

ORIGINAL ARTICLE

Maintenance Fluconazole Therapy for Recurrent Vulvovaginal Candidiasis

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ABSTRACT

BACKGROUND

No safe and convenient regimen has proved to be effective for the management of recurrent vulvovaginal candidiasis.

METHODS

After inducing clinical remission with open-label fluconazole given in three 150-mg doses at 72-hour intervals, we randomly assigned 387 women with recurrent vulvovaginal candidiasis to receive treatment with fluconazole (150 mg) or placebo weekly for six months, followed by six months of observation without therapy. The primary outcome measure was the proportion of women in clinical remission at the end of the first six-month period. Secondary efficacy measures were the clinical outcome at 12 months, vaginal mycologic status, and time to recurrence on the basis of Kaplan–Meier analysis.

RESULTS

Weekly treatment with fluconazole was effective in preventing symptomatic vulvovaginal candidiasis. The proportions of women who remained disease-free at 6, 9, and 12 months in the fluconazole group were 90.8 percent, 73.2 percent, and 42.9 percent, as compared with 35.9 percent, 27.8 percent, and 21.9 percent, respectively, in the placebo group ($P < 0.001$). The median time to clinical recurrence in the fluconazole group was 10.2 months, as compared with 4.0 months in the placebo group ($P < 0.001$). There was no evidence of fluconazole resistance in isolates of *Candida albicans* or of superinfection with *C. glabrata*. Fluconazole was discontinued in one patient because of headache.

CONCLUSIONS

Long-term weekly treatment with fluconazole can reduce the rate of recurrence of symptomatic vulvovaginal candidiasis. However, a long-term cure remains difficult to achieve.

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SINCE RECURRENT VULVOVAGINAL candidiasis is estimated to occur in 5 to 8 percent of women during their reproductive years, millions of women worldwide are affected by the condition.¹⁻³ Not considered a typical sexually transmitted infection, recurrent vulvovaginal candidiasis affects immunocompetent, healthy women in all strata of society.^{2,4} Although the condition has several causes, the majority of women with recurrent infection have no recognizable risk factors.^{5,6} Frequent recurrences of symptomatic vulvovaginitis result in considerable suffering and cost and have a markedly negative effect on sexual relations.⁷

Management approaches include treatment of each individual episode or use of prophylactic antimycotic measures. Previously, several prophylactic regimens were advocated that involved the use of intravaginal antimycotic agents either daily or weekly or oral ketoconazole daily for approximately six months.⁸⁻¹⁷ Although these measures were effective in reducing the rate of recurrence of vulvovaginal candidiasis, they were inconvenient and expensive, and oral ketoconazole was associated with an unacceptable risk of hepatotoxic effects.¹⁸ The availability of fluconazole as a safe, oral antifungal agent with both a favorable spectrum of antifungal activity and favorable pharmacokinetics offered an opportunity to study the effectiveness of the drug for suppressive maintenance prophylaxis in patients with recurrent vulvovaginal candidiasis.¹⁹ After oral administration of a single dose of 150 mg of fluconazole, concentrations of fluconazole above the minimal inhibitory concentration (MIC) that inhibits the growth of 90 percent of candida species isolates (MIC₉₀) are achieved for 72 to 96 hours in vaginal tissue and secretions — an efficacy that allows for weekly administration.²⁰ We performed a multicenter, prospective, randomized study to evaluate the clinical and mycologic efficacy of weekly treatment with fluconazole as compared with placebo in reducing the frequency of clinical episodes of recurrent vulvovaginal candidiasis. Investigators participating in the study are listed in the Appendix.

METHODS

PATIENTS AND PROTOCOL

The study, which took place from 1998 to 2002, was reviewed by the institutional review boards of all participating centers. Written informed consent was obtained from each patient. Eligible patients

were at least 18 years old; had active, acute candida vaginitis (total severity score, ≥ 3); had had a positive result on microscopical examination of vaginal secretions with 10 percent potassium hydroxide; and had had at least four documented episodes of candida vaginitis in the previous 12 months. The severity score was based on the presence of symptoms (e.g., pruritus, irritation, and burning) and vulvovaginal signs (e.g., erythema, edema, and excoriation, or fissures) as previously described.²¹ The severity of each sign or symptom was scored on a scale of 0 (absent or normal) to 3 (severe). The level of vulvovaginal discharge was not scored. Patients were excluded from the study if the microscopical findings could not be confirmed by culture. Other exclusion criteria were pregnancy, mixed infections, known seropositivity for the human immunodeficiency virus (HIV), and receipt of antifungal agents in the previous four weeks.

After enrollment in the open-label induction phase, all patients received three sequential 150-mg doses of fluconazole (Diflucan, Pfizer) orally at 72-hour intervals and were requested to return for evaluation 14 days after enrollment. Patients were prohibited from using topical vaginal or other systemic antifungal agents and topical vaginal steroids at any time during the study. They were also prohibited from using antibiotics during the induction phase. At the first follow-up visit, patients underwent a vaginal examination, which included obtaining vaginal swabs for fungal culture. All patients who were classified as being clinically cured (severity score, < 3) were eligible for random assignment to the placebo-controlled, double-blind, prophylactic phase of the study.²¹ Patients were randomly assigned on the basis of a 1:1 ratio to receive either a single oral, 150-mg dose of fluconazole or an oral placebo tablet weekly for six months. Thereafter, patients were followed without treatment for six months (i.e., the observation phase). Patients were to return for evaluation visits monthly during the maintenance phase and at months 9 and 12 during the observation phase.

At each follow-up visit, a detailed clinical history was obtained, a pelvic examination was performed, and a vaginal fungal culture was obtained. Patients were to discontinue the assigned study treatment if they had a recurrence of vulvovaginal candidiasis, except in cases in which the results of microscopical examination with 10 percent potassium hydroxide and a vaginal fungal culture were negative. In such cases, the patient remained in the

study until the next visit, at which time the study treatment was discontinued if the clinical outcome was still considered to be a recurrence or continued if the clinical outcome was a cure. The study treatment was also discontinued if there was an adverse reaction to the prescribed drug therapy.

At each visit, vaginal swabs were obtained for culture. On receipt of clinical isolates, swab specimens were placed on Sabouraud's dextrose agar and subsequently identified at the species level with the use of the API 20C system (BioMerieux). The clinical isolates were stored at -70°C and transferred as a group to Wayne State University Mycology Laboratory for determination of their in vitro susceptibilities. In vitro susceptibilities of fluconazole were determined by a broth microdilution test according to the National Committee for Clinical Laboratory Standards M27-A method.²² Liver-function tests were performed at study entry, on day 14, and after three and six months of maintenance therapy.

STATISTICAL ANALYSIS

Assuming that fluconazole therapy had a clinical success rate of 80 percent, it was estimated that 91 patients in each treatment group who could be evaluated would be required to detect a treatment difference of 20 percent, with 80 percent power and a two-sided alpha level of 0.05. The modified intention-to-treat population included all patients who had been randomly assigned to receive at least one dose of the study medication (administered in a double-blind manner) and who underwent at least one efficacy evaluation after receiving the first dose of the study medication. The population that could be evaluated for the efficacy analysis, defined at each visit, included all women who met the criteria for inclusion, had not missed two or more consecutive doses of the study drug before the visit, had not taken any prohibited medication, and underwent clinical and mycologic evaluations within the appropriate time frame. A safety analysis included all patients who had taken at least one dose of the study medication.

The primary end point was the proportion of women in clinical remission at the end of the maintenance period (i.e., after six months), with cure defined as a clinical severity score of less than 3, and recurrence defined as a clinical severity score of 3 or more plus vaginal cultures that were positive for yeast.²¹ A secondary end point was the mycologic outcome at six months (i.e., the status on the basis of fungal culture, regardless of the micro-

scopical findings with the use of 10 percent potassium hydroxide). Other variables that were assessed included the results of monthly clinical and mycologic examinations during the maintenance phase and at each of two visits during the six-month observation phase. Statistical comparisons of the study groups were made at the completion of maintenance therapy and at months 9 and 12 with the use of Fisher's exact test or the Cochran-Mantel-Haenszel chi-square test, as appropriate.

Time-to-recurrence data were analyzed by the Kaplan-Meier method and compared with the use of the log-rank test. A logistic-regression model was used to identify host or microbial factors that were associated with success or failure, including in vitro MIC data for baseline *Candida albicans* isolates. Data analyses were performed by two of the authors (Drs. Chu and Sobel); all authors had full access to the original data, and all participated in decisions about the manuscript. Initially, the investigation was organized as two separate trials performed with identical protocols at two groups of institutions. About halfway through the enrollment period (before the data were analyzed), the sponsor decided to combine the parallel trials into a single trial.

RESULTS

STUDY POPULATION

A total of 494 patients with acute symptomatic vulvovaginal candidiasis who had a history of recurrent vulvovaginal candidiasis were enrolled and prescribed three doses of fluconazole to achieve clinical remission. The average age of participants was 33.8 years (range, 18 to 65). On the basis of investigators' assessment, 66.5 percent of the patients were white, 25.6 percent black, and 7.9 percent either Hispanic or of unknown ethnic background. Sixty-seven patients (13.6 percent) were withdrawn from the study because after enrollment their baseline vaginal fungal cultures were negative and thus the diagnosis of vulvovaginal candidiasis could not be confirmed. The results of microbiologic analysis of the baseline vaginal isolates from the remaining 427 patients are shown in Table 1. Of those isolates, 401 (93.9 percent) were identified as *C. albicans* and 13 (3.0 percent) as *C. glabrata*. Five patients dropped out of the study; of the remaining 422 patients who met the baseline criteria for enrollment, 387 (91.7 percent) had a clinical response with resolution of signs and symptoms

and at 14 days were randomly assigned to receive either fluconazole or placebo. Four patients dropped out during the open-label induction phase before randomization because of reported adverse effects (none serious), three patients were lost to follow-up, and seven were withdrawn because of protocol violations. Only nine patients did not have a full clinical remission.

After randomization, 373 patients (96.4 percent of the patients who had a clinical response) were included in the modified intention-to-treat analysis, and 343 patients (88.6 percent) were included in the analysis of efficacy. Patients who were randomly assigned to receive fluconazole and those randomly assigned to receive placebo were similar with regard to age, race or ethnic background, and weight, as well as such predisposing factors as contraceptive method and coexisting illness (e.g., 2 percent of the patients who received fluconazole and 5 percent of the patients who received placebo had diabetes). The microbiologic status of the two study groups is shown in Table 1. Although more patients who received placebo had positive cultures (23 vs. 13 of those who received fluconazole), the difference was not statistically significant. Similarly, more patients who received placebo were infected with species of candida other than *C. albicans* (14 vs. 6). The results were similar in a modified intention-to-treat analysis (data not shown).

During the six-month blinded maintenance phase, patients who received placebo had a significantly higher rate of clinical recurrence than did those receiving fluconazole (Table 2). At six months, 128 of 141 patients receiving fluconazole (90.8 percent) remained well without a clinical recurrence, as compared with 51 of 142 patients receiving placebo (35.9 percent). Symptomatic vulvovaginal candidiasis occurred in 13 of 141 patients receiving fluconazole and 91 of 142 patients receiving placebo (relative risk in the placebo group, 2.53; 95 percent confidence interval, 2.02 to 3.17; $P < 0.001$).

During the six-month observation period after the cessation of therapy (i.e., in months 7 through 12), significantly more episodes of clinical vulvovaginal candidiasis were observed in patients who had previously been protected by fluconazole than in those who had received placebo. However, at the completion of the 12-month study, 54 of 126 patients in the fluconazole group were clinically cured (42.9 percent), as compared with 30 of 137 patients who had received placebo (21.9 percent)

Table 1. Identification of Vaginal Fungal Isolates.

Organism	At Baseline (N=427)	At Randomization (N=343)	
		Fluconazole (N=170)	Placebo (N=173)
<i>number of patients (percent)</i>			
<i>Candida albicans</i>	401 (93.9)	7 (4.1)	9 (5.2)
<i>C. glabrata</i>	13 (3.0)	3 (1.8)	9 (5.2)
<i>C. parapsilosis</i>	3 (0.7)	0	0
<i>C. tropicalis</i>	3 (0.7)	1 (0.6)	0
<i>C. lusitanae</i>	2 (0.5)	1 (0.6)	0
<i>C. guilliermondii</i>	1 (0.2)	1 (0.6)	0
<i>C. krusei</i>	1 (0.2)	0	2 (1.2)
Other candida species	1 (0.2)	0	0
Organisms other than candida	2 (0.5)	0	3 (1.7)
No growth	0	156 (91.8)	150 (86.7)

($P < 0.001$). The modified intention-to-treat analysis had similar results. The difference between the two treatment groups was also demonstrated in a Kaplan–Meier analysis (Fig. 1A). The median time to a clinical recurrence in the fluconazole group was 10.2 months after randomization, as compared with 4.0 months in the placebo group ($P < 0.001$).

Asymptomatic patients whose cultures were positive were not withdrawn from the study. At the end of the six-month maintenance phase, 25 patients receiving fluconazole had had at least one positive vaginal culture, as compared with 94 patients in the placebo group. Mycologic eradication or suppression was documented in 82.1 percent of patients receiving fluconazole and in 28.2 percent of patients receiving placebo ($P < 0.001$). After the cessation of prophylaxis, the rate of a positive vaginal culture was significantly higher in the group that had previously been protected by fluconazole. At the end of one year of study, 36 patients in the fluconazole group had negative cultures, as compared with 21 patients in the placebo group ($P = 0.02$). The median time to mycologic relapse in the fluconazole group was 8.4 months after randomization, as compared with 1.9 months in the placebo group ($P < 0.001$) (Fig. 1B).

Among patients with any positive vaginal cultures during the 12-month study period, there were no significant increases over time in the appearance of isolates of candida species other than *C. albicans*

Table 2. Clinical Outcome after Randomization (Efficacy Analysis).*

Month	Fluconazole (N=170)		Placebo (N=173)		P Value†
	Cure	Recurrence	Cure	Recurrence	
	number/total number (percent)				
Maintenance phase					
1	160/166	6/166	131/154	23/154	
2	149/157	8/157	105/156	51/156	
3	139/148	9/148	79/143	64/143	
4	134/144	10/144	66/145	79/145	
5	130/144	14/144	61/147	86/147	
6	128/141 (90.8)	13/141 (9.2)	51/142 (35.9)	91/142 (64.1)	<0.001
Observation phase					
9	71/97 (73.2)	26/97 (26.8)	37/133 (27.8)	96/133 (72.2)	<0.001
12	54/126 (42.9)	72/126 (57.1)	30/137 (21.9)	107/137 (78.1)	<0.001

* Data were analyzed with the last observation carried forward in the case of patients who did not complete both phases of the study.

† P values are for comparisons between the treatment groups at 6, 9, and 12 months and are based on the Cochran–Mantel–Haenszel test with stratification according to the study site.

in either the fluconazole or the placebo group. Three patients who were randomly assigned to receive fluconazole initially had positive cultures for *C. glabrata*, and during the study, four additional patients became positive for *C. glabrata*. A similarly small increase in vaginal isolates identified as *C. glabrata* occurred in the placebo group. No fluconazole-resistant strains of *C. albicans* (MIC ≥ 64 μg per milliliter) were identified in either group, and no changes in MIC₉₀ values for fluconazole were detected (data not shown).

A stepwise logistic-regression analysis was performed to assess the association of the clinical response with the results of vaginal fungal culture at baseline and with the presence or absence of coexisting illnesses and other factors (including race or ethnic background, the presence or absence of a history of antibiotic and oral-contraceptive use before entry in the study, and the presence or absence of diabetes). None of these prognostic variables were significantly associated with a clinical response, either at the end of maintenance therapy or at the end of the study. The analysis of the time to clinical recurrence showed that among the patients who were infected with *C. albicans* at baseline, 89.8 percent of those who were treated with fluconazole remained clinically cured up to six months after the randomization, as compared with 41.3 percent of the placebo-treated patients.

Forty-six percent of the patients who received fluconazole remained clinically cured up to 12 months after randomization, as compared with 26.6 percent who had received placebo (P<0.001). A positive vaginal culture for any candida species at any time during the maintenance phase predicted a clinical relapse after the cessation of fluconazole therapy.

ADVERSE EVENTS

During the maintenance phase, five patients in the fluconazole group (2.9 percent) and two in the placebo group (1.2 percent) reported at least one adverse event that led to discontinuation of the study drug. Unintended pregnancy (in three patients in the fluconazole group and one in the placebo group) was the most frequently reported reason for withdrawal. One patient in the placebo group withdrew after a car accident. In only one patient was an adverse event (headache) leading to discontinuation thought to be attributable to fluconazole. A patient in whom vulvar vestibulitis was diagnosed also discontinued fluconazole therapy. Liver-function tests were routinely performed at the completion of the induction phase and after three and six months. A mild elevation in aminotransferase levels was detected in only one patient during the maintenance phase (<1 percent); the patient did not discontinue therapy. Adverse events not associated with discontinuation were uncommon (Table 3).

DISCUSSION

In our randomized, prospective, placebo-controlled study, weekly fluconazole administered during a six-month period reduced the frequency of recurrent vulvovaginal candidiasis by more than 90 percent. The results were not unexpected, since previous studies with other antimycotic agents had shown a similar reduction in episodes of candida vaginitis both in patients with HIV infection and in those without HIV infection.^{8-17,23} Previous studies, however, used either intravaginal antimycotic agents, which were inconvenient to administer, or other oral antifungal regimens, which had toxic effects.^{8-17,23} Fluconazole proved to be safe and convenient and did not result in the emergence of less susceptible strains of candida, especially species other than *C. albicans*.

Our study also indicates that effective suppressive prophylaxis, even over a six-month period, does not guarantee a cure during the subsequent six months, after suppressive therapy has been discontinued. A full explanation of this complex phenomenon is still not available, but the data suggest that suppressive prophylaxis with an azole fails to achieve long-term vaginal eradication of candida organisms. Even though patients who are taking fluconazole may have negative cultures for a period of several months, they may still have candida in numbers that are too low for detection by conventional culture methods. Two populations of patients receiving fluconazole prophylaxis can be identified: those in whom yeast eradication occurs and those in whom organisms persist in low numbers, only to increase when prophylaxis is stopped. It is simplistic to attribute this phenomenon only to the properties of the azole agent, since undefined characteristics of the host and the microorganisms may contribute to persistence in spite of inhibitory drug concentrations. In addition, some patients who become culture-positive after the cessation of the fluconazole prophylaxis remain asymptotically colonized, whereas others rapidly become symptomatic. Previous studies have concluded that the development of symptoms in this context reflects a defective host response; however, the role of the pathogen has not been studied.^{4,6}

In spite of the high rate of relapse of symptomatic vaginitis shortly after the cessation of suppressive therapy with fluconazole in our study, the number of patients who remained free of infection at one year was significantly higher in the fluconazole group than in the placebo group. The decision about how to treat patients whose infection recurs after the discontinuation of fluconazole therapy remains controversial. Clinical experience has indicated that a majority of patients elect to repeat the six-month maintenance regimen with fluconazole; however, the optimal duration of secondary suppressive prophylaxis remains unknown, even

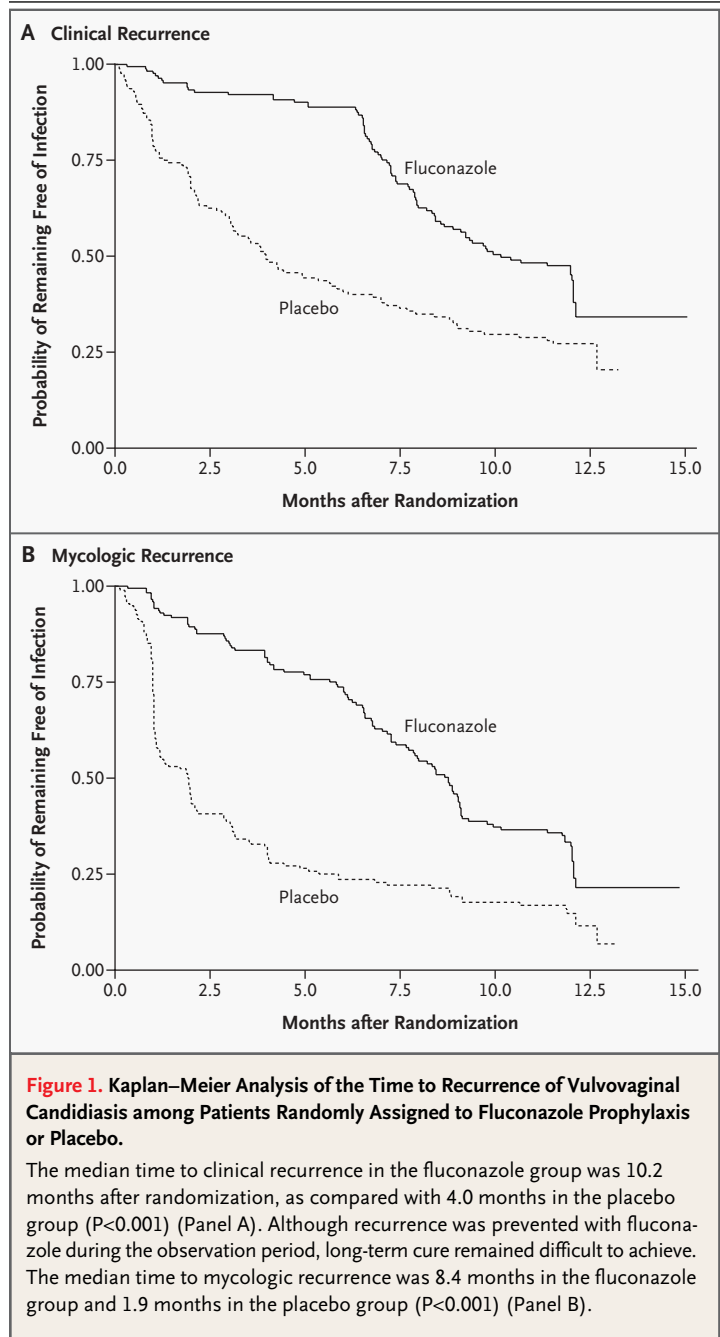


Table 3. Adverse Events.*

Adverse Event	Fluconazole (N=189)	Placebo (N=190)
	no. of patients	
Abdominal pain	11	11
Nausea	9	3
Vomiting	2	3
Diarrhea	7	8
Flatulence	3	1
Headache	25	23
Migraine	4	4
Central nervous system disorder	15	12
Musculoskeletal disorder	15	14
Rash	7	5
Alopecia	0	1
Allergic reaction	7	2
Menstrual disorder	3	0

* The patients included here are those who took at least one dose of the study drug, including treatment in the open-label phase of the study.

though patients receiving the repeated regimen have had a level of protection that is similar to that in our study group. There have been anecdotal reports of women who became asymptomatic but de-

pendent on fluconazole therapy and were monitored for several years, with no adverse effects.

The safety of weekly fluconazole and its pharmacokinetic characteristics are major factors contributing to its overall clinical success. A concern about long-term therapy has been the possibility of the emergence of azole resistance in isolates of *C. albicans* or more frequent isolation of species other than *C. albicans*. Although azole-resistant recurrent oropharyngeal and esophageal candidiasis has been a problem in patients with HIV infection and has been linked to long-term exposure to azoles, such findings did not emerge in our study. Nevertheless, given that a subpopulation of women with recurrent vulvovaginal candidiasis will probably receive fluconazole for a prolonged period of time, additional efficacy and safety studies are needed.

In conclusion, recurrent candida vaginitis, a common and poorly managed condition, can be successfully and safely controlled by weekly suppressive therapy with fluconazole. A long-term cure, however, remains elusive.

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APPENDIX

In addition to the authors, the following investigators participated in the study: P. Nyirjesy, Philadelphia; B.D. Reed, Ann Arbor, Mich.; W.E. Stamm, Seattle; M.W. Heine, Tucson, Ariz.; K. Moss, Seattle; J. Rosen, Coral Gables, Fla.; J. Schwebke, Tuscaloosa, Ala.; P. Siami, Evansville, Ill.; L. Smolenski, Memphis, Tenn.; and R. Jackson, Southfield, Mich.

REFERENCES

1. Foxman B, Marsh JV, Gillespie B, Sobel JD. Frequency and response to vaginal symptoms among white and African American women: results of a random digit dialing survey. *J Womens Health* 1998;7:1167-74.
2. Sobel JD. Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 1985;152:924-35.
3. Spinillo A, Pizzoli G, Colonna L, Nicola S, De Seta F, Guaschino S. Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. *Obstet Gynecol* 1993;81:721-7.
4. Fidel PL Jr, Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. *Clin Microbiol Rev* 1996;9:335-48.
5. Spinillo A, Carratta L, Pizzoli G, et al. Recurrent vaginal candidiasis: results of a cohort study of sexual transmission and intestinal reservoir. *J Reprod Med* 1992;37:343-7.
6. Sobel JD. Pathogenesis of recurrent vulvovaginal candidiasis. *Curr Infect Dis Rep* 2002;4:514-9.
7. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Candida vaginitis: self-reported incidence and associated costs. *Sex Transm Dis* 2000;27:230-5.
8. Sobel JD. Recurrent vulvovaginal candidiasis: a prospective study of the efficacy of maintenance ketoconazole therapy. *N Engl J Med* 1986;4:1455-8.
9. Roth AC, Milsom I, Forssman L, Wahlen P. Intermittent prophylactic treatment of recurrent vaginal candidiasis by postmenstrual application of a 500 mg clotrimazole vaginal tablet. *Genitourin Med* 1990;66:357-60.
10. Merkus JM, Van Heusden AM. Chronic vulvovaginal candidosis: the role of oral treatment. *Br J Clin Pract Suppl* 1990;71:81-4.
11. Sobel JD. Management of recurrent vulvovaginal candidiasis with intermittent ketoconazole prophylaxis. *Obstet Gynecol* 1985;65:435-40.
12. Fong IW. The value of prophylactic (monthly) clotrimazole versus empiric self-treatment in recurrent vaginal candidiasis. *Genitourin Med* 1994;70:124-6.
13. Creatas GC, Charalambidis VM, Zagotzidou EH, Anthopoulos HN, Michailidis DC, Aravantinos DI. Chronic or recurrent vaginal candidosis: short-term treatment and prophylaxis with itraconazole. *Clin Ther* 1993;15:662-71.
14. Davidson F, Mould RF. Recurrent genital candidosis in women and the effect of intermittent prophylactic treatment. *Br J Vener Dis* 1978;54:176-83.
15. Balsdon MJ, Tobin JM. Recurrent vaginal candidosis: prospective study of effectiveness of maintenance miconazole treatment. *Genitourin Med* 1988;64:124-7.

16. Reef SE, Levine WC, McNeil MM, et al. Treatment options for vulvovaginal candidiasis, 1993. *Clin Infect Dis* 1995;20:Suppl 1: S80-S90.
17. Sobel JD, Schmitt C, Meriwether C. Clotrimazole treatment of recurrent and chronic candida vulvovaginitis. *Obstet Gynecol* 1989; 73:330-4.
18. Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy: analysis of 33 cases. *Gastroenterology* 1984;86:503-13.
19. Sobel JD. Treatment of recurrent vulvovaginal candidiasis with maintenance fluconazole. *Int J Obstet Gynecol* 1992;37:17-34.
20. Houang ET, Chappatte O, Byrne D, Macrae PV, Thorpe JE. Fluconazole levels in plasma and vaginal secretions of patients after a 150-milligram single oral dose and rate of eradication of infection in vaginal candidiasis. *Antimicrob Agents Chemother* 1990;34:909-10.
21. Sobel JD, Kapernick PS, Zervos M, et al. Treatment of complicated *Candida* vaginitis: comparison of single and sequential doses of fluconazole. *Am J Obstet Gynecol* 2001;185:363-9.
22. National Committee for Clinical Laboratory Standards. Development of in vitro susceptibility testing criteria and quality control parameter: approved guidelines M27-A. Villanova, Pa.: NCCLS, 1994.
23. Schuman P, Capps L, Peng G, et al. Weekly fluconazole for the prevention of mucosal candidiasis in patients with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997;126:689-96.

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