulfilled Koch's postulates. Again, the condition was considered sexually transmitted. It was characterized by a "fishy" odor and a pH reading between 5 and 6; lower pH readings ruled out this diagnosis. "Clue cells" also characterized gardnerella. Suggested treatments included oral metronidazole 500 mg twice daily for 5 to 7 days, with simultaneous treatment of the male partner; ampicillin 500 mg four times daily for 5 to 7 days; or cephradine 500 mg four times daily for 5 to 7 days as a last resort. Douching with hydrogen peroxide was described as a helpful adjunct.

Distinctions in vaginal bacterial communities between women with and without BV were evident by 1989, and the term bacterial vaginosis appears in the literature.[5,6] By 1992, *Gardnerella vaginalis* was described as having significance in BV, which had also been known as nonspecific vaginosis.[7] Then, BV was acknowledged to have a "polymicrobic etiology."

Current understanding of BV etiology

Today the vaginal microbiome is understood to relate to behavior, sexual health, and sexually transmitted diseases (STDs)[8,9] and affects the host's metabolism and susceptibility to disease. Links between disruptions of normal vaginal flora and pelvic inflammatory disease, miscarriages, and prematurity have long been established.

The vaginal microbiome may be understood through a socioecologic framework,[9] including individual, relational, community, and societal influences. The prevalence of BV varies by ethnic group, and its acquisition in the United States has a stronger association with African Americans. Among US-born black and white women, black women have more microbial diversity and less likelihood of colonization with lactobacilli than white women.

The growth of lactobacilli seems to be stimulated by estrogen; some hormone contraceptives can alter the vaginal microbiota.[9] Oral contraceptives have a consistent association with a decrease in prevalent BV, as do condoms. Alternatively, douching and cigarette smoking are each associated with an increased risk for BV.

In addition to the mysteries surrounding who gets BV and why, debate surrounds its classification.[9] BV may be sexually transmitted or sexually associated. Multiple, new, or more male partners are strongly associated. Women who have sex with women have increased risk compared to women who have sex with men only.

Diet affects the gut microbiome, which in turn may serve as a reservoir for both lactobacilli and BV-associated bacteria. The human microbiota is also affected by the built environment and by stress; thus, combining an unhealthy neighborhood, diet, social conditions, stress, and other factors related to poverty may have unhealthy influences on the vaginal microbiome.

BV consequences

Undiagnosed or untreated BV has ongoing consequences. When the vaginal microbiome is imbalanced, as with BV, it is a risk factor for acquiring STDs, including the herpes simplex virus, human papillomavirus (HPV), human immunodeficiency virus (HIV), gonorrhea, chlamydia, and trichomoniasis. BV is also associated with pelvic inflammatory disease, endometritis, intra-amniotic infections, and even preterm birth.[9]

BV treatments

Existing Centers for Disease Control-recommended treatments are metronidazole 500 mg orally twice a day for 7 days, metronidazole gel 0.75% intravaginally once daily for 5 days, or clindamycin cream 2% intravaginally at bedtime for 7 days.[10] Alcohol should not be consumed during treatment with nitroimidazoles.

In September 2017, the US Food and Drug Administration approved SOLOSEC (secnidazole) 2-g oral granules to treat BV in adult women.[11] SOLOSEC is taken once orally in the form of granules, which is expected to improve compliance and likely reduce recurrences.

In a randomized, placebo-controlled clinical trial, secnidazole 2 g led to clinical response* rates of 67.7% among women with BV, which was confirmed by a central laboratory.[12] Even among women with 4 or more BV episodes, clinical response rates were 57.1%. All treatment-emergent adverse events were mild or moderate in intensity.

Future research needs in BV

Questions about BV and the vaginal microbiome remain unanswered:

- How do network and community-level risk factors affect the vaginal microbiome?
- Is a change in pH from menstruation or unprotected intercourse a trigger?
- Does the effect of overlap and duration of concurrent partnerships on the vaginal microbiota help to explain racial differences consistently seen?
- What is the role of biofilm disruption and probiotic administration in improving cure and preventing recurrences?
- What are the effects of vaginal fluid transfer from healthy donors for recurrent BV, and of treating sex partners?

While researchers continue to contribute to our evolving understanding of the how and why of BV, an innovative new treatment may help to reduce occurrences of this mysterious yet common vaginal infection.

* A clinical responder was defined as "normal" vaginal discharge, negative "whiff" test, and clue cells <20%.

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Indication

SOLOSEC™ (secnidazole) 2-g oral granules is nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in adult women.

Important Safety Information

- SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.
- Vulvo-vaginal candidiasis may develop with SOLOSEC and require treatment with an antifungal agent.
- Potential risk of carcinogenicity in patients taking single-dose SOLOSEC to treat bacterial vaginosis is unclear. Chronic use should be avoided.
- SOLOSEC may pass into breast milk. Patients should discontinue breastfeeding for 96 hours after administration of SOLOSEC.
- SOLOSEC is taken once in the form of granules sprinkled on soft food. The entire contents of a SOLOSEC packet should be consumed within 30 minutes without chewing or crunching the granules. SOLOSEC is not intended to be dissolved in any liquid.
- In clinical studies, the most common adverse events occurring in (≥2%) of patients receiving SOLOSEC 2-g oral granules were vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), dysgeusia (3.4%), vomiting (2.5%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal pruritus (2.0%).

To report SUSPECTED ADVERSE REACTIONS, contact Symbiomix Therapeutics, LLC at 1-844-SOLOSEC (1-844-765-6732) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please visit www.solosechcp.com for Full Prescribing Information.

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