Treatment of vaginitis caused by *Candida glabrata*: Use of topical boric acid and flucytosine

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**OBJECTIVE:** The purpose of this study was to review the treatment outcome and safety of topical therapy with boric acid and flucytosine in women with *Candida glabrata* vaginitis.

**STUDY DESIGN:** This was a retrospective review of case records of 141 women with positive vaginal cultures of *C. glabrata* at two sites, Wayne State University School of Medicine and Ben Gurion University.

**RESULTS:** The boric acid regimen, 600 mg daily for 2 to 3 weeks, achieved clinical and mycologic success in 47 of 73 symptomatic women (64%) in Detroit and 27 of 38 symptomatic women (71%) in Beer Sheba. No advantage was observed in extending therapy for 14 to 21 days. Topical flucytosine cream administered nightly for 14 days was associated with a successful outcome in 27 of 30 of women (90%) whose condition had failed to respond to boric acid andazole therapy. Local side effects were uncommon with both regimens.

**CONCLUSIONS:** Topical boric acid and flucytosine are useful additions to therapy for women with azole-refractory *C. glabrata* vaginitis. (Am J Obstet Gynecol 2003;189:1297-300.)

Key words: Vaginitis, *Candida glabrata*, boric acid, flucytosine

The increased use of vaginal cultures in the treatment of women with chronic recurrent or relapsing vaginitis has provided clinicians with new insights into the *Candida* microorganisms that are responsible for yeast vaginitis. Much attention has been directed at nonalbicans *Candida* species with regard to epidemiologic makeup, clinical manifestations, diagnosis, and treatment issues. In spite of suggestions of a significant trend to increased occurrence of nonalbicans *Candida* infection, more recent studies have failed to confirm an increased incidence. The most common nonalbicans *Candida* species reported is *Candida glabrata*, which has attracted attention because of it is known to reduce in vitro susceptibility to the entire class of azoles and polyene antifungal agents.

Unfortunately, in spite of the increased awareness of vaginitis caused by *C. glabrata*, cases are still too infrequent, especially at a single site, to permit the performance of a randomized prospective controlled study to establish optimal treatment. Even multicenter studies have not been forthcoming. Moreover, the numbers of women who are infected with *C. glabrata* and who are enrolled in *Candida* vaginitis studies have been insufficient to allow separate consideration. Accordingly, practitioners have been provided with relatively poor information regarding treatment effectiveness, which is tainted further by accrual bias. In 1994, we reviewed our experience with 40 women who were infected with *C. glabrata*, some of whom were treated successfully with topical boric acid. Because no new information has been published subsequently, we reviewed the treatment outcomes with boric acid in 141 additional women at two geographic sites with differing patient demographics and report, for the first time, the effectiveness of flucytosine in women whose condition failed to respond to boric acid therapy.

**Methods**

We retrospectively reviewed the medical records of all patients, from whom *C. glabrata* was isolated from vaginal swabs, who were seen at the Wayne State University Vaginitis Clinic between 1992 and 2001. Before record review, approval was obtained from the Wayne State University Investigational Review Board. In addition, one author (W. C.) reviewed case records (n = 39) of women with *C. glabrata* who were seen in a private clinic in Beer Sheba, Israel (1996-2002). None of the patients who are described in the current study have been reported previously.

Medical records were reviewed for demographic details and treatment courses with boric acid, flucytosine, and other antifungics. *C. glabrata* microorganisms were identified on the basis of negative chlamydospore and germ-tube formation and carbon assimilation testing with use of API strips (Sherwood Medical, Plainview, NY).
Table. Comparative susceptibilities of vaginal \textit{C. glabrata} and \textit{C. albicans} to antifungal agents MIC 90 (µg/mL)

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>\textit{C. albicans}</th>
<th>\textit{C. glabrata}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1</td>
<td>0.125</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>0.03</td>
<td>2</td>
</tr>
<tr>
<td>Miconazole</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>Butoconazole</td>
<td>0.03</td>
<td>0.5</td>
</tr>
<tr>
<td>Terconazole</td>
<td>0.03</td>
<td>4</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.03</td>
<td>2</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.5</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.03</td>
<td>1</td>
</tr>
</tbody>
</table>

Boric acid was available as a gelatin capsule that contained 600 mg of boric acid (Professional Compounding Centers of America) and were administered through the vagina once daily for either 14 or 21 days (non-randomized). Fluconazole cream was prepared as described by Horowitz and administered as a nightly 5-g intravaginal dose for 14 days. Fourteen 500-mg capsules of flucytosine (Ancobon) were opened into a mortar and reduced to a fine powder. The powder was levigated with glycerin to form a smooth paste. The levigated mixture was added to a hydrophilic base or cold cream to 45 g. This mixture was blended until smooth, and two 2-ounce ointment tubes were filled. Medical records were examined for documented side and adverse effects. Only symptomatic episodes were treated.

In vitro susceptibility of all \textit{C. glabrata} isolates (Detroit) were determined with the use of the N-27A microdilution National Committee for Clinical Laboratory Standards method.

Results

In the period between 1994 and 2001, 118 isolates of \textit{C. glabrata} were obtained on vaginal culture from 102 patients at the Vaginitis Clinic, Wayne State University. Of the 102 patients, 75 women were white, and 23 women were black. The age range was 16 to 70 years (median age, 41 years); 25 patients were older than 50 years. Predisposing gynecologic factors were rare without the emergence of selective factors except for a past recent history of recurrent bacterial vaginosis (10 patients) and recent desquamative inflammatory vaginitis (10 patients). Not all patients were symptomatic; 73 symptomatic patients received therapy with boric acid. Forty of the 73 patients (55%) who were treated with boric acid were referred to the clinic because of refractory yeast vaginitis, after having had failed repeated courses of azole therapy. Twenty patients were receiving estrogen hormone replacement therapy; only 5 patients (5%) had diabetes mellitus.

Clinical features during the symptomatic episodes of \textit{C. glabrata} vaginitis were indistinguishable from episodes caused by other species. The median vaginal pH was 4.4.

On saline microscopy, budding yeast without hyphal formation were observed in 95 of 118 episode (81%). In 73 episodes of symptomatic vaginitis that were treated with boric acid, 47 patients had improved symptoms and became culture negative (64%), 23 patients remained culture positive with residual symptoms (32%), and 3 patients were lost to follow-up. No difference in outcome was found when patients who were treated for 14 and 21 days were compared. None of the patients stopped boric acid therapy because of local or systemic effects, although occasional complaints of vaginal burning were documented (<10%).

Intravaginal flucytosine cream was offered to 30 patients, 26 of whom had previously received boric acid therapy, with either short-term failure or relapse. Of the 30 patients, 27 patients achieved cure, 2 patients had failure of therapy, and 1 patient was lost to follow-up. All patients completed and tolerated topical flucytosine therapy. No staining of underclothing and sheets was reported. Two patients had failure of flucytosine therapy, both of whom subsequently received oral itraconazole therapy followed by intravaginal nystatin suppositories. One of the 2 patients had successful eradication of \textit{C. glabrata} from the genital tract.

Between 1996 and March 2002, 52 isolates of \textit{C. glabrata} were cultured from 39 patients who were seen at a private vaginitis clinic in Beer Sheba, Israel. Thirty patients were Jewish, and 9 patients were Bedouin (median age, 31 years). Predisposing factors were similarly rare; only 1 patient had diabetes mellitus; however, 8 women were pregnant. Thirty-eight episodes of symptomatic vaginitis were treated with a 14-day course of boric acid (600 mg per day). Clinical and mycologic success was achieved in 27 of 38 patients (71%) whose cases were followed. No patients were treated with flucytosine.

The in vitro susceptibility test results of 100 vaginal isolates of \textit{C. glabrata} that were obtained from the present study population are shown in the Table. The results of azole susceptibility tests are compared with simultaneously tested \textit{C. albicans} vaginal isolates that were obtained from women in the same clinic over the same period. \textit{C. glabrata} isolates are uniformly 10 to 100 times less susceptible to all azoles compared with \textit{C. albicans}. Similarly, reduced susceptibility of \textit{C. glabrata} to amphotericin B was evident. All of the \textit{C. glabrata} isolates were susceptible to flucytosine at low concentrations (<0.25 µg/mL). Isolates of \textit{C. glabrata} were available from three patients for whom flucytosine therapy was unsuccessful. Pretherapy susceptibility revealed minimal inhibitory concentrations of 0.125 µg/mL; hence, no explanation for flucytosine treatment failure is forthcoming. Of interest, however, in one patient the posttreatment \textit{C. glabrata} isolates had rapidly acquired resistance to flucytosine with a minimal inhibitory concentration of >32 µg/mL.
Comment

In a busy referral clinic in Detroit, approximately 10 new patients with C. glabrata infection were seen annually. Moreover, not all patients were symptomatic, qualified, or willing to participate in a randomized study. A prospective, randomized, controlled single-site study was not possible. Regrettably, all published data that are available currently are based on individual case reports or rare case series. The current report is no exception, although 111 patients who were not described previously constitute by far the largest patient population to be studied.

In 1997, we published our experience in treating 26 episodes of vaginitis that were caused by C. glabrata and that were treated with a similar regimen of vaginal boric acid. In this considerably smaller series, the clinical response rate was slightly higher at 81% with mycologic eradication in 77% of cases. In the current series in Detroit, cure rates were approximately 10% lower; however, in addition to study size, uniform inclusion and exclusion criteria were not implemented, except for the presence of positive vaginal cultures for C. glabrata. Nevertheless, the current larger series supports our original report that women whose condition fails to respond to conventional topical azole therapy can be treated safely with boric acid and achieve cure in approximately two thirds of symptomatic episodes.

The current report is the first case series to report treatment outcome with intravaginal flucytosine. Flucytosine has been recognized to have unique in vitro activity against C. glabrata. The topical preparation of flucytosine that was used was based on a formulation used by Horowitz for the treatment of refractory C. tropicalis. There are no other reports of its use for other species of Candida, apart from a recent report by White et al who reported success when flucytosine was compounded together with amphotericin B and used topically in three patients. Our experience with a 90% cure rate with flucytosine is extremely encouraging, and the regimen was well tolerated. The use of oral and parenteral flucytosine is known to cause gastrointestinal and bone marrow toxicity, especially with prolonged use. Our brief vaginal use appeared safe, but no toxicity studies were performed. Long-term use of flucytosine is not recommended. These results are particularly gratifying with the knowledge that none of the newer antifungals are currently under study for yeast vaginitis. The echinocandins with excellent in vitro activity against all Candida species are not absorbed by the oral route; topical preparations are not available.

The newest generation of azoles (voriconazole, posaconazole, and ravuconazole), although more active in vitro against C. glabrata than earlier azoles, are still considerably less active against C. glabrata than C. albicans; moreover, no studies in vaginitis are planned.

Although this retrospective case series was not designed as an epidemiologic study, several features did emerge and deserve further confirmation in prospective studies. Certainly in the Detroit review, C. glabrata vaginitis was often asymptomatic and had frequent coexistent vaginal pathologic condition (eg, recurrent bacterial vaginosis, desquamative inflammatory vaginitis). The higher median age of patients (41 years) is notable compared with patients in the clinic with C. albicans (33 years; data not shown). Vaginal pH, although within the normal range at 4.4, is on the high side and reflects the concomitant pathologic condition and the hypothesized pH preference of C. glabrata. Finally, diabetes mellitus was observed rarely (5%).

On the basis of our observations, topical flucytosine appears more efficacious than boric acid, but no prospective controlled data are available. Accordingly, physicians may choose to offer flucytosine as first-line therapy; however, the latter is expensive compared with boric acid. White et al prepared flucytosine in amphotericin B, which may be synergistic and even more potent. Unfortunately, no comparative data in patients exist, and no animal model of C. glabrata vaginitis is available for comparative study. Resistance development to flucytosine remains an additional concern.

In conclusion, when the conditions of patients with complicated Candida vaginitis from C. glabrata fail to respond to conventional azole therapy, treatment with boric acid vaginal capsules offers a reasonable success rate and is inexpensive and safe when administered by this route. Topical flucytosine vaginal cream has emerged as a highly effective regimen but is not widely available. Vaginitis caused by C. glabrata demands both special efforts and challenge, and additional drugs must be developed to provide effective and convenient treatment.

REFERENCES