Bacterial Vaginosis

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In Brief

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Author Disclosure

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Bacterial vaginosis (BV) is the most common infection of the reproductive tract in females of child-bearing age and is the most common cause of symptomatic vaginal discharge in this group, accounting for approximately 40% to 50% of cases. Estimates of the prevalence of BV range from 10% to more than 50% of reproductive-age women. Between 25% and 50% of BV infections may remain asymptomatic.

BV is characterized by a complex alteration of vaginal flora, with loss of the normally acidic (pH <4.5) vaginal environment that is dominated by hydrogen peroxide-producing lactobacilli, which are protective against the overgrowth of anaerobic bacteria. There is a shift to a less acidic (pH >4.5), anaerobe-dominated environment that is populated by multiple bacterial species, including *Gardnerella vaginalis, Mycoplasma hominis, Mobiluncus*, and species of *Prevotella, Bacteroides, Peptostreptococcus, Fusobacterium,* and *Atopobium vaginae*. A recent study reported that women who have symptomatic BV are infected with an average of 13 different organisms. The diverse microbial profile of BV varies remarkably by location, demographics, and other factors.

In 1955, Gardner and Dukes described the classic "clue cells" of BV and identified *Haemophilus vaginalis*, later classified as *G vaginalis*, as the organism causing BV. For a period of time, the disease was simply known as *G vaginitis.* Although we now know that many organisms are associated with BV, *G vaginalis* is its most sensitive indicator and can be identified in virtually 100% of women who have BV. In contrast to the excellent sensitivity of *G vaginalis* for BV, its specificity of 35% to 40% is mediocre, with up to 50% to 60% of healthy women who have no symptomatic BV being infected with *G vaginalis*.

The rising pH in BV facilitates attachment of bacteria to the epithelial surface of the vaginal mucosa in the form of a dense bacterial biofilm composed primarily of matrices of *G vaginalis,* with substantial contributions of *A vaginae*. The anaerobic bacterial overgrowth produces proteolytic enzymes and decarboxylases that break down vaginal peptides and convert them into volatile malodorous amines that, in turn, cause vaginal transudation and exfoliation of the biofilm-coated epithelial cells of the vaginal surface in the form of the classic bacteria-studded "clue cells" of BV.

Although research supports BV as a sexually transmitted disease, the role of sexual activity in its pathogenesis remains unclear. *G vaginalis* is not identified in prepubertal children who have been screened carefully for being at very low risk for sexual abuse. In contrast, *G vaginalis* was identified by culture in 24% of a group of sexually abused girls, of whom very few had vaginal symptoms and among whom the diagnosis of sexually transmitted infections (STIs) was very infrequent. In the few studies of the epidemiology of *G vaginalis* in men, the organism appears to have been identified in the genital tracts of approximately 3% to 10% of men by miscellaneous detection methods and in various contexts. BV occurs primarily in sexually active, reproductive-age females, particularly in women having new or multiple sexual partners. BV can occur without coitus; oral-genital and hand-genital contact may be even stronger risk factors for BV than penile-vaginal contact. Among female sexual partners, there is a relatively increased incidence of BV with a between-partner consistency in vaginal flora. Factors other than sexual activity associated with BV include douching and cigarette smoking.

The clinical significance of BV extends far beyond its causing annoying vaginal discharge. BV is associated with numerous genital tract infections, including increased susceptibility and transmission of *Chlamydia* infection, gonorrhea, and oncogenic strains of human papillomavirus. BV enhances the replication and vaginal shedding of human immunodeficiency virus and herpes simplex virus-2. BV pathogens ascend into the upper reproductive tract and are associated with pelvic inflammatory disease; an increased incidence of postpartum, postabortion, and posthysterectomy infections; and postpartum and postabortion endometritis. An association between BV and both premature rupture of membranes and preterm birth may be mediated by chorioamnionitis. The increased susceptibility to infection with genital tract pathogens and the associated adverse gynecologic and obstetric outcomes in BV are believed to be mediated through the induction of immune modulation and increased production of proinflammatory cytokines.

Clinically, symptomatic BV presents with a thin, homogenous, white-to-gray vaginal discharge that has an unpleasant, amine-associated "fishy" odor. Typically, erythema, inflammation, and pruritus are absent; only rarely is there dyspareunia or dysuria. The Centers for Disease Control and Prevention (CDC)-recommended Amsel criteria (sensitivity >90%, specificity 77%) require three of four criteria to diagnose BV clinically: 1) thin, white-to-gray, noninflammatory, homogenous discharge that smoothly coats the vaginal walls; 2) positive whiff-amine test (a "fishy" odor produced when a drop of 10% KOH is added to vaginal discharge); 3) vaginal pH greater than 4.5; and 4) greater than 20% clue cells (bacterial-studded epithelial cells) in saline wet mount per high-power microscopic field (most reliable of the four criteria).

If microscopy is unavailable, alternate diagnostic strategies are useful. Nugent scoring, based on Gram staining laboratory-submitted samples of vaginal secretions and grading specimens by BV-like morphotypes, is considered to be the diagnostic gold standard for BV. Other diagnostic methods include targeted DNA probes and rapid test diagnostic cards that indicate elevations of pH and amines. Because of the striking microbial heterogeneity in BV, vaginal culture is far too nonspecific to be used to diagnose BV.

Additional clinical and microscopic clues, combined with determining the pH of the vaginal sample, help to distinguish BV from other common causes of abnormal vaginal discharge such as candidiasis and trichomoniasis. Symptomatic yeast infections, unlike BV, may present with pruritus, erythema, and often a thick, white cottage cheese-like vaginal discharge. Although candidiasis favors the normally acidic vaginal pH, it sometimes may coexist as a mixed infection with BV in its less acidic (pH >4.5) vaginal environment (although this is uncommon). However, this coexistence does not present in the opposite direction; the diagnosis of candidiasis in a normally acidic (pH <4.5) vaginal sample essentially rules out the diagnosis of BV (pH >4.5). Trichomoniasis along with BV is associated with an abnormally elevated pH. Trichomoniasis may coexist silently with BV, and clinicians should scan carefully to rule out the coexistence of the other if either clue cells or trichomonads are identified on wet mount. Pruritus, dyspareunia, and a frothy, greenish, malodorous discharge, combined with the microscopic findings of trichomonads and polymorphonuclear leukocytes, distinguish symptomatic trichomoniasis from BV because BV typically is not associated with inflammation.

BV resolves spontaneously in about one third of affected women. The goal in treating symptomatic females is to alleviate the unpleasant symptoms and reduce the risk of infectious sequelae. Treatment of BV in asymptomatic women is controversial. Some experts advocate treatment of all women who have BV regardless of the presence or absence of symptoms because of the enhanced risk of acquiring other STIs and the risk of adverse gynecologic and obstetric complications. The current CDC STI guidelines, however, advise that therapy for BV in nonpregnant women be directed at relieving symptoms of infection and reducing the risk of infection after abortion or hysterectomy. To reduce the risk of premature rupture of membranes and preterm birth, the recommendation is to screen and treat BV only in pregnant women who have a history of preterm birth. However, screening and treating all pregnant women for BV has not appeared to affect preterm birth rates. Studies indicate no benefits in treating the sexual partners of women who have symptomatic BV.

The most successful therapy for BV in nonpregnant women is metronidazole, either 500 mg orally twice a day for 7 days (with a warning to avoid alcohol consumption) or 0.75% intravaginal gel once a day for 5 days. Metronidazole is particularly attractive for treating BV because it also eradicates any coexisting trichomoniasis. Slightly less effective than metronidazole is a 7-day course of intravaginal 2% clindamycin cream (with a warning that latex condoms may be weakened). Clindamycin resistance and pseudomembranous colitis are risks of clindamycin therapy. A 5-day 1-g/d oral course of tinidazole, a second generation nitroimidazole, which has a longer half-life and fewer adverse effects than metronidazole, is at least as effective as metronidazole.

Treatment of BV can be very frustrating because a standard course of either metronidazole or clindamycin results in a mediocre 60% to 80% cure rate. If symptoms resolve, test-for-cure is unnecessary. Unfortunately, relapse with BV is very common; 30% of

treated women relapse within 3 months and more than 70% relapse within 7 months. Women who have recurrent BV appear to be unable to recolonize their vaginas with the normal, hydrogen peroxide-producing lactobacilli that protect against the overgrowth of anaerobic bacteria. Unfortunately, lactobacilli supplements and yogurt do not contain the species of hydrogen peroxide-producing lactobacilli endemic to the normal female genital tract (although they may help prevent the development of candidiasis during prolonged antibiotic courses for recurrent BV). Behavioral modifications, including abstinence and consistent condom use, may reduce the recurrence of BV.

In summary, the well-documented association of BV with STIs and adverse gynecologic and obstetric outcomes, its biofilm-associated recalcitrance to treatment and eradication, and its frequently asymptomatic presence support this condition being a global gynecologic and obstetric problem that warrants continued research. There is a need to elucidate further the pathogenesis of BV, with several potential goals. One is to develop reliable, inexpensive, and convenient identifiers of coinfection with the highly specific *G vaginalis* and *A vaginae* combination to predict those women who are at particular risk for recurrence and adverse gynecologic and obstetric outcomes. A second is to formulate more effective treatments that may penetrate, disrupt, or dissolve the biofilm matrix. A third is to develop realistic strategies for preventing BV, such as possible targeted vaccines.

Comment. This In Brief emphasizes the benefit of vaginal *Lactobacillus* to maintain a healthy environment for the vagina and cervix. When this environment is altered by the presence of bacterial vaginosis, the challenge to clinicians is to differentiate those women who remain as asymptomatic carriers from those who will become symptomatic and are at risk to suffer sequelae and warrant treatment. An alteration in innate immunity has been hypothesized as a possible explanation for differences in response to the infection and progression to sequelae. If this hypothesis were confirmed, genetic testing of women may be warranted to identify those who would benefit most from treatment. Such identification of at-risk women could minimize unnecessary antibiotic exposure yet ensure that those at risk be treated to prevent significant sequelae. Alternative strategies support the importance of developing targeted vaccines for protection from infection.

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