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Fluconazole Susceptibility of Vaginal Isolates Obtained from Women with Complicated *Candida* Vaginitis: Clinical Implications

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Despite considerable evidence of azole resistance in oral candidiasis due to *Candida* species, little is known about the azole susceptibilities of the genital tract isolates responsible for vaginitis. The fluconazole susceptibilities of vaginal isolates obtained during a multicenter study of 556 women with complicated *Candida* vaginitis were determined by evaluating two fluconazole treatment regimens. Of 393 baseline isolates of *Candida albicans*, 377 (96%) were highly susceptible to fluconazole (MICs, <8 μg/ml) and 14 (3.6%) were resistant (MICs, ≥64 μg/ml). Following fluconazole therapy, one case of in vitro resistance developed during 6 weeks of monitoring. In accordance with the NCCLS definition, in vitro fluconazole resistance correlated poorly with the clinical response, although a trend of a higher mycological failure rate was found (41 versus 19.6% on day 14). By using an alternative breakpoint of 1 μg/ml, based upon the concentrations of fluconazole achievable in vaginal tissue, no significant differences in the clinical and mycological responses were observed when isolates ($n = 250$) for which MICs were ≤1 μg/ml were compared with isolates ($n = 30$) for which MICs were >1 μg/ml, although a trend toward an improved clinical outcome was noted on day 14 (odds ratio, >2.7; 95% confidence interval, 0.91, 8.30). Although clinical failure was uncommon, symptomatic recurrence or mycological relapse almost invariably occurred with highly sensitive strains (MICs, <1.0 μg/ml). In vitro fluconazole resistance developed in 2 of 18 initially susceptible *C. glabrata* isolates following fluconazole exposure. Susceptibility testing for women with complicated *Candida* vaginitis appears to be unjustified.

Candida vaginitis remains a common problem in immunocompetent, healthy women and is predominantly caused by strains of *Candida albicans* (>90%) (14, 17, 19). Only a minority of cases (<10%) are caused by non-*C. albicans Candida* species, usually *C. glabrata*, and despite considerable debate, there is little evidence of a significant increase in infection rates due to the non-*C. albicans Candida* species (14, 17, 19). Given the reports of refractory oral and esophageal candidiasis caused by fluconazole-resistant *C. albicans* strains and, less commonly, non-*C. albicans Candida* species, it is important to monitor the fluconazole susceptibilities of vaginal isolates of the various *Candida* species (1, 3, 5, 8, 11). Recently, a nationwide, multicenter prospective study was performed in which the clinical and mycological efficacies of two dosage regimens of fluconazole in women with complicated *Candida* vaginitis were compared (19). Analysis of the in vitro fluconazole susceptibilities of these vaginal isolates forms the basis of this report. The susceptibilities of a large number of pathogenic isolates of *C. albicans* and non-*C. albicans Candida* species were determined. These determinations allowed (i) detection of preexisting and newly acquired fluconazole resistance and (ii) establishment of a correlation between in vitro susceptibility and clinical response to the two dosage regimens of fluconazole, in which a breakpoint of 1 μg/ml based upon the peak concentrations of fluconazole achieved in vaginal secretions and tissue was used (2).

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MATERIALS AND METHODS

Details of the multicenter prospective study of fluconazole in the treatment of complicated *Candida* vaginitis have been published elsewhere (19). In brief, 556 immunocompetent human immunodeficiency virus (HIV)-negative women with either severe or recurrent *Candida* vaginitis were randomized to receive a single 150-mg dose of fluconazole or two 150-mg doses of fluconazole 3 days apart. Three hundred nine patients evaluable for efficacy were seen at two follow-up visits on days 14 and 35. At each of the three study visits, patients were evaluated clinically and vaginal swabs were obtained for culture. Upon receipt of clinical isolates, swab specimens were plated on Sabouraud glucose agar and subsequently identified to the species level by using the AP1 20C system (BioMerieux). The clinical isolates so obtained were stored at −70°C and transferred en bloc to the Wayne State University Mycology Laboratory for determination of their in vitro susceptibilities. In vitro fluconazole susceptibilities were determined by a broth microdilution test according to the NCCLS M27-A standard (6).

Statistical methods. The clinical and mycological responses at days 14 and 35 between patients for whose isolates the baseline MIC was ≤1 μg/ml and patients for whose isolates the baseline MIC was >1 μg/ml dose were compared statistically by the logistic regression method. A logistic regression model controlling for the severity of vaginitis and the treatment was used to assess the association of pretreatment MICs with the clinical and mycological outcomes at days 14 and 35.

All tests were two tailed, and P values of <0.05 were considered statistically significant.

TABLE 1. Comparative susceptibilities of *C. albicans* vaginal isolates at baseline and follow-up visits

Visit	No. of isolates	MIC (μg/ml)		No. (%) of isolates			
		50%	90%	Resistant (MIC, ≥64 μg/ml)	DD-S (MIC, 16–32 μg/ml)	Susceptible (MIC, ≤8 μg/ml)	Vaginal susceptible (MIC, ≤1 μg/ml)[a]
Baseline	393	0.25	1.0	14 (3.6)	3	377 (95.9)	365 (92.8)
Day 14	73	0.25	1.0	4 (5.5)	1	68 (93.1)	62 (84.9)
Day 35	101	0.25	0.5	3 (3.0)	0	98 (97.0)	96 (95)

[a] Vaginal susceptible refers to the proposed fluconazole breakpoint based upon the levels of fluconazole achievable in vaginal tissue in vivo (2).

RESULTS

Of the original 556 women enrolled in the study, baseline clinical isolates were available from 435 women (78%) and follow-up isolates were available from >95% of patients with at least two study visits. Follow-up vaginal isolates were evaluated only if a corresponding baseline isolate was available.

MICs for *C. albicans*. (i) Baseline isolates. A total of 393 baseline isolates of *C. albicans* were tested (Table 1). By using the susceptibility and resistance definitions widely accepted for both systemic and mucosal infections (9), 377 (96%) of the *C. albicans* isolates were susceptible to fluconazole (MICs, ≤8 μg/ml), 2 (0.4%) were considered dose-dependent susceptible (DD-S; MICs, 16 to 32 μg/ml), and 14 (3.6%) were resistant (MICs, ≥64 μg/ml). The MIC at which 50% of isolates are inhibited (MIC_{50}) and the MIC_{90} for all the baseline *C. albicans* isolates were 0.25 and 1.0 μg/ml, respectively. Given the pharmacokinetics of fluconazole, which achieves concentrations in vaginal tissues and secretions considerably lower than those achieved in serum (2), we also selected ≤1 μg/ml and not ≤8 μg/ml as another potentially clinically relevant susceptibility breakpoint. Accordingly, MICs were ≤1 μg/ml for 365 of 393 isolates (92.8%) and in vitro MICs were >1 μg/ml for 28 isolates (7.2%); the latter concentration exceeds the predicted peak fluconazole concentration in the vagina.

(ii) Fluconazole susceptibility at the day 14 follow-up. As expected, there were fewer vaginal isolates after completion of fluconazole therapy. Seventy-three isolates were obtained from patients who had clinical failures or mycological failures only. Analysis of the 73 vaginal *C. albicans* isolates revealed only 4 (5.5%) resistant isolates (MICs, ≥64 μg/ml) and 1 DD-S isolate. The remaining 68 *C. albicans* isolates were susceptible (MICs, ≤8 μg/ml). The MIC_{50} and MIC_{90} for the 73 isolates of *C. albicans* obtained at the day 14 follow-up were unchanged at 0.25 and 1.0 μg/ml, respectively.

By using the alternative susceptibility breakpoint of ≤1 μg/ml, 62 isolates (84.9%) were determined to be fluconazole susceptible. Thus, the vast majority of early fluconazole clinical and mycological failures occurred in patients infected with susceptible strains of *C. albicans* (93.1%); in fact, most failures (84.9%) occurred with extremely susceptible strains for which the fluconazole MICs were ≤1 μg/ml.

(iii) Fluconazole susceptibility at the day 35 follow-up. The vaginal isolates obtained on the first follow-up (day 14) visit reflected the isolates from all patients with clinical and mycological failures. Patients who failed clinically at day 14 were dropped from the study, and hence, no cultures were later performed for these patients. However, isolates of *C. albicans* were obtained from 101 patients on day 35. Some of the patients had become symptomatic once more, but the majority were asymptomatic. Among the 101 isolates, 3 were fluconazole resistant (MICs, ≥64 μg/ml). No DD-S strains were identified. Among the remaining 98 isolates, fluconazole MICs were ≤1 μg/ml for 96 of them, indicating once more that clinical and mycological relapses occurred in patients infected with strains highly susceptible to fluconazole. The MIC_{50} and MIC_{90} for the 101 *C. albicans* isolates at the day 35 visit were 0.25 and 0.5 μg/ml, respectively.

Correlation of baseline fluconazole susceptibility of *C. albicans* with clinical and mycological outcomes. By using the baseline in vitro fluconazole susceptibility data for 280 *C. albicans* isolates obtained from patients evaluable for efficacy, pretreatment MICs were correlated with the clinical and mycological outcomes following fluconazole therapy (Table 2). The baseline MIC was >1 μg/ml for only 30 *C. albicans* isolates, and these isolates were compared with 250 isolates of *C. albicans* for which the MIC was ≤1 μg/ml. Rates of clinical success at day 14 were 93.2% (233 of 250 isolates) and 83.3% (25 of 30 isolates) for the groups of patients infected with isolates for which the MICs were low and high, respectively (no significant difference). At day 35, clinical success rates in the groups of patients infected with isolates for which the MICs were low and high were 76.8% (192 of 250 isolates) and 73.3% (22 of 30 isolates), respectively (no significant difference). By using the logistic regression model and controlling for the severity of vaginitis and the treatment regimen (one versus two doses of fluconazole), the odds of having clinical success in patients for whose isolates the baseline MICs were ≤1 μg/ml were >2.7 times that in patients for whose isolates the baseline MICs were >1 μg/ml at day 14 (95% confidence interval [CI], 0.91, 8.30). By day 35, the odds of having clinical success in patients for whose isolates the baseline MICs were ≤1 μg/ml were 1.2 times those in patients for whose isolates the baseline MICs were >1 μg/ml (95% CI, 0.49, 2.78). These odds ratios were not statistically significant.

TABLE 2. Correlation of in-vitro susceptibility and treatment outcome

Baseline MIC (μg/ml)	No. of patients with the indicated result/total no. of patients (%)			
	Day 14		Day 35	
	Success	Culture negative	Success	Culture negative
≤1	233/250 (93)	201/250 (80)	192/250 (77)	153/250 (61)
>1	25/30 (83)	20/30 (67)	22/30 (74)	15/30 (50)
≥64	12/12 (100)	7/12 (58)	9/11 (82)	6/11 (55)

At day 14, 80.4% (201 of 250 patients) and 66.7% (20 of 30 patients) of the patients for whose isolates the fluconazole MICs were low and high were vaginal culture negative, respectively. At day 35, eradication rates were 61.2% (153 of 250 patients) and 50.0% (15 of 30 patients), respectively. In the logistic regression analysis that controlled for the severity of vaginitis and the treatment regimen, the odds of having mycological eradication in patients for whose isolates baseline MICs were ≤1 μg/ml were twice those in patients for whose isolates the baseline MICs were >1 μg/ml at day 14 (95% CI, 0.87, 4.58) and 1.6 times at day 35 (95% C1, 0.72, 3.34), but statistical significance was not achieved.

Finally, despite the small numbers of patients, we compared the clinical and mycological responses for patients infected with susceptible *C. albicans* isolates (MICs, ≤1 μg/ml; $n = 250$) with the responses observed in the 14 patients for whose isolates the MICs were ≥64 μg/ml. Among the 12 patients available for follow-up, all 12 patients infected with resistant *C. albicans* strains improved or responded clinically by the time of the first follow-up visit and only 2 patients failed clinically by day 35. These patients fared less well mycologically, with persistent culture positivity found for 5 of 12 (41%) patients at day 14, which was double the rate for patients infected with susceptible strains (19.6%) but only slightly higher than the rate at day 35: 5 of 11 (45%) versus 97 of 250 (38.8%), respectively (Table 2).

Among patients infected with susceptible *C. albicans* isolates at the baseline, longitudinal comparison of in vitro susceptibilities revealed the development of fluconazole resistance in an isolate from only one patient. The baseline fluconazole MIC for the isolate from this patient was 0.125 μg/ml, and the MIC for the isolate recovered at the first follow-up visit was >64 μg/ml. Nevertheless, clinical improvement continued, and at the final visit, the patient was clinically cured and culture negative.

MICs for *C. glabrata*. A total of 44 isolates of *C. glabrata* were isolated at any time during the study, and 2 (4.5%) were resistant to fluconazole (≥ 64 μg/ml). No isolates for which MICs were 16 to 32 μg/ml were encountered. Thus, for 42 of 44 (95%) isolates MICs were 8 μg/ml or less and, hence, could be considered fluconazole susceptible. However, by using the susceptibility breakpoint of ≤1 μg/ml, only four isolates (9.1%) were susceptible to fluconazole, with the fluconazole MIC being 2 to 8 μg/ml for 86% of the *C. glabrata* isolates, concentrations not achievable in the vagina. The MIC_{50} and MIC_{90} for all *C. glabrata* isolates were 4 and 8 μg/ml, respectively.

Due to the paucity of *C. glabrata* isolates ($n = 44$), detailed comparison of longitudinally obtained isolates was not possible. The mean and median MICs remained unchanged. No fluconazole-resistant (MIC, ≥64 μg/ml) *C. glabrata* isolates were detected at the baseline. Two isolates of *C. glabrata* resistant to fluconazole (MICs, ≥64 μg/ml) emerged following exposure to fluconazole.

DISCUSSION

Although annual monitoring of the azole susceptibilities of blood isolates of *Candida* species is now widely performed, similar information on the susceptibilities of isolates of *Candida* responsible for symptomatic vaginitis is not available (7), Occasionally, publications have reported on the azole susceptibilities of vaginal isolates at individual medical centers (4), and case reports of fluconazole resistance among isolates from patients with refractory vaginitis are provided only rarely (15).

Recently, in vitro azole susceptibility data describing vaginal isolates obtained from a large cohort of HIV-positive women and risk behavior-matched HIV-negative women were published (18). However, the vaginal isolates were obtained from asymptomatic women colonized with *Candida* and not symptomatic women with *Candida* vaginitis. In that study of 647 vaginal isolates of *C. albicans* obtained over 2 years, only 2 isolates (<1%) were resistant to fluconazole and a similar number showed dose-dependent susceptibility to fluconazole (18) Similarly, a large multicenter prospective study of *Candida* vaginitis in women with AIDS failed to identify fluconazole-resistant vaginitis (13). Accordingly, the finding in the present study of 14 baseline isolates of *C. albicans* with fluconazole resistance (3.6%) should be viewed with concern and emphasizes the need for continued surveillance.

The short follow-up and duration of therapy in the present study precluded the drawing of any major conclusion regarding the acquisition of fluconazole resistance. Nevertheless, no change in the MIC_{50}s or the MIC_{90}s for the *C. albicans* vaginal isolates occurred when baseline and follow-up isolates were compared. *C. glabrata* strains from two patients developed resistance to fluconazole. A progressive reduction in fluconazole susceptibility in *C. glabrata* vaginal isolates following exposure to fluconazole has been reported previously (18). In the same longitudinal study, no corresponding increase in fluconazole MICs was seen for *C. albicans* isolates (18).

Clinically relevant susceptibility breakpoints have been suggested by Rex et al. (9) on the basis of a correlation of the clinical responses of patients infected with both blood and oral isolates of *C. albicans* and in vitro susceptibility data. We also analyzed the clinical responses of patients and the mycological eradication rates using a breakpoint which took into consideration the vaginal pharmacokinetic characteristics of fluconazole, although that breakpoint has not been validated as being clinically relevant by studies with humans or animals. Houang et al. (2) measured the fluconazole levels in vaginal secretions of patients following administration of a single 150-mg dose of fluconazole. The peak concentrations of fluconazole in vaginal secretions rarely exceeded 2.0 μg/ml; hence, we correlated the response to fluconazole therapy using a fluconazole MIC of ≤1 μg/ml as the susceptibility breakpoint. By use of these more stringent criteria, 93% of the baseline *C. albicans* isolates were still highly susceptible and would theoretically be inhibited by the predicted fluconazole concentrations. In fact, >90% of these patients responded extremely well clinically. Surprisingly, patients infected with microorganisms for which the MICs were higher (>1 μg/ml), including those infected with strains for which the MICs were ≥64 μg/ml, appeared to respond clinically, as did those patients infected with highly susceptible strains. However, a trend toward reduced mycological eradication rates was observed in patients infected with less susceptible strains. Hence, patients infected with *C. albicans* strains demonstrating reduced in vitro susceptibility to fluconazole could be expected to improve clinically and respond to fluconazole treatment but would be more likely to remain colonized and would be colonized with a population of organisms suffi-

ciently large to be detected by routine culture of vaginal specimens. These individuals would therefore remain at risk for a subsequent recurrence of symptomatic disease when conditions associated with relapse develop. Nevertheless, the reason why patients infected with resistant and relatively resistant *C. albicans* strains did so well clinically is unclear. Perhaps a reduction in the vaginal population below a critical threshold is all that is needed to facilitate clinical improvement.

The most striking observation is that the overwhelming majority of women who failed clinically at both follow-up visits did so as a result of infection with *C. albicans* strains highly susceptible to fluconazole. Similarly, most persistently culture-positive women were infected with fluconazole-susceptible strains, emphasizing the limitation of azoles as fungistatic agents in the management of *Candida* vaginitis. Both systemic and topical azole agents appear to be similarly limited in their abilities to eradicate *Candida* from the vagina, despite impressive clinical success rates (17). The roles of the vaginal environment and local defense mechanisms in contributing to drug-associated vaginal yeast eradication or persistence have not been adequately defined and may be underestimated. Poorly controlled diabetic patients represent an example of individuals with a vaginal microenvironment that facilitates *Candida* persistence after azole therapy. Similarly, *C. glabrata* and other but not all non-*C. albicans Candida* species for which MICs are higher are more likely to persist (16, 19).

Several studies have demonstrated the clinical usefulness of in vitro susceptibility testing of yeasts by use of the NCCLS reference method (6, 10, 12, 20). In principle, standards applied to oropharyngeal candidiasis are such that one should anticipate a favorable response in 60 to 100% (usually 90%) of patients treated with antifungals to which the organism is susceptible in vitro, whereas one would anticipate a favorable response in 0 to 60% of patients infected with organisms exhibiting in vitro resistance (the 90/60 rule). Although the present study was biased by the inclusion of only patients with complicated *Candida* vaginitis and not those with mild and uncomplicated diseases, the results can still be used to validate the usefulness of in vitro susceptibility in predicting the outcome of therapy. The logistic regressive model that adjusted for several patient variables revealed that women infected with *C. albicans* isolates highly susceptible to fluconazole (MICs, ≤ 1 μg/ml) were 2.7 times more likely to respond clinically than women infected with isolates for which the MICs were above the concentration of fluconazole achievable in vaginal tissue. Moreover, the advantage of low MICs was even more apparent with regard to the mycological eradication of vaginal *C. albicans* strains. Finally, this principle is supported by the poor clinical and mycological outcomes seen for patients infected with *C. glabrata*, for which, predictably, fluconazole MICs are above the concentrations of fluconazole achievable in vaginal tissue (16, 19).

On the basis of the results of this study, we do not recommend in vitro susceptibility testing for all patients with severe or recurrent *Candida* vaginitis. It is reasonable to perform susceptibility tests for women who have poor clinical and mycological responses in individual episodes or for those receiving maintenance suppressive azole regimens who have breakthrough infections. Studies to validate these recommendations are in progress.

In summary, complicated *Candida* vaginitis caused by fluconazole-resistant *C. albicans* remains uncommon. Why women infected with highly susceptible strains of *C. albicans* occasionally fail to respond clinically and why many more improve clinically but remain colonized with *C. albicans* following fluconazole therapy remain unresolved but may be due to the fungistatic nature of azole agents. Organisms for which MICs are higher showed a trend toward vaginal persistence. Routine susceptibility testing of vaginal *C. albicans* isolates from women with complicated (severe or recurrent) vaginitis is not justified.

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