Bacterial Vaginosis

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Bacterial vaginosis, the most prevalent cause of vaginal discharge in the United States, is characterized microbiologically by a shift in the vagina away from a lactobacillus-predominant flora and toward a predominantly anaerobic milieu. The cause of bacterial vaginosis is unknown, but the epidemiology of the syndrome suggests that it is sexually associated. Bacterial vaginosis has been associated with various complications, such as pelvic inflammatory disease, preterm birth, postoperative gynecologic infections, and abnormal Pap smears. Abnormal vaginal flora may also be a biologic risk factor for sexually transmitted diseases, including HIV infection.

Introduction

Vaginal infections are a major cause of morbidity in the United States and worldwide. Of these infections, bacterial vaginosis (BV) is the most prevalent but the least well understood. Although the clinical and microbiologic characteristics of BV are known, the cause of the syndrome remains a mystery.

The prevalence of BV in the general US population is 20% to 25% [1,2]. In populations at high risk for sexually transmitted diseases (STDs), the prevalence may be as high as 50% to 60% [3,4]. Little information on incidence is available. Bacterial vaginosis has never been proven to be an STD, but it behaves as one epidemiologically, and most authorities therefore describe it as "sexually associated." Epidemiologic risk factors for BV include a history of multiple sexual partners, a recent change in sexual partners, and a history of STD. Douching has also been associated with BV, although the cause and effect relationships in this association are unknown [1,5–7]. The epidemiologic profile of BV strongly resembles that of an STD, but the rare reported occurrence of BV in sexually inexperienced women and the failure of treatment of the male partner to prevent recurrent BV in studies in the 1980s are cited as evidence against sexual transmission [8–11].

Characteristics of Infection

The microbiologic changes that characterize BV have been well studied. In women with BV, lactobacilli (especially hydrogen peroxide–producing strains) are greatly diminished, and large numbers of anaerobic and facultatively anaerobic bacteria seem to "take over." These organisms include *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides* species, *Prevotella* and *Porphyromonas* species, *Peptostreptococcus*, and *Mobiluncus* species [2,12,13]. Although most of these organisms may be present in small numbers in the normal vagina, *Mobiluncus* species are seldom detected in normal persons on culture or Gram stain [14]. This observation has led to the speculation that *Mobiluncus* species may be specifically involved in the pathogenesis of BV. Although the normal vaginal flora is described as consisting primarily of lactobacilli, variations in the day-to-day composition of the flora on Gram stain are common. Studies suggest that only about 25% of women maintain a lactobacillus-predominant flora throughout the menstrual cycle. Others have transient, sometimes dramatic changes, with most changes occurring around the time of menses [15•,16•,17,18]. Whether the women who have these changes have an increased risk for BV is unclear.

Clinically, women with symptomatic BV present with vaginal discharge and odor; the odor may be most prominent after intercourse. Recurrent episodes are common. Half of all women who meet the clinical diagnostic criteria for BV are asymptomatic. Although the microbiologic changes seem to be identical in symptomatic and asymptomatic women, the clinical significance of asymptomatic BV is unclear. Current treatment recommendations for nonpregnant women state that only symptomatic women should be treated [19•]. It has been suggested that poor symptom recognition is a factor in asymptomatic infection [1].

Diagnosis

Because the precise cause of BV remains unknown, the diagnosis of BV generally involves description of the clinical syndrome. Some physicians still use a syndromic approach based on the patient's reported symptoms with or without the clinician's characterization of the discharge. Ryan *et al.* [20•] recently compared reported symptoms with microbiologic diagnoses. They found that vaginal discharge was most likely to result from BV or trichomoniasis, whereas vaginal yeast infections were most often associated with pruritus. Nonetheless, the syndromic approach should be reserved for situations in which resources are too limited to allow a specific diagnosis. A specific diagnosis

should be sought whenever possible so that appropriate therapy and counseling can be provided. Culture of vaginal secretions for *Gardnerella* species is not a valid diagnostic test for BV. *Gardnerella* species may be present in lower concentrations in many women without BV [21].

The Amsel criteria defines BV by the presence of three of four factors: 1) a homogenous vaginal discharge, 2) a vaginal pH greater than 4.5, 3) a positive "whiff" test result (a fishy odor when vaginal secretions are mixed with 10% potassium hydroxide), and 4) clue cells in the vaginal fluid wet prep [1]. These individual variables may be influenced by recent behaviors and may be subjectively interpreted. For example, if a sample is contaminated with cervical secretions, the pH will be falsely elevated. Blood, semen, and recent douching may also interfere with pH testing. In a recent study of the accuracy of olfactory amine detection (the whiff test) [22], half of the participants surveyed incorrectly identified at least one negative control as positive and 17% failed to detect an amine odor among the samples with the highest concentrations.

Gram stain of the vaginal secretions can be used diagnostically with standardized interpretive criteria. The Nugent method, the most widely used approach, gives a score of 0 to 10 based on the quantities of lactobacilli (large gram-positive rods), *Gardnerella* (small gram-variable coccobacilli), and *Mobiluncus* (curved rods) morphotypes. Scores of 0 to 3 represent normal flora, scores of 4 to 6 represent intermediate flora, and scores of 7 to 10 represent BV [23]. With this method, self-obtained specimens have been shown to be equivalent to those obtained by clinicians [15•]. The Gram stain criteria for the diagnosis of BV have been shown to be significantly correlated with the Amsel criteria [4]. Although this method is mainly used in research settings, it is applicable to the clinical setting.

Commercially available tests for the diagnosis of BV include two card tests and a DNA-probe method. A rapid card test detects proline aminopeptidase, an enzyme found in the vaginal secretions of women with BV (FemExam *G. vaginalis* PIP Activity TestCard, Litmus Concepts, Inc., Santa Clara, CA). Another card test, which detects elevated pH and amines (FemExam pH and Amine TestCard, Cooper Surgical, Shelton, CT), may be useful for determining which patients should be more fully evaluated. The Affirm VPIII (Becton Dickinson, Sparks, MD) is a semiautomated test that detects high concentrations of *Gardnerella* species through use of a DNA probe.

Treatment

Treatment of BV has traditionally been targeted toward eradication of the anaerobic flora. Metronidazole and clindamycin can be used in oral or topical intravaginal preparations. The recently updated Centers for Disease Control and Prevention guidelines for the treatment of STDs recommend treating symptomatic nonpregnant women with oral metronidazole 500 mg twice a day, or clindamycin 2% intravaginal cream at bedtime for 7 days or metronidazole gel 0.75% twice daily for 5 days. Alternative regimens include oral metronidazole in a single 2-g dose or clindamycin, 300 mg orally twice daily for 7 days [19•]. The US Food and Drug Administration recently approved a once-daily dosing regimen for metronidazole gel and an extended-release oral metronidazole regimen (750 mg once daily for 7 days) for the treatment of BV. Although clinicians often use acetic acid gel to treat BV, a randomized, double-blind, placebo-controlled trial showed that this treatment lacks efficacy (Holly *et al.* Unpublished data). For pregnant women, the Centers for Disease Control and Prevention recommend using metronidazole, 250 mg three times daily for 7 days, on the basis of data from a preterm delivery prevention study [19•,24]. There is concern that topical preparations used to eradicate BV in this setting may not be adequate for the treatment of possible subclinical upper tract infections, but limited data are available. Treatment of male partners is currently not recommended. There are no definite recommendations for the treatment or prevention of recurrent BV, but there is interest in using intermittent dosing of metronidazole gel as prophylaxis for recurrent infection [25]. Anecdotally, women report that consistent use of condoms is helpful in preventing recurrence. Another suggested treatment is recolonization of the vaginal flora with a vaginal suppository that contains an exogenous strain of hydrogen peroxide–producing *Lactobacillus crispatus*. This product is currently being studied in clinical trials [26].

Complications

In addition to being the most common cause of vaginitis in the United States, BV has been linked to several complications such as preterm birth, postpartum endometritis, postabortal pelvic inflammatory disease, posthysterectomy cuff cellulitis, abnormal Pap smears, and increased risk for STDs, including HIV infection.

It has been shown that bacteria associated with BV can ascend into the upper genital tract in both pregnant and nonpregnant women. Hillier *et al.* [27] cultured the chorioamnion in women with and without preterm delivery and found that organisms associated with BV were isolated significantly more often from cases than from controls. Korn *et al.* [28] examined endometrial biopsy specimens from nonpregnant women with and without BV and without clinical evidence of upper tract infection. They found that BV-associated bacteria were isolated significantly more often from women with BV and that the colonized women also had histologic evidence of endometritis. These studies suggest that in women with BV, bacteria may ascend into the upper genital tract and produce subclinical inflammation.

In multiple studies [29–31], BV has been consistently associated with preterm birth. Organisms associated with BV can cause a subclinical chorioamnionitis that may trigger cytokine production and lead to preterm labor [32]. Recently completed prospective studies have examined the

efficacy of BV treatment as a way to prevent preterm delivery. Hauth *et al.* [24] found that treating BV with both metronidazole and erythromycin in a cohort of women at high risk for preterm delivery resulted in a significant reduction of this outcome. However, these results are not necessarily applicable to the general population. It is also difficult to ascertain the role of erythromycin, which was used because of its efficacy against ureaplasmas, in this setting. A second study, recently presented in abstract form [33], did not find that asymptomatic pregnant women with BV benefited from receiving two 2-g doses of metronidazole 48 hours apart. This treatment regimen, although apparently adequate for the eradication of BV, may not have been successful at curing subclinical upper tract colonization or infection. Until further data are available on the ability of specific dosing regimens to effectively treat upper tract infections, it may be difficult to know whether antimicrobial therapy helps reduce rates of preterm birth in low-risk women with BV. An association has also been found between maternal periodontal disease and preterm birth. *Fusobacterium* species, which are commonly associated with periodontal disease, have been isolated from amniotic fluid; this suggests the possibility of an oral-hematogenous route of infection [34•].

The epidemiologic association between abnormal vaginal flora and STDs has long been appreciated. Bacterial vaginosis is a common coinfection among women with trichomoniasis, gonorrhea, chlamydia, and pelvic inflammatory disease [6,35–38]. Anaerobes may play an important etiologic role in the pathogenesis of pelvic inflammatory disease and are often isolated from tubal cultures [39,40]. There also seems to be an association between nongonococcal, nonchlamydial cervicitis and BV, which suggests a possible etiologic role for BV in this syndrome [41]. One hypothesis about the association of BV with STDs is that hydrogen peroxide–producing lactobacilli, which are generally lacking in BV, are an important defense mechanism against pathogens. In vitro studies have shown that hydrogen peroxide–producing lactobacilli are capable of inhibiting pathogens, including HIV [42–44]. Recent clinical studies have also suggested that abnormal vaginal flora may be a risk factor for the acquisition of HIV. Among a cohort of commercial sex workers in Thailand, BV was independently associated with HIV seropositivity [45]. In a prospective study of pregnant women in Malawi, abnormal vaginal flora was a risk factor for the acquisition of HIV [46•].

Bacterial vaginosis has been associated with abnormal Papanicolaou smears. In a retrospective study, Platz-Christensen *et al.* [47] found a significant association between the presence of clue cells on Papanicolaou smears and cervical intraepithelial neoplasia. These authors speculate that BV may act as a promoter for human papillomavirus, possibly via the production of nitrosamines by the BV flora. A second hypothesis is that the normal lactobacillus-predominant vaginal flora suppresses human papillomavirus but abnormal vaginal flora does not [48]. Prospective studies are needed to confirm an etiologic role for BV in cervical cancer.

Conclusions

In light of the above complications linked to BV, there has been renewed interest in this prevalent syndrome. However, lack of understanding of the pathogenesis of BV has been an impediment to diagnostic, therapeutic, and epidemiologic studies. Emphasis should be placed on determining the cause of BV.

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