# Bacterial Vaginosis: Resistance, Recurrence, and/or Reinfection?

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**(See the article by Schwebke and Desmond on pages 213–9)**

Bacterial vaginosis (BV) is one of the most common infections among sexually active women that is responsive to antibiotics. BV is present in at least 15% of the sexually active population; this makes BV 3–4 times more common than urinary tract infections, many times more common than *Trichomonas vaginalis* infection (even among sexually transmitted disease clinic populations), and much more common than vulvovaginal candidiasis. Furthermore, BV is linked to a wide variety of serious upper genital tract infections, including amniotic fluid infection, chorioamnionitis, and preterm delivery; postpartum endometritis and post–Cesarean delivery wound infection; posthysterectomy infection; postabortion endometritis; and, to a lesser degree, pelvic inflammatory disease. Thus, the need for successful treatment of BV in both symptomatic and selected asymptomatic populations is compelling.

However, this is 2006, fifty-one years after Dr. Gardner first reported the presence of the condition we now call BV. At this late date, we have only limited—and clearly not conclusive—evidence with regard to 3 fundamental issues: whether BV is an infection, the microbial cause of BV, and effective treatment. This deplorable state calls for a vast expansion of research into fundamental, important questions. The association of BV with multiple upper genital tract infections, particularly after surgery, strongly suggests the presence of an infectious agent. Production of BV by the experimental inoculation of such infectious material into women [1] and concordance of BV among lesbian couples [2] further suggests infection.

Although *Gardnerella vaginalis* and selected anaerobic bacteria can be found in virtually all women with BV, DNA technology demonstrates the presence of a large number of unculturable or very difficult-to-culture anaerobes [3], and a causative role has not been established for any of these microbes. One theory even holds that destabilization of *Lactobacillus* species is the key in development of BV and that *G. vaginalis* and the anaerobes are secondary invaders. Certainly, no single bacteria is considered causative of BV.

Without a specific bacteria to treat, it certainly is understandable that treatment of BV also is in a sorry state. In fact, the reported rate at which antibiotics "cure" BV has actually decreased from >90% of cases when metronidazole was first used to a present range of 50%–80% of cases [4], and most reports indicate rates at the lower end of this range. How can cure rates steadily decrease over 30 years? First, the criteria used in the definition of BV have changed from clinical criteria to Gram stain–based criteria, and the definition of "cure" has varied, but these reasons are more a theoretical than a real explanation for the decrease in cure rates. Second, the bacteria that either cause BV or cause the anaerobic overgrowth may have become relatively more resistant to metronidazole (the most common treating agent) or to clindamycin (the other common treating agent). Third, this infection may be reintroduced back into the vagina as a result of reinfection.

In this issue of *Clinical Infectious Diseases*, Schwebke and Desmond [5] have waded into a field that would discourage all but the very strong. Still, they are to be commended for performing one of the few antibiotic-dosing studies of BV [6, 7]. Using a large number of 420 subjects who returned for the first follow-up examination in a randomized, double-blind study design, Schwebke and Desmond examined 3 key issues: duration of therapy, definition of BV, and reinfection/suboptimal resolution.

In their report, a significantly higher pooled cure rate occurred 1 week after receipt of the last dose for those receiving 14-day regimens of metronidazole (62%), compared with those receiving 7-day reg-

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imens (43%; $P < .001$) [5]. Unfortunately, the pooled cure rate 21 days after receipt of the last dose was similar in the 14-day regimen (43%) and 7-day regimen (51%) groups. Thus, the longer 14-day regimen of metronidazole produced a definite, albeit temporary, effect on BV, compared with the 7-day regimen. However, it remains unclear from this data whether this temporary effect is related to undertreatment associated with resistance, reinfection, or both.

In fact, resistance to treatment is suggested by the failure of the 14-day metronidazole regimen to cure 38% of women at day 7 of follow-up—a failure rate that increased to 57% a short 2 weeks later. Resistance to therapy is further suggested by the finding that the worst BV (as assessed on the basis of by Gram stain criteria) responded most poorly. Direct testing of antibiotic resistance awaits identification of the microbial cause of BV.

At the same time, the effect of reinfection is suggested by a 50% higher cure rate among subjects who abstained from sex or consistently used condoms [5]. A curious finding was the 80% higher cure rate among subjects who did not douche. Among other possibilities, the douching finding is consistent both with a possible disturbance of vaginal flora from douching and with a possible reintroduction of bacteria (if the same douching equipment was used repetitively). A future treatment study on the complexity of BV treatment is needed in which no exposure occurs either to a sexual partner or to douching to eliminate, at least on a short-term basis, the possibility of reinfection.

The report did conclusively demonstrate that azithromycin added little to the effect of metronidazole. It was also demonstrated that a 14-day course of metronidazole was superior to a 7-day course, regardless of whether cure was defined by clinical or Gram stain criteria. The authors appropriately point out that a major limitation of the study was the high number of subjects who dropped out of the study, although this fact was unlikely to change the overall conclusions.

The conclusions of this large, double-blind trial is that metronidazole, even when administered for 14 days, has limited effect on BV. A limited effect such as this would not be expected if BV was caused by a single bacteria with susceptibility to metronidazole. Thus, much additional and difficult work is required to define the causative bacteria of BV and determine its susceptibility to antibiotics beside metronidazole and azithromycin. I would also further suspect a role of reinfection in BV. Almost everyone would have to conclude that further basic research is required on BV before much effect can be expected on the rather dismal cure rates for this common and important infection.

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