# Microbiologic Response to Treatment of Bacterial Vaginosis with Topical Clindamycin or Metronidazole

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To compare the frequencies, concentrations, and antimicrobial susceptibilities of vaginal microbes isolated from women with bacterial vaginosis (BV) before and after therapy, 119 nonpregnant women aged 18 to 45 with clinical and Gram stain evidence of BV were randomized to receive intravaginal clindamycin or metronidazole. Vaginal swabs were collected at baseline and 7 to 12 days, 35 to 45 days, and 70 to 90 days following therapy for quantitative vaginal culture. For the 99 women completing all four visits, statistical analyses were performed comparing differences in vaginal microflora between the two treatment arms and between visits in the same treatment group. Antimicrobial susceptibility testing using the agar dilution method was performed for anaerobic gram-negative rods. Although both therapies resulted in decreased colonization by *Gardnerella vaginalis* and *Mycoplasma hominis*, only metronidazole treatment resulted in a significant decrease in the frequency and concentration of *Prevotella bivia* and black-pigmented *Prevotella* species. Of the 865 anaerobic gram-negative rods evaluated for susceptibility, only 3 (0.3%) were resistant to metronidazole, whereas clindamycin resistance increased significantly for *P. bivia* and black-pigmented anaerobic gram-negative rods persisting following clindamycin therapy. Clindamycin-resistant subpopulations of *P. bivia* and black-pigmented *Prevotella* species emerged 7 to 12 days after therapy even among women colonized initially by clindamycin-susceptible strains. These resistant subpopulations persisted at high frequencies (42 to 50%) 70 to 90 days following therapy. The two topical agents for treatment of BV have differing microbiologic effects on the vaginal microflora. The emergence of clindamycin-resistant anaerobic gram-negative rods following therapy is of concern.

Bacterial vaginosis (BV) is a common lower genital tract syndrome affecting women of reproductive age. Microbes associated with BV are part of the endogenous flora of the vagina, and the acquisition of BV results when there are changes of the normal flora of the vagina, causing an increased prevalence of *Gardnerella vaginalis*, *Mycoplasma hominis*, and anaerobic organisms and a decreased prevalence of the dominant *Lactobacillus* species. Acquisition of BV is associated with adverse outcomes among nonpregnant and pregnant women. Previous studies have shown that the alteration of the normal flora could increase the risk of acquiring BV, human immunodeficiency virus type 1, or sexually transmitted diseases (8, 18). Furthermore, BV has been found to be associated with preterm labor, preterm delivery, low birth weight, postcesarean endometritis, and postabortion pelvic inflammatory disease (12, 15, 30).

The treatments recommended by the Centers for Disease Control for BV are either metronidazole or clindamycin administered orally or intravaginally (6). Metronidazole is a nitroimidazole with activity against anaerobic organisms, while clindamycin, a macrolide, has a broad spectrum of activity against a variety of microbes including aerobic and anaerobic organisms.

Despite treatment with either metronidazole or clindamycin, similar percentages of women (approximately 10 to 15%) fail therapy after 1 month (9). The proportion of women who relapse also increases over time. The recurrence rate of BV is approximately 30% at 3 months and approximately 50 to 80% at 1 year following therapy with either drug (5, 10, 29). Current therapy for managing recurrent BV is repeated treatment with antibiotics. An obvious problem and important health issue associated with repeated exposure to the same antibiotic is resistance of those microbes targeted by the drug, which can result in an alteration of flora and possible persistence of BV-associated pathogens. Resistance to metronidazole, despite its use for over 3 decades, is rare (14, 27). Recent studies have shown an emergence of clindamycin-resistant genital organisms among clinically relevant bacteria, including group B streptococci (17, 20).

Although no head-to-head comparison studies have evaluated the microbiologic responses, separate placebo-controlled trials of metronidazole and clindamycin suggest that there may be different microbiological responses following therapy with these two agents (9). This paper provides a detailed microbiologic analysis of a previously published clinical trial of bacterial vaginosis (4). Our objectives were to compare the frequencies and median concentrations of major constituents of the vaginal microflora before and after treatment to assess for metronidazole and clindamycin resistance among anaerobic components of the microflora before and after therapy and to evaluate whether antimicrobial susceptibility accounts for the persistence of anaerobic gram-negative rods following therapy.

(A portion of this research was presented at the 104th General Meeting of the American Society for Microbiology, New Orleans, Louisiana, 23 to 27 May 2004.)

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## MATERIALS AND METHODS

**Patient population.** A total of 119 premenopausal, nonpregnant women aged 18 to 45 with a clinical and Gram stain diagnosis of BV were recruited from the Allegheny Health Department, Family Health Council Clinic of Aliquippa and Magee-Womens Hospital in Pittsburgh for a single-blind study. Written informed consent of the protocol was obtained from each study participant prior to enrollment. The protocol was approved by the institutional review board of Magee-Womens Hospital of the University of Pittsburgh Medical Center.

Clinical diagnosis of BV was determined using the criteria of Amsel et al. (1). The patient had to exhibit three or more of the following criteria to qualify: homogenous vaginal discharge, >20% clue cells on wet mount, elevated pH ($\geq$4.7) of vaginal discharge, and release of a fishy amine odor upon addition of 10% potassium hydroxide solution to vaginal fluid. A Gram stain score of $\geq$4 based on the criteria for BV assessment developed by Nugent et al. was required for Gram stain diagnosis (22). Any patient having any of the following exclusion criteria was excluded from participation: pregnancy, known allergy to metronidazole or clindamycin, concurrent antibiotic use, menstruation, presence of an intrauterine device, <18 years of age, known active infection due to chlamydia, gonorrheas, or trichomonas, or clinically apparent herpes simplex infection. The study population had a mean ($\pm$ standard deviation) age of 27 ($\pm$5.8) years and was predominantly African American (70%) and unmarried (90%). Some college education was reported by 57% of the women, and 56% reported smoking cigarettes, while only 5% reported douching in the past 30 days. Most (75%) of the women reported use of nonhormonal contraception, and 87% were currently sexually active.

**Treatment.** Upon enrollment, women were randomized to receive one of two treatments, clindamycin vaginal ovules (Pfizer, New York, NY) once daily for 3 days or metronidazole vaginal gel (3 M Pharmaceuticals, St. Paul, MN) once daily for 5 days. Women were randomized with equal frequencies to the two treatment arms using a permuted block design with a block size of eight. Following randomization, the two groups did not differ with respect to any demographic or behavioral characteristics except mean age, which was 25 + 5.5 years in the metronidazole treatment group and 28 + 5.9 years in the clindamycin treatment group ($P = 0.03$). Following enrollment and treatment, women were to follow up at 7 to 12 days after finishing the last dose of medication and 35 to 45 days and 70 to 90 days after treatment. If women were diagnosed with BV at a follow-up visit, they were retreated with the therapy they were initially randomized to receive. A clinical cure was defined as the absence of clue cells on wet mount in addition to the absence of two or more clinical signs (no homogenous discharge, pH less than 4.7, no amine odor upon addition of potassium hydroxide). Only the subset of 99 women completing all four visits and having evaluable culture results from those visits was included in the present analysis.

Vaginal swabs were obtained at baseline (pretreatment) and at the three consecutive follow-up visits following treatment. Vaginal swabs were obtained by placing a nonlubricated speculum into the vagina and swabbing the lateral wall discharge with a Dacron polyester fiber-tipped swab (Fisher Scientific, Pittsburgh, PA). The swabs were placed into a Port-a-Cul anaerobic transport device (Becton Dickinson, Sparks, MD) and transported to the laboratory, where they were processed within 24 h of collection.

**Isolation and identification.** Quantitative vaginal culturing was performed as previously described (11). The *Lactobacillus* spp. isolated were identified by Gram stain showing gram-positive rods, characteristic ground glass colony morphology, and negative catalase reaction. Hydrogen peroxide ($H_2O_2$) detection of the *Lactobacillus* spp. isolated was performed as previously described and briefly by a qualitative method in which isolates are inoculated onto a brucella agar base supplemented with 3,3',5,5'-tetramethylbenzidine and horseradish peroxidase. Anaerobic incubation at 37°C for 48 to 72 h followed by exposure to air for 30 min results in a blue pigment if there is $H_2O_2$ production and no pigment if $H_2O_2$ production is absent (24). The *Gardnerella vaginalis* isolates were identified by their characteristic colony morphology, beta hemolysis on human bilayer agar with Tween (Becton Dickinson, Rockville, MD), Gram stain showing gram-variable pleomorphic rods, and negative catalase reaction. The *Mycoplasma hominis* and *Ureaplasma urealyticum* isolates were identified by their characteristic colony morphology on A-8 agar, prepared in-house. The *Escherichia coli* isolates were identified by their colony morphology, Gram stain showing gram-negative rods, and positive indole (Sigma, St. Louis, MO) test. The anaerobic gram-negative bacteria isolated were identified by Gram stain, a lack of growth on aerobically incubated media, susceptibility to a 20% bile disk (bile and disk, Becton Dickinson), susceptibility to colistin (Becton Dickinson), and 4-methylumbelliferone spot testing (19). A previous study comparing oligonucleotide probes and 4-methylumbelliferyl spot testing to conventional methods for the identification of *P. bivia* tested 267 anaerobic gram-negative rods and found that

isolates that probe positive for *P. bivia* also had a unique 4-methylumbelliferyl spot pattern distinct from any other American Type Culture Collection strain or clinical isolate that was negative by probe. The reproducibility and concordance of these two methods suggested that spot testing for *P. bivia* is a reliable method for identification. A study comparing oligonucleotide probes and spot testing for the other nonpigmented *Prevotella* spp. has not yet been undertaken; therefore, reliable phenotypic tests for identification do not exist, and this results in the grouping of these organisms (25). The anaerobic gram-negative rods selected for antimicrobial susceptibility testing were those colony types isolated in the highest concentrations. These isolates were stock-frozen in litmus milk (Becton Dickinson) at −70°C until susceptibility testing was performed.

**Antimicrobial susceptibility testing.** Antimicrobial susceptibility testing using the agar dilution method approved by the NCCLS and as previously described was performed to determine the MICs of 865 isolates of anaerobic gram-negative rods belonging to the following groups of bacteria: *Prevotella bivia*, nonpigmented *Prevotella* species, black-pigmented *Prevotella* species, *Porphyromonas* species, and *Bacteroides* species (4, 21). The technologists selecting the isolates for susceptibility testing and performing the susceptibility testing were blind as to the antibiotic treatment group and clinical response to therapy.

MICs were determined using the NCCLS guidelines. The breakpoints of resistance are $\geq$32 μg/ml for metronidazole and $\geq$8 μg/ml for clindamycin.

**Statistical analyses.** All statistical analyses were performed using SPSS statistical software release 12.0.1 (SPSS Inc., Chicago, IL). Fisher's exact test was used to evaluate differences in colonization frequencies of microbes and clinical efficacy between the clindamycin and metronidazole treatment groups. Fisher's exact test was also used to compare frequencies of loss and acquisition of microbes between treatment groups among those whose colonization status changed between the enrollment and first follow-up visit. A chi-square test for linear trend was used to evaluate the change in the percentage of resistant isolates from enrollment through the third follow-up visit within the clindamycin group. A chi-square test was used to evaluate differences in colonization frequencies of microbes at the first follow-up visit between those who were not colonized, those who were colonized with a clindamycin-susceptible isolate, and those who were colonized with a clindamycin-resistant isolate at enrollment. The Mann-Whitney U test was used to evaluate differences in the median concentration of microbes between treatment groups among those who were colonized at each visit. Cochran's Q and Friedman's tests were used to evaluate differences in colonization frequencies and median concentrations of microbes between visits in each subject within treatment groups. The concentration for noncolonized visits was set to 0 so that all participants and visits could be included in the analyses. All statistical tests were evaluated at the 0.05 significance level.

## RESULTS

A graphical analysis comparing the changes observed among the vaginal microorganisms associated with BV isolated at baseline and 7 to 12 days, 35 to 45 days, and 70 to 90 days following therapy with metronidazole or clindamycin is presented in Fig. 1.

The presence of $H_2O_2$-producing lactobacilli is considered an indicator of optimal vaginal ecology, and a significant increase in colonization by $H_2O_2$-producing *Lactobacillus* species was observed among women following therapy with either metronidazole or clindamycin over the 90 days of follow-up ($P < 0.001$). However, the proportion of women colonized by $H_2O_2$-producing lactobacilli differed at baseline for the two treatment groups. Clindamycin treatment resulted in a larger increase in colonization by *E. coli* than metronidazole treatment, although these differences did not reach statistical significance (data not shown). A significant decrease in colonization by *G. vaginalis* and *M. hominis* ($P < 0.001$) was observed among women following therapy with either clindamycin or metronidazole. Women treated with metronidazole had a significant decrease in colonization by *U. urealyticum* (94% to 79%, $P < 0.001$) compared with clindamycin-treated women (73% to 65%, $P = 0.3$). Following therapy with metronidazole, there was a significant decrease in colonization among two
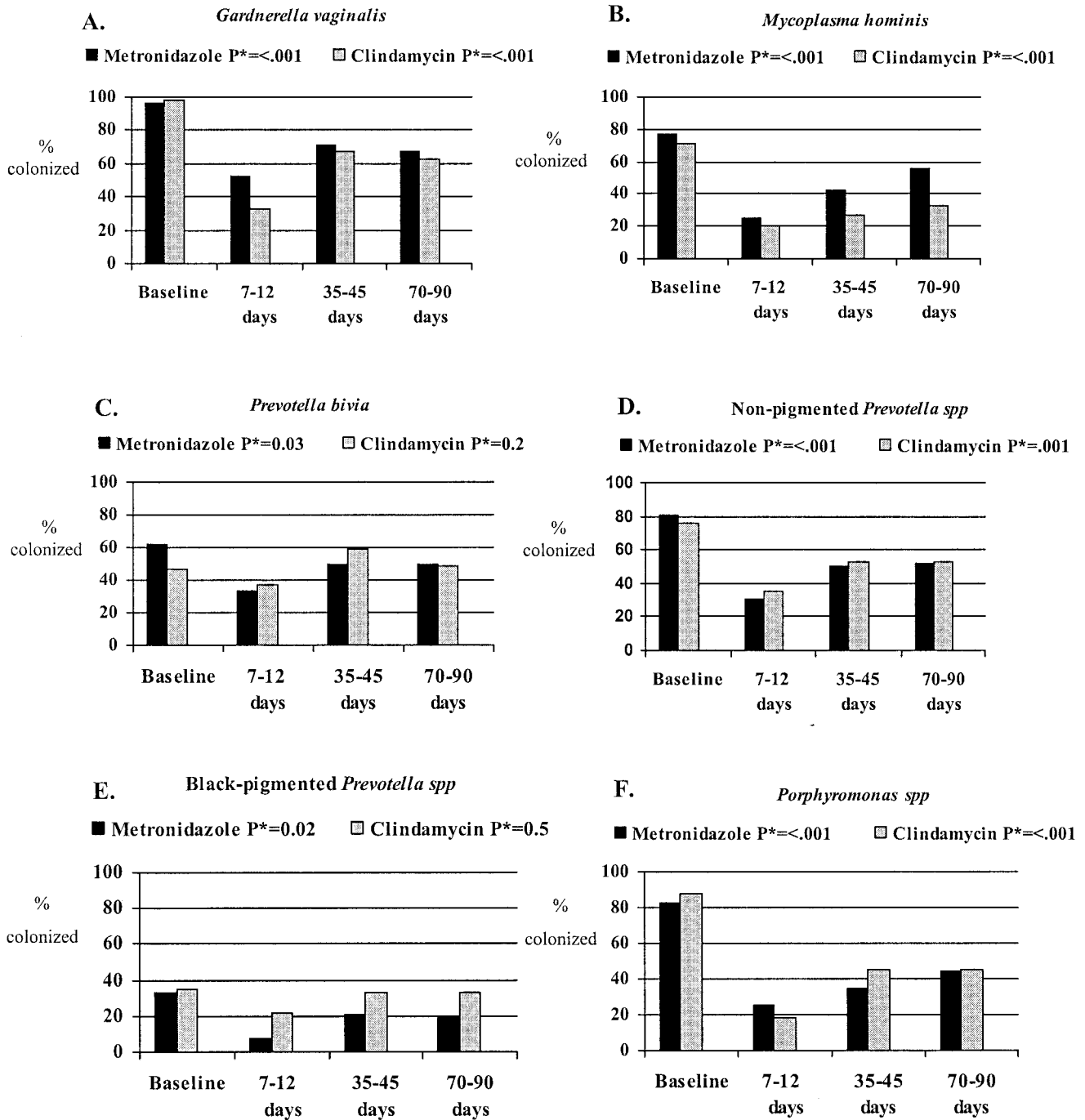
FIG. 1. Changes in vaginal microbiology from baseline among women with BV after therapy with topical metronidazole or clindamycin. (D) Nonpigmented *Prevotella* spp. include the following: *P. oralis, P. buccalis, P. veroralis, P. oulorum, P. oris, P. buccae, P. capillosus,* and *P. disiens.* (E) Black-pigmented *Prevotella* spp. include the following: *P. intermedia, P. corporis, P. denticola, P. loescheii, P. melaninogenica,* and *B. levii.* (F) *Porphyromonas* spp. include *P. asaccharolytica, P. endodontalis,* and *P. gingivalis.* Asterisks indicate that Cochran's Q test was performed to determine the *P* value for the frequency of microbes between visits.

groups of anaerobic gram-negative rods associated with BV, *P. bivia* ($P = 0.03$) and black-pigmented *Prevotella* spp. ($P = 0.02$), but a significant decrease in these organisms was not observed among women who were treated with clindamycin (Fig. 1). Both *Porphyromonas* spp. and nonpigmented *Pre-*

*votella* spp. decreased significantly following treatment with either regimen.

Antimicrobial susceptibility testing of anaerobic gram-negative rods recovered from the women before and after treatment (Table 1) revealed a marked and sustained increase in

TABLE 1. Percentages of anaerobic gram-negative rods resistant to clindamycin and metronidazole before and after therapy

| Group | Visit | No. of isolates tested | No. (%) of drug-resistant isolates from patients treated with[a]: | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | Clindamycin | | Metronidazole | |
| | | | Clindamycin resistant | Metronidazole resistant | Clindamycin resistant | Metronidazole resistant |
| *P. bivia* | Pretreatment | 60 | 5 (8) | 0 | 10 (17) | 0 |
| | 7–12 days | 39 | 20 (51) | 0 | 2 (5) | 0 |
| | 35–45 days | 61 | 23 (38) | 0 | 7 (11) | 0 |
| | 70–90 days | 53 | 22 (42) | 0 | 5 (9) | 0 |
| Nonpigmented *Prevotella* spp. | Pretreatment | 108 | 15 (14) | 0 | 7 (6) | 1 (1) |
| | 7–12 days | 40 | 17 (43) | 0 | 3 (8) | 1 (3) |
| | 35–45 days | 85 | 24 (28) | 0 | 7 (8) | 0 |
| | 70–90 days | 68 | 17 (25) | 0 | 9 (13) | 0 |
| Black-pigmented *Prevotella* spp. | Pretreatment | 56 | 6 (11) | 0 | 7 (13) | 0 |
| | 7–12 days | 22 | 15 (68) | 0 | 2 (9) | 0 |
| | 35–45 days | 44 | 16 (36) | 0 | 3 (7) | 1 (2) |
| | 70–90 days | 36 | 17 (47) | 0 | 4 (11) | 0 |
| *Porphyromonas* spp. | Pretreatment | 89 | 3 (3) | 0 | 2 (2) | 0 |
| | 7–12 days | 14 | 2 (14) | 0 | 2 (14) | 0 |
| | 35–45 days | 41 | 15 (37) | 0 | 2 (5) | 0 |
| | 70–90 days | 31 | 13 (50) | 0 | 3 (10) | 0 |
| *Bacteroides* spp. | Pretreatment | 5 | 0 | 0 | 0 | 0 |
| | 7–12 days | 3 | 0 | 0 | 0 | 0 |
| | 35–45 days | 5 | 1 (20) | 0 | 2 (40) | 0 |
| | 70–90 days | 5 | 1 (20) | 0 | 1 (20) | 0 |

[a] $P$ values are from chi-square tests for linear trend. $P$ values for clindamycin results are as follows: for *P. bivia*, <0.001; for nonpigmented *Prevotella* spp., 0.08; for black-pigmented *Prevotella* spp., <0001; for *Porphyromonas* spp., <0.001; and for *Bacteroides* spp., 0.2. $P$ values for metronidazole results are as follows: for *P. bivia*, 0.3; for nonpigmented *Prevotella* spp., 0.2; for black-pigmented *Prevotella* spp., 0.6; for *Porphyromonas* spp., 0.1; and for *Bacteroides* spp., 0.2.

the proportion of clindamycin-resistant anaerobic gram-negative rods from women following therapy with clindamycin but not metronidazole. While up to three anaerobic gram-negative rods were selected for each visit, the number of isolates tested for any given visit differed because not all women had multiple types of anaerobic gram-negative rods recovered after therapy. The proportions of *P. bivia*, nonpigmented *Prevotella*, black-pigmented *Prevotella*, *Porphyromonas*, and *Bacteroides* isolates resistant to clindamycin before treatment with clindamycin were 8%, 14%, 11%, 3%, and 0%, respectively. However, at 7 to 12 days following therapy with clindamycin, the percentages of clindamycin-resistant isolates were 51%, 43%, 68%, 14%, and 0%, respectively. Isolates recovered 35 to 45 days and 70 to 90 days following therapy also exhibited increased resistance (Table 1). There was no difference in the proportion of women having at least one anaerobic gram-negative rod resistant to clindamycin among women who received one clindamycin treatment regimen versus those who were treated two or more times (data not shown). While clindamycin-resistant anaerobic gram-negative rods were isolated from the women who were treated with topical metronidazolebefore therapy, the proportion of isolates expressing clindamycin resistance did not increase following metronidazole therapy (Table 1). These data suggest that the increase in clindamycin-resistant isolates following clindamycin therapy is attributable to clindamycin exposure rather than treatment of BV per se.

In order to evaluate whether the lack of clindamycin efficacy against *P. bivia* and black-pigmented *Prevotella* spp. was due to persistence of clindamycin-resistant strains, an analysis of or-

ganism frequencies at follow-up stratified by clindamycin susceptibility at baseline was performed. This analysis showed that the presence of clindamycin-resistant *P. bivia* or black-pigmented *Prevotella* spp. at baseline was not predictive of colonization by clindamycin-resistant strains at follow-up (Table 2). For example, of 19 women who were colonized by clindamycin-susceptible *P. bivia* at baseline, 10 were colonized by *P. bivia* at follow-up, and 9 of these isolates were clindamycin resistant. Thus, there was a complete shift from clindamycin-susceptible to clindamycin-resistant *P. bivia* 7 to 12 days following clindamycin therapy. Among women not initially colonized by either *P. bivia* or black-pigmented anaerobic gram-negative rods, colonization was common at follow-up (27 to 55%), and most of the colonizing strains were clindamycin resistant. These data suggest that clindamycin subpopulations of anaerobic gram-negative rods emerge rapidly following short-term topical clindamycin exposure.

The clinical responses to BV treatment did not differ for the two treatment groups following therapy. At 7 to 12 days, cure rates were 79% and 88% for metronidazole and clindamycin ($P$ = 0.3). At 35 to 45 days, the cure rates were 62% and 55%, respectively ($P$ = 0.5), and rates were 58% and 55% ($P$ = 0.8) 70 to 90 days after therapy.

**DISCUSSION**

Despite similarities in clinical responses observed among women treated with metronidazole and clindamycin, the data from the present study suggest that treatment with clindamycin

TABLE 2. Frequency of *Prevotella bivia* and black-pigmented *Prevotella* species before and after topical clindamycin therapy, stratified by clindamycin susceptibility

| Pretreatment culture or statistic | No. (%) of isolates positive[b] for given organism/total no. of isolates | No. (%) of isolates resistant to clindamycin/total no. of isolates[b] |
|---|---|---|
| *P. bivia* present | | |
| Clindamycin susceptible ($n = 19$) | 10/19 (52%) | 9/10 (90%) |
| Clindamycin resistant ($n = 5$) | 3/5 (60%) | 3/3 (100%) |
| *P. bivia* absent ($n = 22$) | 6/22 (27%) | 6/6 (100%) |
| *P* value[a] | $P = 0.2$ | $P = 0.6$ |
| Black-pigmented *Prevotella* present | | |
| Clindamycin susceptible ($n = 15$) | 1/15 (7%) | 1/1 (100%) |
| Clindamycin resistant ($n = 6$) | 1/6 (17%) | 1/1 (100%) |
| Black-pigmented *Prevotella* absent ($n = 20$) | 11/20 (55%) | 10/11 (91%) |
| *P* value[a] | $P = 0.007$ | $P = 0.9$ |

[a] *P* values are from chi-square tests.
[b] The numbers of positive and clindamycin-resistant cultures were determined 7 to 12 days posttreatment.

yields a different microbial flora pattern following therapy for BV and that the anaerobic gram-negative rods persisting after therapy are usually resistant to clindamycin but not metronidazole.

The increase in colonization by *Lactobacillus* spp. during the week following therapy with metronidazole but not clindamycin is expected, since clindamycin has a broad spectrum of activity against anaerobic as well as aerobic and facultative organisms, like *Lactobacillus* spp. (2). Metronidazole is a nitroimidazole with activity against obligately anaerobic organisms. Aerobic and facultative organisms are generally not inhibited by nitroimidazoles because their mechanism of action, the reduction of the nitro group, is dependent upon the absence of oxygen (7).

Surprisingly, there was a similar reduction observed in vaginal colonization by *G. vaginalis* and *M. hominis* after therapy with either metronidazole or clindamycin and a significant decrease in vaginal colonization by *U. urealyticum* among women treated with metronidazole but not clindamycin. Clindamycin has activity against these organisms, while metronidazole generally does not. A possible explanation for metronidazole having activity against these organisms is that previous studies have reported the hydroxymetabolite of metronidazole, a compound formed when metronidazole is metabolized by the liver or from the breakdown of metronidazole by anaerobic bacteria during its action, has antimicrobial activity and may have activity against *G. vaginalis* (13, 14, 26, 28). A previous study has suggested that eradication of nitroimidazole-susceptible anaerobic organisms may lead to a decreased colonization by nonsusceptible organisms like *G. vaginalis* and *M. hominis* (9). This suggests that antimicrobial agents having activity against *G. vaginalis* and genital mycoplasmas have no clear therapeutic advantage for the treatment of BV.

Anaerobic gram-negative rods are reported BV pathogens and are isolated from virtually all women with BV. A previous study has found that *P. bivia* and the *Prevotella corporis/Bacteroides levii* group, a black-pigmented group of organisms, are significantly associated with BV (11). There was a significant decrease in colonization among these two groups of anaerobic gram-negative rods in women after therapy with metronidazole compared with women who were treated with clindamycin. Antimicrobial susceptibility testing of *P. bivia* and black-pig-

mented *Prevotella* spp. revealed that 51% and 68% of the isolates, respectively, were resistant to clindamycin following therapy with clindamycin but not metronidazole. Increased metronidazole resistance was not observed among these groups of bacteria regardless of whether women were treated with clindamycin or metronidazole. This suggests that clindamycin-resistant anaerobic gram-negative rods are present among the mixed population of bacteria colonizing the vagina, and treatment with clindamycin results in selection for clindamycin-resistant anaerobic gram-negative rods following therapy. This was not observed following therapy with metronidazole.

Surprisingly, there was no difference observed in the proportion of clindamycin-resistant *Bacteroides* species isolated before or after therapy with clindamycin or metronidazole. Clindamycin resistance is highly associated with the *Bacteroides fragilis* group, and previous studies have shown increased resistance among this group occurring over the past decade (3, 16). A possible reason increased resistance was not observed was because the *B. fragilis* group isolates were generally recovered at densities of $10^3$ CFU per gram of vaginal fluid and were not the predominant anaerobic species chosen for susceptibility testing.

We found that women who were treated with clindamycin, regardless of whether they were colonized with susceptible or resistant anaerobic gram-negative rods, were likely to be colonized with resistant *P. bivia* or black-pigmented *Prevotella* spp. 7 to 12 days after therapy. We recognize that there are limitations to our study. There were women from whom both susceptible and resistant *P. bivia* or black-pigmented *Prevotella* spp. were isolated during the same visit, which suggests that among the mixed population of bacteria colonizing the vagina there are subtypes of each group of bacteria present as well. It was not our aim to isolate and characterize all anaerobic gram-negative rods present in the culture but rather to focus on the predominant anaerobes of the microflora. During initial isolation from culture, only one colony type for each group of anaerobic gram-negative rods present was selected, and we recognize that we may not have identified subpopulations of resistant or susceptible *P. bivia* or black-pigmented *Prevotella* spp. at any one visit. While isolating multiple colony types of all of the anaerobic gram-negative rods present might have pro-

vided us a more comprehensive understanding of resistance patterns observed among the colonizing strains of anaerobic gram-negative rods, our study has still documented the emergence of clindamycin-resistant organisms as the dominant populations after treatment.

The emergence of clindamycin resistance following treatment is not a novel finding. In 1986, Ohm-Smith et al. reported on the emergence of clindamycin-resistant anaerobic bacteria from the endometria of women with pelvic soft tissue infections (23). As in the present study, they found no correlation between antibiotic resistance and clinical response to therapy. Further, they reported that four of seven (57%) of the anaerobic gram-negative rods recovered following treatment were resistant to clindamycin. The present study differs from that 1986 study in that the frequency of clindamycin resistance at baseline has increased over the past 2 decades, a larger number of isolates was evaluated, and women were monitored for persistence of resistant organisms for 70 to 90 days. The emergence and persistence of clindamycin-resistant populations of anaerobes in the vagina following topical therapy may have implications for the future use of clindamycin for treatment of pelvic infections, because most organisms causing pelvic infections are derived from the lower reproductive tract.

In summary, treatment with clindamycin and treatment with metronidazole for BV result in different microbiological patterns following therapy. While both topical metronidazole and clindamycin yielded similar clinical responses to treatment, metronidazole may be superior to clindamycin based on the low level of resistance and its capacity to eradicate anaerobic gram-negative rods from the vagina.

## ACKNOWLEDGMENTS

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