EDITORIAL COMMENTARY

A Persistent(ly) Enigmatic Ecological Mystery: Bacterial Vaginosis

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(See the article by Bradshaw et al., on pages 1478–86.)

Considering the vagina’s central role in women’s susceptibility to acquiring sexually transmitted infections (STIs), including HIV, we have a remarkably limited understanding of its microflora and mucosal immunology. We have known for >2 decades that the “normal” vagina is dominated by hydrogen peroxide–producing Lactobacillus species, particularly L. crispatus and L. jensenii [1]. Quantitative declines in numbers of these vaginal lactobacilli have been associated with an increased risk of the acquisition of bacterial vaginosis (BV) [2], gonorrhea [3], and HIV infection [3] and with cervicitis [4]. BV itself, in which the relative lack of lactobacilli is accompanied by a profound increase in the quantity of vaginal anaerobic bacteria, has been associated with an increased risk of some STIs [5] and HIV infection [6, 7]. BV is the most prevalent vaginal infection in women of reproductive age—it affects 8%–23% of women and is the most common cause of vaginal symptoms prompting women to seek medical care. Despite this, our collective knowledge of the etiology of BV and of treatment that best sustains normal, Lactobacillus–predominant vaginal flora remains grossly incomplete. When I speak to health-care providers around the country about BV, I am amazed at the depths of their resourcefulness in trying to find a treatment that helps their patients [8]—resourcefulness that is probably directly related to their (not to mention their patients’) desperation in failing to satisfactorily treat this condition.

The pace of research on BV has recently accelerated, spurred in part by the critical implications of evidence supporting links between BV and the risks for adverse pregnancy outcomes (including preterm delivery and the delivery of low-birth-weight infants) and the acquisition of HIV infection. Investigation into the cytokine profiles associated with BV [9] has confirmed that not all BV is pathophysiologically identical—an observation that comes as no surprise to those familiar with data supporting BV’s role in preterm delivery [10]. Why a minority of pregnant women with BV have adverse consequences is not yet clear, but the factors that favor these costly outcomes may include host response (low levels of IgA to Gardnerella vaginalis hemolysin or the tumor necrosis factor–2 allele) and the specific BV–associated bacteria involved (high quantities of anaerobic gram-negative rods, as detected by cultivation–based methodology, or bacteria that produce higher levels of sialidase and/or protease) [11–13]. Moreover, the role of sexual transmission in causing or promoting BV continues to be a topic of debate, as highlighted by data in lesbians (who have a high prevalence of BV as well as concordance for BV within monogamous couples) and on the potential role of condoms in preventing recurrence [14–16]. The application of molecular techniques to the identification of BV–associated bacteria—specifically, 16s rDNA analysis—has begun to breach the barriers imposed by traditional microbiologic cultivation and has yielded provocative findings. G. vaginalis, which has long been known to be ubiquitous but not specific for BV, is perhaps one of the least interesting players. Among the newly defined bacteria that may have very high specificity for BV are Atopobium vaginae, Megasphaera–α, members of the candidate division TM7 (a relatively undescribed group), Eggerthella–like uncultured bacteria, and at least 3 newly described members of the Clostridiales order that have long been known to be ubiquitous but not specific for BV, or perhaps one of the least interesting players. Among the newly defined bacteria that may have very high specificity for BV are Atopobium vaginae, Megasphaera–α, members of the candidate division TM7 (a relatively undescribed group), Eggerthella–like uncultured bacteria, and at least 3 newly described members of the Clostridiales order that have not yet been successfully cultivated [17, 18]. Whether these newly described bacteria might preferentially contribute to adverse outcomes associated with BV or to an increased risk of the persistence and/or recurrence of BV is not yet known.

In this issue of the Journal of Infectious Diseases, Bradshaw et al. [19] make a considerable contribution to defining the nat-
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Recurrence rates of BV among the 139 women studied were exceedingly high. By 12 months after enrollment, 58% of subjects had had a new episode of BV, and 69% had a Gram stain consistent with abnormal vaginal flora. Rates of persistent BV, measured 1 month after enrollment, were also high (23%). Report of a past history of BV, a regular sex partner throughout the study, and sex with another woman at any point during the study were associated with a significantly higher risk of the recurrence of BV, whereas the use of hormonal contraception was associated with a risk reduction. The authors note, however, that the strength of the latter association was modified when condom use for vaginal sex was retained in the multivariate model, which suggests that hormonal and behavioral factors are intimately related. Report of sex work was also a risk for the subsequent detection of abnormal vaginal flora.

Considered together, the risks for recurrent BV support a role for sex—possibly actual sexual transmission of a pathogen or inciting factor—in the pathogenesis of BV. Importantly and intriguingly, these risks are likely distinct from those associated with the acquisition of “traditional” bacterial STIs, such as Chlamydia trachomatis and Neisseria gonorrhoeae infection, in women. For these STIs, report of the recent (typically, the past 30–60 days) initiation of sex with a new partner has been consistently associated in numerous studies with an increased likelihood of infection. Of note, Bradshaw et al. [19] found that neither the report of a new sex partner, current douching, current smoking, recent condom use, nor the number of male sex partners was significantly associated with risk of the recurrence of BV. So what is it about sex that appears to be so strongly associated with BV? As has been highlighted by other studies, the investigators’ ability to isolate any independent effects of specific sexual practices—especially oral and/or anal sex—was precluded by the fact that these practices were not reported to occur in the absence of vaginal sex. The methodical study of sexual behavior is challenging at best; when a superimposed objective is to relate specific behaviors to biomedical outcomes as complex as the dynamics of vaginal flora, the challenges are considerable. Careful studies such as this should begin to disentangle some of these complex relationships.

The study by Bradshaw et al. [19] has several major strengths. Most of the women enrolled (94%) provided at least 1 follow-up sample. As the authors note, only 1 other study has been published on long-term recurrences of BV, and follow-up rates in that study were low. Bradshaw et al. paid particularly careful attention to the methodological challenges inherent in prospective BV studies—notably, variations in the criteria used for enrollment and the definition of cure. In particular, they broadened enrollment criteria to include women who fulfilled Amsel criteria in the setting of an intermediate Nugent score. Outcomes for women enrolled under these “expanded” criteria did not differ from those for women enrolled on the basis of Nugent score alone (although, given the enrollment criteria, they all had symptoms, which is perhaps an important distinction). Despite attendance at a sexual-health clinic, subjects had relatively few STIs detected by use of highly sensitive diagnostic tests, which allowed for an enhanced ability to focus on BV and the possible selection for greater compliance with follow-up. Most subjects had had BV before—some as many as 10 times—a number that should not surprise practitioners who care for women with vaginal complaints. A number of potential risk factors for the recurrence of BV were assessed, including hygiene, hormonal, and sexual risk behaviors. Critically, the impact of BV and the amelioration of related symptoms on sexual satisfaction were also measured—a woefully neglected area in clinical research on vaginitis.

The implications of this important study do come with some caveats. The authors studied only women with symptomatic BV, and the results might have been dissimilar if they had included or studied primarily asymptomatic women. Either the characteristics or quantity of individual BV-associated bacteria could conceivably affect the likelihood of both symptoms and recurrences of BV. Women with HIV infection, who also were excluded, have an extremely high prevalence of BV in some settings, and BV may promote genital shedding and the transmission of HIV [20]; this group is clearly a high priority for prospective studies of vaginal flora. The mean age of subjects was almost 30 years, which is probably representative of women with the highest age-specific prevalence of BV but is practically geriatric in terms of the concomitant risk of bacterial STIs. A study in a predominantly younger population with a relatively high ongoing risk of acquiring C. trachomatis, N. gonorrhoeae, and trichomoniasis might yield different insights. Details on subjects’ condom use were not available—a limitation that the authors note may, in part, explain the lack of association between this variable and the recurrence of BV. The type of hormonal contraception was also not described. Finally, although sex with a female partner during follow-up was associated with recurrence, the investigators were not able to examine specific practices or subject characteristics that might illuminate exactly what confers risk within this group of women.
One final finding deserves mention: subjects commonly reported adverse effects associated with metronidazole, including a very high rate of self-reported vulvovaginal candidiasis. This—along with the impressive rates of the recurrence of BV overall—clearly supports the urgent need for alternate therapies aimed at the killing of BV-associated bacteria and the restoration of vaginal Lactobacillus species. Variation in vaginal flora and how this variation relates to an enhanced risk of adverse outcomes, especially in HIV-infected women, is an understudied but extremely important topic in women’s health and in infectious diseases. What drives this variation and how to accurately integrate the perspectives of the host and of a potential pathogenic effect somehow linked to sexual behavior is a mystery that must be explored.

References