Bacterial vaginosis—more questions than answers

Over the past decade there has been a notable increase in clinician and patient awareness of bacterial vaginosis (BV) as a frequent cause of vaginal discharge. There has also been considerable interest in the role of BV in upper genital tract infections such as pelvic inflammatory disease (PID) and preterm labour and delivery. Ironically, this prevalent and well studied condition remains puzzling in terms of aetiology and pathogenesis.

As the most frequent cause of vaginal discharge, BV occurs in 20–25% of the general population and in up to 50% of women attending sexually transmitted diseases (STD) clinics. Studies have shown that clinicians making empirical diagnoses without the aid of laboratory testing will frequently misdiagnose the aetiology of a vaginal infection, yet in many practices empirical diagnoses continue to be the norm. The major symptoms associated with BV are odour and vaginal discharge. Fruitis is usually not prominent.

Bacterial vaginosis may be defined either by clinical or microbiological variables. The clinical or Amsel criteria allow for the diagnosis of BV when three of the following four criteria are met: (1) vaginal pH > 4·5, (2) positive “whiff” test when vaginal fluid is mixed with 10% KOH, (3) presence of clue cells, squamous epithelial cells covered with bacteria, and (4) presence of a homogeneous vaginal discharge. Microbiologically, the syndrome of BV is defined by a shift in vaginal microbes away from a lactobacillus predominant flora to a vaginal milieu in which there are greatly increased numbers of bacteria consisting mainly of anaerobes and facultative anaerobes (Gardnerella, mycoplasmas, Prevotella/Porphyromonas, Mobiluncus) and diminished numbers of lactobacilli, especially those that produce hydrogen peroxide. These shifts in flora can be demonstrated by Gram stain and a standardised method of determining the presence of BV by Gram stain has been developed, the Nugent method. Shifts in the bacterial flora can also be appreciated by closely examining the bacteria on the saline wet mount. In patients with BV, the large rods consistent with lactobacilli will be absent and replaced by large numbers of coccobacilli and perhaps motile, curved rods (Mobiluncus). Comparison of the Amsel and Nugent criteria has shown that the Nugent criteria have a sensitivity of 89% compared with the Amsel criteria but a specificity of 83%. The latter raises questions about the true sensitivity of the Amsel criteria and suggests that perhaps the Gram stain should be considered the gold standard.

The aetiology of BV remains unknown. In fact, the most basic of questions regarding its pathogenesis remain unanswered. For example, is it the result of bacterial overgrowth or is it a transmissible infection? If it is an overgrowth phenomenon, what are the triggers that disrupt the flora? If it is transmissible, what are the pathogens and how are they transmitted? Recent studies of women with “normal vaginal flora” have shown that, at least in some women, variability is the rule and not the exception.

Priestley et al examined the vaginal flora of healthy female volunteers by use of self collected vaginal smears. These samples, collected from two to seven times per week, showed remarkable variability in the normal vaginal flora. Of 26 subjects, only four women had lactobacillus, the predominant flora throughout the study. Symptoms were intermittently reported by the women in this study, but the presence of symptoms did not correlate with microbiological changes as detected on Gram stain. We have also examined normal volunteers, examining daily self obtained Gram stains. Our findings concur with those of Priestley et al, in that we found two distinct vaginal flora patterns—one in which only lactobacilli are present throughout the month and the other in which these lactobacillus predominant days are interspersed with days having moderate to large numbers of Gardnerella/Bacteroides morphotypes. The greatest period of variability in these patients occurred at the time of the menses. It is interesting to hypothesise that women with this “unstable” vaginal flora pattern may be at greater risk of developing persistent changes—that is, BV.

Thus far, it is not known why some women have such shifts in their vaginal flora. Priestley et al’s study was unable to determine an association between external factors and changes in the vaginal flora, although they did not examine the role of vaginal douching which has been suggested as having an influence in the pathogenesis of this syndrome. Perhaps the difference between these two groups of women is related to the behaviour of their sexual partners instead of their own. In many ways, BV behaves as if it were an STD. Epidemiologically, BV occurs primarily in sexually active women who have had multiple sexual partners or a recent new partner and it is frequently a coinfection with other STDs. Bacteria associated with BV have been cultured from the male genital tract, particularly among partners of women with BV. In this issue of *Genitourinary Medicine*, Keane et al (p 373) describe their results from a study of sexual partners which examined the association between abnormal vaginal flora in the female and non-gonococcal urethritis (NGU) in the male. The investigators found a significant correlation between the presence of NGU and abnormal vaginal flora which was even stronger when only men without evidence of chlamydial infection were analysed. Although the authors concede that their findings may have been influenced by their inability to study the partners of all the index cases enrolled, this study provides interesting preliminary data concerning a possible aetiology for a non-gonococcal, non-chlamydial urethritis.

A follow up study with a large number of patients as well as more sensitive detection techniques for chlamydia and trichomoniasis should be performed. Of interest is that we have found a similar association between abnormal vaginal flora and non-gonococcal, non-chlamydial cervicitis in women, discussed below. Anecdotally, some women with recurrent BV have found that consistent use of
condoms has kept them free of symptoms. However, treatment studies of male partners of women with BV have demonstrated no benefit in terms of cure of recurrence rates in the women. Additional studies may be needed to further examine the issue of treatment of the male partner, perhaps examining both systemic and topically applied agents.

Treatment of BV currently relies on the eradication of the anaerobic/facultatively anaerobic organisms by the use of either metronidazole or clindamyacin. The preferred dose of oral metronidazole is 500 mg twice a day. Although the 2 g dose given immediately may enhance compliance, the 7 day regimen has superior efficacy particularly when cure rates at 3 weeks after therapy are compared (86 versus 46%). Both metronidazole and clindamyacin are now available in topical formulations with cure rates equivalent to that of oral. Although topical preparations avoid unpleasant systemic side effects, there are now increasing theoretical concerns that control of anaerobes in the lower genital tract may not be adequate to prevent the upper tract complications associated with BV.

Half of all women with BV are asymptomatic and the debate continues over the need to treat asymptomatic BV. Most clinicians currently do not treat for asymptomatic BV despite data linking BV with STDs. Important work by Hillier and others has shown that hydrogen peroxide producing lactobacilli are potentially important to the health of the lower female genital tract. Numerous studies have shown an association between the presence of BV and STDs, including HIV. In a study by Saig et al., female sexual contacts of males with gonorrhoea were more likely to become infected if they lacked inhibitory lactobacilli. Among female commercial sex workers in Thailand, HIV seropositivity was significantly correlated with BV after controlling for behavioural factors and other STDs. Although prospective studies are needed to confirm these observations, data such as these suggest that treatment of BV, whether symptomatic or asymptomatic, with re-establishment of the normal vaginal flora, may be an important adjunctive means of controlling STDs.

Data continue to accumulate on the complications associated with BV. Studies have documented the ability of BV related organisms to ascend into the upper genital tract in both the pregnant and non-pregnant patient. The epidemiological association between BV and preterm delivery has been well documented by numerous investigators. For the pregnant patient, studies designed to determine if the treatment of BV will prevent preterm labour and delivery are ongoing with a definitive conclusion yet to be reached. In a study of Hauth et al., treatment with erythromycin and metronidazole decreased the outcome of preterm labour among women deemed to be at risk for this event, especially among those women with BV. Although it provides important data, the design of this study—that is, two drugs and a select population, does not provide us with guidelines for the general population. Beyond this initial question of whether treatment of BV in pregnancy will prevent preterm delivery, are issues dealing with the appropriate diagnostic test to use in this setting, the antibiotic regimen of choice, the timing of therapy, and the necessity of a “test of cure.”

In the non-pregnant patient, parallel questions regarding treatment of BV as a means to prevent PID will be far more difficult to answer.

Preliminary data have also implicated BV in the pathogenesis of lower genital tract processes such as endocervicitis and cervical atypia. In a pilot study of appropriate treatment for patients with clinically defined BV and cervicitis, we found that among women who only received treatment appropriate for cervicitis, cervical inflammation persisted more frequently than in the group who had received concomitant treatment for BV and cervicitis. Although not statistically significant, this raises questions regarding a role for anaerobes in the aetiology of non-gonococcal, non-chlamydial cervicitis. With regard to cervical atypia, retrospective data suggest that treatment with metronidazole in women with atypical Papanicolaou smears significantly may improve the likelihood of a subsequent normal Papanicolaou stain when compared with women not receiving treatment. Well designed, prospective studies are needed before any definite conclusions can be made.

In summary, although the definition and diagnosis of BV are well standardised, questions regarding pathogenesis and potential complications abound. Further studies are urgently needed to resolve the pathogenesis of BV and to determine the impact of treatment of this condition on various important outcomes in both the pregnant and non-pregnant patient. Until these answers are available, BV will remain one of the most prevalent enigmas in the field of medicine.
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