ORIGINAL RESEARCH

Effect of Antibiotics on Vulvovaginal Candidiasis: A MetroNet Study

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***Purpose*: Vulvovaginal candidiasis (VVC) is believed common after systemic antibiotic therapy, yet few studies demonstrate this association. In this pilot study, we evaluate the effect of short-course oral antibiotic use on VVC.**

***Methods*: Nonpregnant women aged 18 to 64 years who required ≥3 days oral antibiotics for nongynecological diseases were recruited from a family medicine office. Age-matched (±5 years) women seen in the same clinic for noninfectious problems were recruited as controls. The main outcomes are incidence of symptomatic VVC and prevalence of positive vaginal *Candida* culture 4 to 6 weeks after antibiotics.**

***Results*: Eighty (44 in antibiotic group) women were recruited; 14 of 79 (95% CI, 0.11–0.28) had asymptomatic vaginal *Candida* cultures positive at baseline. During follow-up, 10 of 27 (95% CI, 0.22–0.56) women in antibiotic group were *Candida* culture positive. In contrast, 3 of 27 (95% CI, 0.04–0.28) women in the control group were *Candida* culture positive (relative risk, 3.33; $P = .03$). Meanwhile, 6 of 27 (95% CI, 0.11–0.41) women in antibiotic group developed symptomatic VVC whereas none (95% CI, 0–0.12) of the women in the control group developed vaginal symptoms (relative risk, ∞; $P = .02$). Baseline *Candida* culture did not predict subsequent symptomatic VVC after antibiotics.**

***Conclusion*: In this pilot study, the use of short courses of oral antibiotics seems to increase prevalence of asymptomatic vaginal *Candida* colonization and incidence of symptomatic VVC. Larger cohort studies are needed to confirm these findings. (J Am Board Fam Med 2008;21:261–268.)**

Although vulvovaginal candidiasis (VVC) is one of the most common forms of vaginitis in women of childbearing age, its etiology remains poorly understood.[1–4] Approximately 13 million cases are reported annually in the United States, prompting 10 million gynecologic office visits,[5–7] and the frequency continues to increase.[6–8] Although the widespread use of antibiotics has been suggested as one of the major factors contributing to the rising incidence of VVC,[1–4,9] the evidence supporting this hypothesis has been limited.[7] Most existing studies have been limited by their retrospective nature,[10–14] lack of control groups,[15,16] and lack of mycology culture data.[17,18]

Accordingly, existing data on the risk of developing antibiotic-associated VVC are conflicting.[1,2,7,14] For example, some case-control studies[19,20] found no evidence of an association between antibiotic agents and symptomatic VCC, whereas others reached an opposite conclusion.[10,13,21] The results from a prospective study of 250 pregnant women concluded that extensive antibiotic use posed little risk for the development of yeast infection.[22]

In addition to antibiotics, other hypothesized risk factors for VVC include pregnancy; a history of VVC; sexual practices (especially receptive oral sex); oral hormones, either contraceptive or replacement therapy; diabetes mellitus and other immunodeficiency states; and African American ethnicity.[1,2,19,23] However, definitive evidence relating each of these factors is limited.[2,4] Epidemiologic studies have failed to measure the true attack rate and have been unable to specifically identify char-

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acteristics of the at-risk subpopulation.[4,7] In addition, there has been little progress in understanding pathogenesis of antibiotic-associated VVC.[4,7] There is a critical need for high quality, well-controlled clinical studies investigating the relationship between antibiotic use and the development of VVC.[7]

We designed a prospective cohort study of nonpregnant adult women treated with a short course of oral antibiotics for a range of nongynecological infections to determine the incidence of VVC over the first 4 to 6 weeks after antibiotic therapy and explore the risk factors of antibiotic-associated VVC. The specific aims of this pilot study were to (1) evaluate the feasibility of the methods to be used in a later larger study and (2) estimate the incidence of symptomatic VVC and prevalence of *Candida* colonization after a short course of antibiotics.

Methods

Study Design and Population

Participants were recruited from a single family medicine office that was a member of the Metro-Net practice-based research network, which serves a diverse urban and suburban patient population, with approximately 50% African American patients. The Wayne State University Human Investigation Committee approved the study protocol.

Nonpregnant women between 18 and 64 years of age, free of vaginal symptoms at enrollment and who were prescribed ≥3 days antibiotics for a nongynecologic diagnosis (such as upper respiratory infection), were recruited as patients and designated as the antibiotic group. The control group women were age-matched (±5 years) to the individuals in the antibiotic group and seen in the same clinic for noninfectious problems or preventive visits. Pregnant women and women who had taken systemic or vaginal antibiotics, systemic or vaginal antifungal agents, or systemic corticosteroids in the previous 4 weeks were excluded from the study. All eligible women were invited for participation in the study. The response rate for the antibiotic group was approximately 80%, and the response rate for the control group was approximately 70%. The most common reason for decline of participation in the study was "no time for follow-ups."

Data Collection Protocol

After informed consent, participants were asked to complete an enrollment questionnaire that included detailed questions regarding hypothesized risk factors of VVC (personal/sexual habits, history of yeast vaginitis diagnoses during lifetime and past year) and demographic factors. The average time to complete this questionnaire was 15 minutes. Women were asked to self-collect vaginal specimens using sterile swabs for fungal culture, Gram stain of vaginal flora, and vaginal pH. After enrollment and swab collection, participants were instructed to return for follow-up visits at 1 to 2 weeks and 4 to 6 weeks after starting the antibiotic therapy (antibiotic group) or after the enrollment visit (control group).

At each follow-up visit, symptoms of VVC were reassessed by a short questionnaire (average of 2 minutes to complete). If a participant remained asymptomatic, she was instructed to self-collect a vaginal specimen for fungal culture, Gram stain, and pH as before. If a participant reported any vaginal symptoms (eg, burning, itching, discharge, redness, swelling, soreness, or pain), she was examined by a physician who completed an assessment form including the physical findings and obtained vaginal specimen for fungal culture, Gram stain, and other diagnostic testing (ie, wet mount and 10% KOH microscopic examination, vaginal pH, Whiff test, sexually transmitted disease screening, etc, as needed). If a participant developed vaginal symptoms between follow-up visits, she was instructed to call the office and to be seen by a physician within 24 hours. Free antifungal agents were provided if symptomatic VVC occurred during the follow-up period. Participants were compensated for their time with a gift card to a local grocery store at the time of the follow-up visit.

Asymptomatic *Candida* colonization was defined as the presence of *Candida* organisms on a culture and the lack of a report of vaginal symptoms on the questionnaire and/or in response to physician questioning. A positive fungal culture and/or the presence of pseudohyphae on the 10% KOH smear, plus self-report of one or more vaginal symptoms (eg, burning, itching, discharge, redness, swelling, soreness or pain), was defined symptomatic VVC, barring the presence of other causes of vaginitis.

Specimen Preparation and Laboratory Analyses

Vaginal swabs were collected at all 3 visits for all participants, regardless of symptoms, and evaluated

for fungal culture, Gram stain, and vaginal pH. Microscopy tests (10% KOH smear and saline wet mount) were performed only when women complained of vaginal symptoms. Once collected, the vaginal swabs were immediately inoculated onto fungal culture agar plates (Sabouraud dextrose agar), smeared on a slide for Gram stain, and on pH paper for pH determination. The labeled culture plates were initially stored in a refrigerator in the office, and then transported to the laboratory within 48 hours. The culture plates were incubated at 30° C. All *Candida* isolates, including *C. albicans* and *non-C. albicans* species, were identified by means of germ-tube formation in human serum, chlamydospore production, and the API 20C yeast identification system (Analytab Products, Hazelwood, MO).

The slides for Gram stain were air-dried and stored at room temperature and then transported to the laboratory weekly. The vaginal smears were then Gram stained and evaluated under magnification ×1000. Nugent's criteria, a standardized scoring system, were used to assess the vaginal flora.[24]

Data Analyses

The main outcome measures were the incidence of symptomatic VVC and the prevalence of positive vaginal *Candida* cultures at 1 to 2 weeks and 4 to 6 weeks after antibiotics. Both univariate analysis and multivariate analysis were used for the data analysis. The cumulative incidence of symptomatic VVC and prevalence of asymptomatic *Candida* colonization were computed in each group over the entire follow-up period. The crude relative risk and 95% CI and adjusted relative risk and its 95% CI were then computed.

Potential confounders (including age, race, history of VVC, baseline fungal culture, education, smoking, receptive oral sex, and birth control pills/patches) were evaluated in multivariate analyses using a forward selection procedure. Because of the small sample size, we retained the 2 variables that changed the outcome estimates the most (ie, oral sex and smoking for *Candida* colonization; oral sex and race for symptomatic VVC). Baseline culture may be an important factor associated with the outcome[22,25] and so we adjusted for this variable in all models. We used exact logistic regression to accommodate the small sample size.[26,27] Because there were only a small number of women who had diabetes, were postmenopausal, or on hormone replacement therapy, we did not adjust for diabetes, menopausal status, or hormone replacement therapy. $P < .05$ was considered statistically significant. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

Results

Characteristics of the Study Sample

Eighty women between 19 and 62 years of age were enrolled in the study. Of these, 44 women were in the antibiotic group and 36 were in control group. Table 1 shows the characteristics of the study sample by group status. Approximately one third of the sample self-identified as African-American and one quarter as smokers; 42.9% reported practice of receptive oral sex in a typical 4-week period and approximately 90% reported a history of life time VVC. Table 1 also shows that the baseline characteristics of the antibiotic and control groups were similar ($P > .05$).

Because approximately one third of patients were lost to follow-up, we compared the characteristics between the group of patients who were lost to follow-up and the group of patients who had at least one follow-up visit. The group of patients who were lost to follow-up were 8 years younger (on average) than the group who had follow-up visits ($P < .001$). Otherwise, they were fairly similar ($P > .05$) in all the other characteristics showed in Table 1.

Outcomes of the Study Sample

At baseline, there were 14 women (17.7%; 95% CI, 0.11–0.28) with positive *Candida* culture (ie, asymptomatic *Candida* colonization) (Table 2). A similar number of women in the 2 groups were colonized. Specifically, 8 women (18.2%; 95% CI, 0.10–0.32) in the antibiotic group and 6 women (17.1%; 95% CI, 0.08–0.33) in the control group had baseline *Candida* colonization.

There were 27 (61.4%) women in the antibiotic group and 27 (75.0%) women in control group who had at least one follow-up visit. Among the participants in the antibiotic group who had at least one follow-up visit, 10 (37.0%; 95% CI, 0.22–0.56) had positive *Candida* cultures, and 6 (22.2%; 95% CI, 0.11–0.41) developed symptomatic VVC at follow-up. Another patient developed bacterial vaginosis with negative fungal culture during follow-up. In contrast, among control group participants who had at least one follow-up visit, 3 (11.1%; 95% CI,

Table 1. Demographic and Health Characteristics of Study Sample by Treatment Group

Characteristics	Antibiotic (n = 44) (n [%])	Control (n = 36) (n [%])	*P*
Age in years			.79
18–35	18 (41.9)	12 (34.3)	
36–50	21 (48.8)	20 (57.1)	
≥50	4 (9.3)	3 (8.6)	
Missing	1	1	
Race			.37
White	19 (48.7)	16 (48.5)	
African American	16 (41.0)	10 (30.3)	
Other	4 (10.3)	7 (21.2)	
Missing	5	3	
Education			.13
≤High school	5 (12.8)	7 (21.2)	
Some college	21 (53.8)	10 (30.3)	
≥College degree	13 (33.3)	16 (48.5)	
Missing	5	3	
Marital status			.77
Married	9 (23.1)	10 (30.3)	
Single	14 (35.9)	10 (30.3)	
Separated/divorced/widowed	16 (41.1)	13 (39.4)	
Missing	5	3	
Post-menopausal			.28
Yes	6 (15.4)	8 (25.8)	
No	33 (84.6)	23 (74.2)	
Missing	5	5	
Current smoker			.72
Yes	9 (27.3)	8 (23.5)	
No	24 (72.7)	26 (76.5)	
Missing	11	2	
History of yeast vaginitis			.23*
Yes	37 (94.9)	27 (84.4)	
No	2 (5.1)	5 (15.6)	
Missing	5	4	
Receptive oral sex			.30
Yes	18 (48.6)	12 (36.4)	
No	19 (51.4)	21 (63.6)	
Missing	7	3	
Diabetes mellitus			.66*
Yes	3 (13.6)	2 (8.3)	
No	19 (86.4)	22 (91.7)	
Missing	22	12	
Birth control pill/patch			.74*
Yes	6 (16.2)	4 (12.1)	
No	31 (83.8)	29 (87.9)	
Missing	7	3	
Hormone replacement therapy			.12*
Yes	0 (0)	6 (37.5)	
No	7 (100)	10 (62.5)	
Missing	37	20	

*Fisher's exact test.

0.04–0.28) had positive *Candida* cultures, and none (95% CI, 0–0.12) developed symptomatic VVC at follow-up (Table 2).

Compared with the control group in the unadjusted analysis (Table 2), the relative risk of having positive *Candida* culture after antibiotic therapy was 3.33 (95% CI, 1.03–10.79). Because none of the women in the control group developed symptomatic VVC, the relative risk for developing symptomatic VVC after antibiotic therapy was infinity (∞) ($P = .02$) (Table 2). In the adjusted analysis (eg, baseline culture, oral sex, and smoking or race) using exact logistic regression, the odds ratio of having positive *Candida* culture after antibiotics was 7.84 (95% CI, 1.26–88.79); the odds ratio of developing symptomatic VVC was 4.81 (95% CI, 0.55-∞) (data not shown).

Because of approximately one-third attrition rate, we did an unadjusted sensitivity analysis by including all of the women who were lost to follow-up with the following hypothetical scenarios. If we assume that all missing women in the antibiotic group had positive *Candida* culture and developed symptomatic VVC at follow-up, and all missing women in control group had negative *Candida* culture and remained asymptomatic, then the relative risk of having positive *Candida* culture and symptomatic VVC after antibiotic therapy would be 7.36 and ∞, respectively. On the other hand, if we assume the opposite of above (ie, all missing women in the antibiotic group had negative culture and were asymptomatic, and all missing women in the control group had positive culture and developed symptomatic VVC), then the relative risk of having positive *Candida* culture and symptomatic VVC after antibiotic therapy would be 0.68 and 0.49, respectively. Because these 2 extreme scenarios are unlikely to be true, we also calculated the relative risks in each hypothetical scenarios assuming 0% to 100% women who were lost to follow-up developed positive *Candida* culture or symptomatic VVC regardless of antibiotic use (Table 3). Assuming that women who developed symptoms would return, then the first row in Table 3 indicates that the relative risk of symptomatic VVC after taking antibiotics would be ∞. However, other studies[7] suggest that 5% to 30% of women develop symptomatic VVC after antibiotic use, in which case Table 3 suggests the relative risk of symptomatic VVC after antibiotic use would be between 11.21 and 3.03.

Table 2. Baseline and Follow-up *Candida* Culture and Follow-up Symptomatic VVC by Treatment Group

	Baseline *Candida* Culture			Follow-Up *Candida* Culture			Follow-Up Symptomatic VVC		
	Positive (n [%])	Negative (n [%])	Missing (n)	Positive (n [%])	Negative (n [%])	Missing (n)	Positive (n [%])	Negative (n [%])	Missing (n)
Antibiotic group	8 (18.2)	36 (81.8)	0	10 (37.0)	17 (63.0)	17	6 (22.2)	21 (77.8)[†]	17
Control group	6 (17.1)	29 (82.9)	1	3 (11.1)	24 (88.9)	9	0 (0)	26 (100)	10
RR* (95% CI)	1.06 (0.41 – 2.77) $P = .91$			3.33 (1.03 – 10.79) $P = .03$				∞[‡] $P = .02$	

*Relative risk of univariate analysis.
[†]One patient developed bacterial vaginosis.
[‡]One cell had zero in the 2 × 2 table for the calculation of relative risk.

We also performed explorative data analysis to identify possible factors associated with baseline *Candida* colonization. After adjusting for race, marital status, and history of yeast infection, receptive oral sex was the only factor that was significantly associated with baseline *Candida* colonization (data not shown). Women with positive baseline *Candida* culture were not more likely to develop symptomatic VVC after receiving antibiotics as compared with women with negative baseline *Candida* culture (data not shown).

Timeline of Developing Symptomatic VVC After Antibiotic Treatment

Seven women in the antibiotic group developed vaginal symptoms within the first 4 to 6 weeks of follow-up. Six of the 7 women developed symptomatic VVC, and the other developed bacterial vaginosis. Among the 6 women with symptomatic VVC, 5 had reported vaginal symptoms within the first 3 weeks (all had positive *Candida* culture at follow-up) and the other developed symptoms in the sixth week after initiating antibiotics (positive KOH but negative culture). Only 2 of the 6 women who developed symptomatic VVC after taking antibiotics had positive baseline culture (one had 1 colony of *C. albicans* and the other had 1 colony of *C. glabrata*), but none had yeast visualized on Gram stain slides. The woman who developed bacterial vaginosis had a negative baseline yeast culture and reported her symptoms in the third week after antibiotics.

Table 3. Relative Risk Estimate of Outcomes of Interest in Hypothetical Scenarios of Women Lost to Follow-up

Lost to Follow-up Developed Outcome of Interest, Regardless of Antibiotic Use (%)	Outcomes of Interest	
	RR of Positive *Candida* Culture After Antibiotic Use	RR of Symptomatic VVC After Antibiotic Use
0	2.73	∞*
5	2.57	11.21
10	2.45	6.30
20	2.28	3.85
30	2.17	3.03
50	2.02	2.37
70	1.93	2.09
100	1.84	1.88

*One cell had zero in the 2 × 2 table for the calculation of relative risk.
RR, relative risk; VVC, vulvovaginal candidiasis.

Discussion

We found that a short course of oral antibiotics was associated with both increased prevalence of positive vaginal *Candida* colonization and increased incidence of symptomatic VVC during 4 to 6 weeks of using antibiotic therapy.

At baseline, approximately 18% of asymptomatic women had positive *Candida* cultures in the present study, a percentage consistent with the literature. Previous studies have reported prevalence estimates of *Candida* colonization between 10% and 20%,[1,28,29] with a range of 10% to 50% of healthy adult women in cross-sectional studies.[14,25,30,31] A recent longitudinal cohort study[32] demonstrated that vaginal yeast colonization may be transient in most women, although 70% of young, sexually active women were vaginally colonized by *Candida* at some time during a period of 1 year, with an average point prevalence of 30%. Although our study sample was small, we also noticed yeast colonization status changed during the 4 to 6 weeks of follow-up among women not taking antibiotics (data not shown).

Although the precise relationship between yeast colonization and symptomatic yeast vaginitis is not entirely clear, yeast colonization is considered a necessary precursor for subsequent symptomatic VVC.[4] Furthermore, several studies reported a positive association in both nonpregnant and pregnant women.[22,25] In this pilot study, we found that receptive oral sex was the only factor that was significantly associated with baseline *Candida* colonization after adjusting for potential confounders. This finding is consistent with previous reports of an association between vaginal candidiasis and orogenital sex.[19,23,33] We hypothesized that baseline *Candida* culture obtained in asymptomatic women requiring antibiotic therapy for nongenital infection may predict which women would develop symptomatic VVC after antibiotic therapy. However, in our analyses, baseline culture status did not predict subsequent symptomatic VVC following antibiotics. The explanation might reflect a lack of sensitivity of vaginal fungal culture in detecting low level *Candida* colonization in asymptomatic women.[25] Future large, longitudinal investigations may enhance our understanding of the relationship between yeast colonization and antibiotic-associated symptomatic VVC.

Approximately 22% (6 of 27) of women developed symptomatic VVC during the 4 to 6 weeks after taking short-course oral antibiotics, a rate similar to the 23% and 28% reported by Pirotta et al[34] and Bluestein et al,[31] respectively. Our results are consistent with previous studies that demonstrated that antibiotic use seems to be a short-term risk factor for symptomatic VVC and that excess risk occurs in the first month after antibiotic use.[10,31,35] In 2 older clinical studies by Caruso[36] and Oriel and Waterworth,[37] the prevalence of a vaginal culture of *Candida* increased from approximately 10% at baseline to approximately 30% after 2 to 3 weeks of treatment with tetracyclines in nonpregnant adult women, which was similar to our finding. Unfortunately, both studies failed to report the percentages of women who developed vaginal symptoms. More recently, Bluestein et al[31] reported a 35% *Candida* colonization at baseline that increased to 50% after 10 days of antibiotic therapy. Pirotta et al[34] reported increased *Candida* colonization from 21% at baseline to 37% 2 weeks after antibiotics, and 23% of women developed symptomatic VVC after antibiotics, similar to our findings. However, none of these studies included a nonantibiotic group for comparison.

Critical factors determining individual susceptibility to antibiotic-associated VVC remain to be discovered. Identification of susceptibility factors will probably lead to new approaches to prevent the disease. Larger studies are necessary to determine the high-risk group of women with susceptibility factors. Nevertheless, it must be emphasized that not all patients who developed vaginal symptoms after antibiotic use have vaginal candidiasis. As in the present series, one of the 7 women who became symptomatic after antibiotic use was confirmed to have bacterial vaginosis. Because the supposedly characteristic symptoms and signs of yeast vaginitis can be present in other conditions,[38–40] a positive identification of yeast by wet mount or culture may be necessary for accurate diagnosis.[38–40]

There are several strengths of this study. To our knowledge, this is the first prospective cohort study of women taking oral antibiotics being monitored for signs and symptoms of vaginitis both clinically and mycologically that also compared the results to a control group of women not exposed to antibiotics. The study was conducted in a traditional family medicine center, a real-world example of the primary care setting, compared with most other studies that have been in selected populations, often those with gynecological problems. Therefore, our findings may be more generalizable to the primary care patient population than findings from venereal clinics or tertiary hospitals.

We also recognize several limitations to this study. First, it is a pilot study with various types of antibiotics, dosages, and durations. The small sample size limits our ability to further determine the effects of antibiotic type, dosage, or duration on the primary outcomes. Second, we used patient self-collected vaginal specimens to overcome some of the recruitment barriers, which could potentially affect vaginal sample quality. This self-collection method has been used successfully in several vaginitis studies[33,41,42] and has saved time and promoted study participation. In addition, the vaginal sample was comparable in specimen quality to the traditional physician-collected sample by direct visualization with a speculum examination.[41–43]

Approximately one third of study participants were lost to follow-up. It is possible that some women may have developed vaginitis symptoms and sought care at another facility or self-treated

with over-the-counter antifungal medication. It may be more likely that women lost to follow-up did not develop symptoms, resulting in less prompting to follow-up. In addition, we did try to contact those participants lost to follow-up to ascertain whether symptoms had developed and to encourage follow-up. We were only able to contact approximately one third of them and ascertain that no one had developed symptoms. In addition, we offered free antifungal medication to encourage study subjects to return to our clinic for care if they developed vaginal symptoms during the follow-up period. Our sensitivity analysis indicates that if all the missing women, regardless of antibiotic use, were culture and symptom negative, positive associations between antibiotic use and positive culture/symptoms were still present.

Conclusion

A short course of oral antibiotics was associated with increased prevalence of positive *Candida* colonization. Approximately 22% of women developed symptomatic VVC during the 4 to 6 weeks after antibiotic therapy. Larger cohort studies are needed to confirm these results and to establish risk factors for this complication of antibiotic therapy.

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