Bacterial Vaginosis

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Bacterial vaginosis (nonspecific vaginitis) is a polymicrobial, superficial vaginal infection caused by an increase in anaerobic organisms and a concomitant decrease in lactobacilli. Gardnerella vaginalis, once thought to be the sole etiologic agent, is probably one of several endogenous members of the vaginal flora that overgrow in women with bacterial vaginosis. Whether the growth of anaerobes or a primary decrease in lactobacilli is the initial pathogenic event remains unclear. Epidemiological studies have revealed that current or previous infections caused by Trichomonas organisms, increased sexual activity, and intrauterine device use are risk factors for this condition. Studies have indicated that bacterial vaginosis, previously thought to be a benign illness, is associated with some morbidity in pregnant women. Symptoms remain unreliable in the diagnosis of bacterial vaginosis. Diagnostic efficacy is best achieved by utilizing clinical signs. Assessment of cure is best accomplished by Gram stain, not clinical criteria. Metronidazole, 500 mg orally for seven days, remains the treatment of choice; however, a 2-g single dose of metronidazole represents a reasonable alternative if cost and compliance issues predominate in a clinical situation. Although a recent study supports the contention that treatment of the male sexual partner of women with bacterial vaginosis is effective, a general recommendation cannot be made with confidence on the issue of sexual partner treatment until other supporting work is done.

Bacterial vaginosis (nonspecific vaginitis) is often perceived by primary care physicians to be a rather ill-defined, ambiguous clinical entity. This ambiguity has not been helped by the many names associated with this condition, including Hemophilus vaginalis vaginitis and Gardnerella vaginalis vaginitis. Although often changing identity, this ubiquitous disease accounts for up to one half of all cases of vaginitis presenting to primary care physicians.[1] The current name, bacterial vaginosis, seems to be the most logical and appropriate clinical designation. Etiologically, bacterial vaginosis is a polymicrobial infection caused by anaerobic bacteria (bacterial). Clinically, bacterial vaginosis presents as a superficial vaginal infection characterized by few irritative symptoms and no inflammatory response (vaginosis).

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Since 1955 research on bacterial vaginosis has accumulated amid confusion and controversy. Much of the confusion can be attributed to the lack of uniform case definition applied to studied populations and to an intense focus on G vaginalis rather than on the clinical disease the organism was purported to cause. Given the previous confusion over the etiology, the problems surrounding case definitions, and recent excellent research, this review was undertaken to examine the etiology, epidemiology, diagnosis, treatment, and prognosis of the clinical entity bacterial vaginosis.

ETIOLOGY

The superficial vaginal infection now known as bacterial vaginosis was formally characterized by Gardner and Dukes in 1955.[2] They postulated that bacterial vaginosis was caused by Hemophilus vaginalis, now known as Gardnerella vaginalis. Gardner failed, however, to satisfy all four of Koch's postulates with G vaginalis alone (Table 1). When Gardner introduced G vaginalis grown from cultures of women with bacterial vaginosis into the vaginas of normal women, no infection occurred; when he put

TABLE 1. EVIDENCE UTILIZED BY GARDNER AND DUKE[2] TO SATISFY KOCH'S POSTULATES

1. The bacterium must be observed in every case of the disease; 92% of the patients with a primary diagnosis of bacterial vaginosis had Gardnerella vaginalis observed
2. The bacterium must be isolated and grown in pure culture: this was accomplished in each of the 141 cases with positive G vaginalis cultures
3. The bacterium in pure culture must, when inoculated into a susceptible animal, give rise to the disease: 10 of 13 patients inoculated with G vaginalis from culture failed to develop clinical disease, but 11 of 15 patients inoculated with vaginal secretions directly from infected patients developed clinical disease
4. The bacterium must be observed in, and recovered from, the experimentally inoculated animal: 3 of 3 patients inoculated had G vaginalis recovered

vaginal discharge from women with bacterial vaginosis directly into the vaginas of normal women, bacterial vaginosis did develop. Despite this finding, Gardner concluded that bacterial vaginosis was caused by G vaginalis, apparently assuming nothing else could have caused the infection. Recent studies have shown, however, that several anaerobes in addition to G vaginalis are present in women with bacterial vaginosis.[3–8]

Role of Gardnerella vaginalis

The belief that G vaginalis is the sole cause of bacterial vaginosis began to change when numerous investigators grew G vaginalis from the vaginas of women with no clinical evidence of bacterial vaginosis.[9–19] Vontver and Eschenbach[1] reviewed studies that showed that G vaginalis could be isolated from the vaginas of 40 percent to 50 percent of asymptomatic women who had no clinical signs of bacterial vaginosis. Recent studies by McCormack et al[20] and Amsel et al[3] confirmed the prevalence of G vaginalis in asymptomatic women who had no clinical signs of bacterial vaginosis to be between 40 percent and 50 percent. In addition, Amsel et al found an association of G vaginalis with bacterial vaginosis; in contrast, McCormack et al concluded that there was no association of G vaginalis with an abnormal vaginal discharge. Although eradication of G vaginalis has been shown to be highly associated with treatment outcome,[9] other studies have found that the abolition of signs and symptoms of bacterial vaginosis is not always associated with eradication of G vaginalis.[21–23] Bump et al[4] have recently shown that 85 percent of asymptomatic women who have G vaginalis isolated from their vaginas are only transiently colonized. These and other studies suggest G vaginalis may be part of the normal vaginal flora in women who do not have bacterial vaginosis. Women having bacterial vaginosis, however, will often have greater concentrations of G vaginalis than women not experiencing bacterial vaginosis.[1] It is most plausible, then, that G vaginalis is a member of the normal vaginal flora that overgrows in women with bacterial vaginosis.

Role of Anaerobic Bacteria

Numerous investigators have reported an increase in the number of anaerobes in women with symptomatic bacterial vaginosis.[1,7,9,23–25] Spiegel et al[26] demonstrated the presence of anaerobic bacteria when they performed quantitative anaerobic cultures of vaginal fluid from both women with bacterial vaginosis (before and after seven-day therapy with metronidazole) and normal women. Women with bacterial vaginosis were found to have significantly more Peptococcus, Bacteroides, and G vaginalis organisms ($P < .005$). Clinical improvement after treatment with metronidazole correlated with eradication or suppression of these anaerobic organisms. Thomason et al[7] showed that of women whose vaginal fluid contained curved rods, as determined by wet mount, all had clinical bacterial vaginosis and had a tenfold increased prevalence of vaginal colonization by anaerobic gram-negative bacteria. In addition, black-pigment-producing Bacteroides[7,27] and Mycoplasma hominis[27] have also been found to be associated with symptomatic bacterial vaginosis.

Anaerobic bacteria are indisputably increased in bacterial vaginosis and no doubt play a causal role. As pointed out by Spiegel et al,[26] anaerobic infections are generally caused by endogenous bacteria. Whether overgrowth is the primary pathogenic event or merely a consequence of a yet unknown inciting event is still unclear. The majority of research has focused on isolating one or more pathogens, with little effort directed at exploring the ubiquitous decrease of lactobacilli apparent in women with bacterial vaginosis.

Role of Lactobacillus

Facultative lactobacilli produce hydrogen peroxide and usually keep the growth of vaginal organisms in check by maintaining vaginal pH at acidic levels. Numerous investigators have confirmed that women with bacterial vaginosis have decreased lactobacilli.[8,9,26,28,29] The inverse relationship between anaerobic organisms and lactobacilli in women with bacterial vaginosis has been verified in microscopy[6,28] and culture studies.[25,29] A reduction of vaginal hydrogen-peroxide-producing lactobacilli may allow the unrestrained growth of vaginal anaerobes, producing clinical disease. After treatment with metronidazole, regrowth of lactobacilli occurs, which decreases

vaginal pH while increasing oxidation-reduction potential to the normal level inhibitory to vaginal anaerobes. That lactobacilli do not reappear following treatment with amoxicillin and ampicillin, two agents much less effective than metronidazole in the treatment of bacterial vaginosis,[19,30] is further evidence of the role of lactobacilli in the pathogenesis of bacterial vaginosis. Does something kill the lactobacilli, which then allows vaginal anaerobes to increase in numbers, causing bacterial vaginosis, or does bacterial vaginosis begin by a large inoculation or overgrowth of anaerobes that then destroy the lactobacilli?

Role of Mobiluncus

As early as 1913 curved motile rods have been associated with pathologic vaginal discharge.[31] Comma-shaped bacteria have been observed in stained[32] and wet[26] vaginal smears from women with bacterial vaginosis. Spiegel et al[29] have detected curved rods by direct Gram stain of vaginal fluid from 31 of 61 (51 percent) women with bacterial vaginosis vs 0 of 42 normal controls ($P = .001$). These curved, motile, anaerobic rods have been found to be associated with vaginal discharge[31,33,34] and clinical signs and symptoms of bacterial vaginosis.[7,28,35] Anaerobic curved rods have not been detected in studies of the anaerobic and facultative flora of the healthy premenopausal vagina,[36,37] cervix,[38,39] and the premenarchal vagina.[40]

Spiegel et al[28] have determined that these curved rods of vaginal origin are sufficiently different from any named genera to warrant their placement in a new genus called Mobiluncus. Although resistant to metronidazole in vitro, Spiegel et al initially demonstrated that they disappear when patients with bacterial vaginosis are treated.[24]

EPIDEMIOLOGY

Historically, investigators have focused on the epidemiology of G vaginalis instead of the clinical entity it is purported to cause. This oversight, coupled with diverse methods for isolating this organism and a lack of uniform case definition, has contributed to a diversity of opinions regarding the epidemiology of bacterial vaginosis. Studies using clinical criteria reveal that intrauterine device (IUD) use, current or previous infections caused by Trichomonas organisms, and increased sexual activity are associated with bacterial vaginosis.

Contraception

Oral contraceptives, spermicidal jelly, and the IUD have all been implicated in the development of bacterial vaginosis. Sexually active women using a spermicidal foam or jelly are less likely to develop bacterial vaginosis than women using no contraception at all ($P < .05$).[3] The nature of this possible protective effect is unknown.

Oral contraceptives were found to be associated with positive G vaginalis culture[12,14] and were once thought to exert a protective effect because they increase vaginal epithelial glycogen content, therefore increasing the number of lactobacilli.[41] Epidemiologic data from Amsel et al[3] and Bump et al,[4] using a clinical diagnosis of bacterial vaginosis, failed to support this hypothesis.

The use of an IUD has been strongly associated with bacterial vaginosis ($P < .001$).[3] Although suggested to be a result of the increased sexual behavior among IUD users,[41] the positive association of IUD use with bacterial vaginosis remains statistically significant when compared with other forms of contraception.[30] Amsel et al[3] have found that over one half of all IUD users in their study had bacterial vaginosis. Goldacre and colleagues[25] have additionally demonstrated an association of gram-negative anaerobes with use of an IUD and with symptomatic discharge. How these or other factors associated with an IUD influence the growth of anaerobes is not currently known.

Sexually Transmitted Diseases

A large university-based study revealed that previous Trichomonas infection is a significant bacterial vaginosis risk factor ($P < .001$), but found no significant association with herpes simplex virus or Neisseria gonorrhoeae.[3] Levison et al[18] have reported a significant association between the presence of Trichomonas and Bacteroides in vaginal fluid. Concomitant Trichomonas infection makes the diagnosis of bacterial vaginosis more difficult.[42] Concomitant or previous Trichomonas infection may actually increase the risk of developing bacterial vaginosis, or the association may result from the confounding effect of another determinant, such as sexual activity.

Sexual Activity

The role of sexual transmission in the acquisition of bacterial vaginosis has been one of controversy since the formal description of the disease in 1955. Studies have shown that the number of sexual partners and a past history of sexually transmitted diseases are more common in patients with bacterial vaginosis.[14,43–45] Gardner and Dukes[2] originally isolated G vaginalis from the urethra of 45 of 47 husbands of wives with bacterial vaginosis. They concluded that men were capable of reinfecting their sexual partner and advocated the use of a condom.

Pheifer et al[9] demonstrated that bacterial vaginosis recurrence developed in 6 of 11 women who had intercourse

with untreated partners vs 2 of 46 women who abstained from intercourse throughout the duration of the study ($P < .001$). Eschenbach et al[46] have found that the recurrence rate of bacterial vaginosis is similar in women with bacterial vaginosis who have male partners with G vaginalis isolated from their urethras vs those who do not have G vaginalis isolated. They also noted, however, a significant reduction in recovery of G vaginalis from the urethras of treated male contacts of women with bacterial vaginosis, even though they noted no significant difference in cure rates as judged by clinical criteria when the male partner was treated. Recently, Mengel showed that treating the male sexual partner with a 2-g single dose of metronidazole improved initial cure rates in women with bacterial vaginosis.[47]

Even though the evidence supporting sexual transmission in bacterial vaginosis seems strong, the sexual transmission of anaerobic bacteria has been considered unlikely because anaerobes other than G vaginalis have not been commonly recovered from the male urethra.[48] This low recovery rate may be due to the poor methods available for isolating anaerobes. Although it is likely that G vaginalis can be sexually transmitted, it appears more prudent to conclude that sexual exposure to an as yet unknown inciting event during intercourse, not necessarily G vaginalis, is responsible for bacterial vaginosis recurrence. Biochemical products in semen, microorganisms, and other factors associated with intercourse may play a role in the transmission of bacterial vaginosis. Future studies need to be performed that examine the transmissibility of anaerobic organisms and other factors associated with sexual activity in clinically defined cases of bacterial vaginosis.

DIAGNOSIS

Knowledge that bacterial vaginosis is not caused by a single pathogen is necessary to understand diagnostic strategies. Recognition of the presence of clinical disease, not growth of G vaginalis on vaginal cultures, is the goal of diagnosis. Furthermore, since primary care physicians are most likely to encounter patients with bacterial vaginosis, inexpensive diagnostic procedures that are capable of providing results quickly are important. It is fortunate that the most efficacious means of establishing the diagnosis of bacterial vaginosis are consistent with the needs of the primary care physician.

Utilization of clinical criteria initially described by Gardner and Dukes[2] and later formulated into a diagnostic tool by Amsel et al[3] is the diagnostic method of choice. Symptoms exhibit great variability and therefore possess substantial limitations as diagnostic criteria for bacterial vaginosis.[20,36,49] Amsel et al[3] found a little over 50 percent of women with bacterial vaginosis to be asymptomatic in a screened population presenting to a university clinic.

TABLE 2. VAGINAL DISCHARGE CHARACTERISTICS IN WOMEN WITH BACTERIAL VAGINOSIS

Characteristic	Normal	Bacterial Vaginosis
Present at interoitus	No	Yes
Viscosity	High	Low
Color	White	Gray
Consistency	Floccular	Homogeneous
Location	Dependent portion	Adherent to vaginal wall
pH	<4.5	>4.5
Clue cells	No	Yes

Laboratory cultures and chromatography, although used in research studies, are cumbersome and expensive, and provide no increased diagnostic efficacy in patients with symptomatic bacterial vaginosis.[49] These techniques, however, will continue to provide valuable information regarding the pathogenesis and etiology of bacterial vaginosis.

Clinical Criteria

Gardner and Dukes[2] carefully identified clinical signs for distinguishing women with bacterial vaginosis from women without bacterial vaginosis. The increased discharge they observed in women with bacterial vaginosis is characterized in Table 2. The clinical diagnosis of bacterial vaginosis can be made if any three of the following four criteria are present: (1) gray, homogeneous discharge, (2) pH > 4.5, (3) fishy odor with application of 10 percent potassium hydroxide (KOH), and (4) clue cells. Amsel et al[3] showed that 47 of 48 (98 percent) women with three of four signs had cultures positive for G vaginalis vs 80 of 199 (40 percent) who did not have three of the four criteria.

A recent study showed that testing with all four criteria may not be necessary. In the first nonintervention study to examine the natural course of both signs and laboratory findings indicative of bacterial vaginosis, Bump et al[4] observed that a positive sniff test or the presence of clue cells most accurately predicts the presence of an abnormal discharge. Furthermore, once one was performed, the other three clinical signs did not add significantly to the predictive value. Given the lack of expense and ease of performing the four clinical tests, it is probably best to do so until additional evidence confirms this finding.

Homogeneous Gray Discharge

A thin, homogeneous, foul-smelling discharge that is adherent to the vaginal walls is characteristic of bacterial vaginosis. The discharge should not be confused with cervical mucous, which is characteristically clear, indicating the absence of an inflammatory response. A milky-like consistency that is distinctly nonfloccular, nongranular, nonstringy, and not clumped is most characteristic. The discharge is clear to gray in color but has occasionally been reported as green, yellow, or even white.[1-4] The quantity of discharge is difficult to assess and is therefore not recommended as part of the discharge evaluation.

Vaginal pH > 4.5

Vaginal pH is best determined by swabbing the lateral or posterior fornices of the vagina with a cotton-tipped swab and then placing the sample directly on a pH indicator tape. One must avoid sampling the cervical mucous, which has a higher pH (7 to 7.5) than vaginal fluid. Gardner and Dukes[2] found that normal women's vaginal pH ranged from 3.8 to 4.2, while women with bacterial vaginosis had a vaginal pH > 4.6. Chen et al[50] found that untreated patients with bacterial vaginosis had a vaginal pH > 4.6, and successfully treated bacterial vaginosis patients had a vaginal pH < 4.3. Amsel et al[3] showed that the number of women with bacterial vaginosis increases with increasing pH, and that a pH of 4.5 was most discriminatory for differentiating women without from women with bacterial vaginosis. A pH > 4.5 provides 81 percent sensitivity, 67 percent specificity, a negative predictive value of 91 percent, and a positive predictive value of 43 percent; therefore, pH alone is most effective at correctly excluding individuals who do not have bacterial vaginosis, although not solely efficacious as a positive indicator of disease.

Potassium Hydroxide Test

Vaginal malodor is not always symptomatic but can nearly always be elicited, if present, by the addition of 10 percent KOH to a slide of vaginal discharge. A cotton-tipped swab is used to mix vaginal fluid with two drops of 10 percent KOH on a glass slide. The sniff test is positive if a fishy amine-like odor is liberated. The odor has been shown to be directly related to increasing pH.[42] Pheifer et al[9] reported that 67 percent of women with an abnormal discharge vs no women who were clinically normal had a fishy odor upon addition of KOH to a slide of their vaginal fluid. This test has been reported to have a positive predictive value of 76 percent,[3] and has recently been shown by Bump et al[4] to be the most powerful single predictor of bacterial vaginosis.

Clue Cells

Clue cells are exfoliated squamous epithelial cells that appear under light microscope to be heavily stippled and granular in appearance with obscured borders resulting from the adherence of gram-negative to gram-variable coccobacilli. Clue cells are found by obtaining a second sample of vaginal fluid with a cotton-tipped swab and adding two drops of normal saline to the sample on a glass slide. The slide is then examined in each of ten low-power fields. A clue cell identified in each of the ten low-power fields is a positive test. Although several investigators have confirmed the usefulness of this test, others have not found a close correlation between clue cells and G vaginalis cultures.[2,3,9,43] Although greater than 90 percent of patients who have clue cells have positive cultures for G vaginalis,[3,51] Eschenbach and others[52-54] have pointed out that the type of organism adherent to the clue cell has yet to be demonstrated as G vaginalis. Bump et al[4] has recently shown that the presence of clue cells most accurately predicts the existence of an abnormal discharge. Using clinical criteria, Holmes et al[55] have shown that 90 percent of women with bacterial vaginosis have clue cells vs 10 percent of those who do not.

Gram Stain

Recently an old technique, the Gram-stained slide, has been utilized in the diagnosis of bacterial vaginosis. Small, gram-negative coccobacillary organisms of the Gardnerella morphotype, small, gram-negative curved rods, and the absence of large, gram-positive rod-shaped bacteria resembling the Lactobacillus morphotype characterize the vaginal discharge of a patient with bacterial vaginosis. This microscopic picture was found by Spiegel et al[28] to be present in 25 of 25 women with bacterial vaginosis vs 0 of 35 women without bacterial vaginosis. Although a small study, the work of Spiegel et al does indicate that the Gram-stained slide appears to have excellent sensitivity and specificity for diagnosing bacterial vaginosis.

Mengel[47] recently observed that 17 of 25 (68 percent) women considered clinically cured from bacterial vaginosis infections were not cured by Gram-stained slide criteria. Furthermore, a group of Gram-stained slides in this study did not fulfill the criteria for normal or bacterial vaginosis. This category referred to as "other" by Mengel contained Lactobacillus and G vaginalis morphotypes in low quantities together with a high quantity of mixed facultative and anaerobic morphotypes. In the study by Mengel, "other" was not cured by metronidazole. Mengel concluded that the inability of clinical signs to distinguish "other" from bacterial vaginosis and the failure of metronidazole therapy to cure "other" suggested the need to use a Gram stain to confirm the presence of bacterial

vaginosis when it is suspected from clinical examination. Mengel postulated that "other" may represent another, as yet uncharacterized, vaginal infection or an infection of the upper genital tract such as cervicitis. Despite the uncertain cause of the Gram-stained slide classification "other," the Gram-stained slide of a patient's vaginal discharge is an excellent test to confirm the clinical diagnosis of bacterial vaginosis, to assess bacterial vaginosis cure, and to prevent the needless use of metronidazole in patients with "other."

TREATMENT

Patient Treatment

The efficacy of metronidazole, 500 mg orally, twice a day for seven days, has been established by numerous studies.[24,33,46,56–58] Because of unpleasant side effects associated with metronidazole use, including a metallic taste in the mouth, gastrointestinal irritability, a disulfiram-like reaction following alcohol consumption, and the high cost of a seven-day course, studies examining the efficacy of shorter courses of metronidazole therapy were planned and executed in the early 1980s. These studies were prompted by the findings of several investigators that increased patient compliance results when a single 2-g dose of metronidazole, instead of the seven-day regimen, is given for the treatment of vaginal infections caused by Trichomonas.[59–62]

In the first of these studies, Minkowski[63] showed that 531 of 609 (87 percent) adolescent women with culture-positive bacterial vaginosis became culture negative and asymptomatic after a single 2-g dose of metronidazole. Unfortunately this study did not control for reinfection from male contacts, a control group of women receiving a seven-day course was not formed, and cultures positive for G vaginalis were used for inclusion criteria and cure assessment. Balsdon,[64] using three of four clinical criteria as inclusion criteria for bacterial vaginosis, found that 29 of 30 women were cured in one week with a single 2-g dose of metronidazole. Recurrence rates of between 10 percent and 20 percent, depending upon the time of assessment after treatment, were noticed and may have resulted from failure to treat the male sexual partner. Unfortunately, Balsdon also did not form a control group.

After concluding that 500 mg, twice daily for three or five days, was inferior to a single 2-g dose of metronidazole and the more accepted regimen of 500 mg, twice daily for seven days, Eschenbach et al[46] conducted a double-blinded, placebo-controlled trial comparing single-dose to the seven-day regimen. Women who received the single dose had higher rates of symptoms 21 days after completion of therapy ($P = <.05$). These same women also exhibited a higher percentage of anaerobe-associated abnormal organic acids and cultures positive for G vaginalis at the visit on day 29. Unfortunately no control of possible male reinfection occurred, as male partners were given the option of taking the same metronidazole regimen as the female patient. No data on which male partners elected treatment were presented. Thus, recurrence or reinfection could have been responsible for the higher rate of symptoms observed in women receiving the single dose.

Swedberg et al[65] also investigated single-dose metronidazole therapy vs the seven-day regimen in a single-blinded, randomized trial that did control for treatment of the male partner. Swedberg et al concluded that the 2-g single dose was inferior to the seven-day course, as women had higher rates of symptoms and cultures positive for G vaginalis 21 days after beginning therapy. Unfortunately, Swedberg and colleagues had a high dropout rate, 40 percent after the visit on day 21. Because their study involved small numbers of women in each group, this high dropout rate might have adversely affected their results and caused them to make a spurious conclusion.

Recently, Purdon et al,[56] in a nonrandomized, nonblinded study that effectively controlled for reinfection by the male partner, found 67 percent of women treated with a 2-g single dose compared with 81 percent of those receiving the seven-day regimen were culture negative for G vaginalis seven to ten days following treatment. Purdon et al concluded that the single 2-g dose is an acceptable alternative to a seven-day course when cost and compliance are a consideration. The Purdon et al conclusion of no real difference in cure rates may be due to a type II error, however, as the number of study subjects was small. Most recently, Mengel et al, in a randomized, placebo-controlled, double-blinded, clinical trial of 140 women who presented to primary care physicians with bacterial vaginosis diagnosed by clinical criteria, showed that metronidazole, 500 mg twice daily for seven days, was not statistically superior to a single 2-g dose. Furthermore, the likelihood of a type II error was small, since the study achieved an estimated 85 percent statistical power of detecting a 20 percent difference in cure rates.*

An analysis of all studies to date suggests that metronidazole in dosages of 500 mg twice daily for seven days or a single 2-g dose is equally efficacious for the treatment of women with symptomatic bacterial vaginosis in a primary care setting. Clearly, further comparison trials in nonprimary care settings need to be performed before the single-dose option can be widely adopted.

* *Further information available from author on request.*

Sexual Partner Treatment

Difficulty in ascertaining the true cause of bacterial vaginosis and the apparent lack of clinical manifestations in the man has made the study of sexual transmission, and thus the efficacy of treating male partners, a formidable task. The currently accepted standard treatment for bacterial vaginosis (metronidazole, 500 mg twice daily for seven days) yields good initial cure rates. About 25 percent of women develop a recurrence within six weeks of therapy, however.[9] This high incidence of recurrence has led some investigators to postulate that bacterial vaginosis recurrences may be due to reinfection from the male partner.[42,66]

Despite evidence for sexual transmission, studies by Eschenbach et al[46] and Swedberg et al,[65] in which the sexual partners of women with bacterial vaginosis have been treated, have not shown improved cure rates or reduction of recurrence rates in female partners. Unfortunately, numerous flaws cloud their conclusions. In these studies, two different treatment regimens were used within each study to treat the male partner, and the data from these groups were incorrectly pooled to conclude that treatment of the male partner made no difference. Furthermore, both studies lacked adequate power to conclude no difference. Their conclusions may be due to a type II error.[66]

Mengel et al* also studied the issue of male treatment. Their double-blinded, randomized, placebo-controlled trial was performed to test the hypothesis that a 2-g single dose of metronidazole for male partners of women with bacterial vaginosis was more effective than placebo in improving cure rate and decreasing recurrence rate. Specifically, bacterial vaginosis cure rates, as diagnosed by Gram-stained slide, were statistically significantly better when men were treated than untreated at two weeks ($P < .05$), and almost significant at five weeks ($P = .12$) following initiation of treatment. Statistically significant benefits of partner treatment with respect to percentage of women with symptoms at eight weeks after initiating therapy ($P < .05$) were also observed. There was no difference, however, in percentage of women achieving clinical cure (three of four criteria) when their partners were treated, and there was no significant reduction in recurrence eight weeks after initiation of therapy. Mengel et al concluded that single 2-g metronidazole treatment of male sexual partners of women with symptomatic bacterial vaginosis is more effective than placebo in treating bacterial vaginosis infections in the primary care setting. Unfortunately, partner treatment with a single dose of metronidazole does not appear to confer a long-lasting effect. Mengel et al suggested that this failure of metronidazole to confer a long-lasting effect may be due to a resurgence of bacterial vaginosis organisms in the male genital tract. Even though metronidazole has been shown to penetrate male genital tissues in amounts similar to that in serum,[67] organisms associated with bacterial vaginosis (G vaginalis, Mobiluncus) can be fairly insensitive to metronidazole.[68] Further research exploring longer courses of metronidazole treatment as well as other antimicrobial agents is indicated, since it is now apparent that treatment of the male sexual partner in women with bacterial vaginosis can have a therapeutic benefit.

* Further information available from author on request.

PROGNOSIS

Currently there is no evidence supporting an increase in mortality in women with bacterial vaginosis. There is, however, an emerging body of evidence that should warrant concern because it links bacterial vaginosis with increased pregnancy morbidity. A recent study by Gravett et al[69] has shown that pregnant women with similar demographic and obstetric risk factors who have bacterial vaginosis give birth earlier (37.8 weeks vs 38.5 weeks, $P = .05$) and have neonates with a lower mean birthweight (2,960 g vs 3,184 g) than women without bacterial vaginosis. Multivariate analysis also revealed a significant association between bacterial vaginosis and preterm rupture of the membranes and preterm labor. Hillier et al[40] additionally observed that women with bacterial vaginosis were more likely to deliver preterm (<37 weeks' gestation) than were women with normal vaginal flora (44 percent vs 28 percent, $P = .03$). It is currently hypothesized that bacterial vaginosis lowers cervical immunity, and this state may predispose to the development of chorioamnionitis and premature labor. Additional research is needed to clarify which organism or organisms associated with bacterial vaginosis correlate with these adverse pregnancy outcomes and whether synergistic interactions resulting from the increased concentration of anaerobes and decreased lactobacilli are responsible.

CONCLUSIONS

Bacterial vaginosis is emerging from the nonspecific vaginitis "wastebasket." The development of clearly defined diagnostic criteria and effective treatment strategies means that bacterial vaginosis will no longer be a diagnosis of exclusion. Although much has been discovered about the cause, epidemiology, diagnosis, treatment, and prognosis of bacterial vaginosis, much still needs to be learned. The development of treatment strategies to improve pregnancy

outcome in women with bacterial vaginosis, further studies of patient and partner treatment, and characterization of the cause of the Gram-stained slide categorization "other" are three areas in urgent need of attention from primary care researchers.

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