# Prevalence of *Candida glabrata* and Its Response to Boric Acid Vaginal Suppositories in Comparison With Oral Fluconazole in Patients With Diabetes and Vulvovaginal Candidiasis

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**OBJECTIVE** — A large proportion of vulvovaginal candidiasis (VVC) in diabetes is due to non–*albicans Candida* species such as *C. glabrata* and *C. tropicalis*. Observational studies indicate that diabetic patients with *C. glabrata* VVC respond poorly to azole drugs. We evaluated the response to oral fluconazole and boric acid vaginal suppositories in diabetic patients with VVC.

**RESEARCH DESIGN AND METHODS** — A total of 112 consecutive diabetic patients with VVC were block randomized to receive either single-dose oral 150-mg fluconazole or boric acid vaginal suppositories (600 mg/day for 14 days). The primary efficacy outcome was the mycological cure in patients with *C. glabrata* VVC in the two treatment arms. The secondary outcomes were the mycological cure in *C. albicans* VVC, overall mycological cure irrespective of the type of *Candida* species, frequencies of yeast on direct microscopy, and clinical symptoms and signs of VVC on the 15th day of treatment. Intention-to-treat (ITT; $n = 111$) and per-protocol (PP; $n = 99$) analyses were performed.

**RESULTS** — *C. glabrata* was isolated in 68 (61.3%) and *C. albicans* in 32 (28.8%) of 111 subjects. Patients with *C. glabrata* VVC showed higher mycological cure with boric acid compared with fluconazole in the ITT (21 of 33, 63.6% vs. 10 of 35, 28.6%; $P = 0.01$) and PP analyses (21 of 29, 72.4% vs. 10 of 30, 33.3%; $P = 0.01$). The secondary efficacy outcomes were not significantly different in the two treatment arms in the ITT and PP analyses.

**CONCLUSIONS** — Diabetic women with *C. glabrata* VVC show higher mycological cure with boric acid vaginal suppositories given for 14 days in comparison with single-dose oral 150-mg fluconazole.

*Diabetes Care* 30:312–317, 2007

Patients with diabetes are at increased risk of developing vulvovaginal candidiasis (VVC) (1–8). Unlike nondiabetic women, these patients have a higher proportion of colonization/infection due to non–*albicans Candida* species such as *C. glabrata* and *C. tropicalis* (4,6–8). In contrast, *C. albicans* VVC is more frequent in nondiabetic women (9). Moreover, diabetic patients with *C. glabrata* VVC respond poorly to single oral doses of 150 mg fluconazole (8). *C. glabrata* demonstrates intrinsically reduced susceptibility to azole drugs (10–13).

Redondo-Lopez et al. (10) and other investigators have reported the successful use of vaginal boric acid suppositories in the management of patients with *C. glabrata* (10,14,15) as well as *C. albicans* VVC (16–18). In view of the higher frequency of *C. glabrata* VVC among diabetic women and their poor response to fluconazole, there is a need for a therapeutic regimen that is effective against both *C. glabrata* and *C. albicans*. To the best of our knowledge, there is no previous study reporting the effect of boric acid vaginal suppositories in diabetic women with VVC. In the current open-label, randomized trial, we report the response to oral fluconazole and boric acid vaginal suppositories in diabetic patients with VVC.

## RESEARCH DESIGN AND METHODS

This was a randomized, open-label comparison of 2 weeks' duration between single-dose oral 150-mg fluconazole and 14 days of treatment with boric acid vaginal suppositories (600 mg/day) in 112 consecutive patients with diabetes (type 2 diabetes, $n = 77$ and type 1 diabetes, $n = 35$) and VVC conducted during 2004–2006. Diabetes was diagnosed as per the American Diabetes Association Expert Committee criteria (19). Patients already on insulin or oral hypoglycemic agents also were included. Any patient with onset of diabetes before age 30 years who had received continuous insulin treatment since diagnosis was considered to have type 1 diabetes. Subjects excluded were those who were pregnant, sexually inactive girls, those aged >65 years, those with renal insufficiency (serum creatinine >1.8 mg/dl), and those on steroid therapy. Patients who did not give consent for pelvic examination, those treated for vaginal discharge during the past 3 months, and

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Received for publication 18 July 2006 and accepted in revised form 22 October 2006.

**Abbreviations:** HVS, high vaginal swab; ITT, intention to treat; PP, per-protocol; VVC, vulvovaginal candidiasis.

DOI: 10.2337/dc06-1469. Clinical trial reg. no. NCT00353561, clinicaltrials.gov.

symptomatic patients in whom *Candida* growth was not detected on fungal culture were also excluded. A1C was measured in all the subjects to assess their glycemic control (normal range: 5.4–7.0%) at visit 1. The institutional ethics committee of the All India Institute of Medical Sciences approved the study protocol, and all the subjects were examined after their informed consent.

### Diagnosis of VVC

A large number of diabetic patients were assessed for symptoms and signs of VVC including vaginal discharge, vulval pruritus, burning sensation, vulval edema, and vaginal congestion at visit 1 (20). Two sterile cotton-tipped commercial swabs were used to collect discharge from high vagina and transported to the mycology laboratory without delay. One of the swabs was used to determine the presence of yeast by direct microscopy, while the other was used for fungal culture. The VVC was diagnosed in the presence of clinical signs and symptoms and growth of *Candida* species on culture of the high vaginal swab (HVS).

Detection and identification of the yeast up to the species level was done in the mycology laboratory of the All India Institute of Medical Sciences as per the standard protocols (21,22). The criteria for laboratory diagnosis were *1*) direct demonstration of the yeast by Gram's staining and *2*) culture on Sabouraud's dextrose agar supplemented with 2 mg/ml gentamicin, with and without cyclohexamide (0.5%). Identification of *Candida* species was performed by examining colony morphology, germ tube test, hyphal morphology, and chlamydospore formation on cornmeal agar, triphenyl tetrazolium reduction test, fermentation and assimilation of different sugars, and cycloheximide susceptibility.

### Randomization and concealment

Following identification of *Candida* growth on HVSs, subjects were assigned to receive single-dose oral 150-mg fluconazole or boric acid vaginal suppositories (600 mg/day) for 14 days in a 1:1 ratio using a randomization list with random permutated blocks, length of 4, at the clinic site (visit 2). The randomization list was generated using a Microsoft Excel spreadsheet as described in detail (available at http://www.childrens-mercy.org/stats/plan/random.asp). Block randomization was used to ensure the balance in the number of patients in the two treatment arms.

A statistician generated the entire randomization sequence list in advance, and allocations were sequentially numbered from the beginning to end. A female clinical investigator (D.R.) carried out genital examinations for VVC, including an HVS for fungal culture for all consecutive diabetic patients attending the endocrine outpatients clinic and gave a serial number to all the patients examined. Following a report of yeast growth, two clinicians (D.R. and R.G.) assigned patients to a treatment arm, as per the serial order of the clinical examination and randomization list sequence number, in an irreversible manner. One of these two clinicians (R.G.) was not involved with clinical examination. Patients were allocated to treatment arm following reports of yeast growth but before the results of *Candida* species were available. The serial order of the randomization list was not disclosed to the patients until the treatment was assigned.

The intake of fluconazole was supervised to ensure compliance. Patients receiving boric acid were instructed to insert one boric acid–filled gelatin capsule (600 mg) intravaginally every night for 14 uninterrupted days either by a plastic applicator or dispensed by hand as per their preference. Two extra capsules were given, and unused capsules were counted on the follow-up visit to assess compliance. Patients in both treatment arms were reassessed on the 15th day of therapy (visit 3). To minimize interobserver variation, the same investigator carried out the repeat clinical assessment at visit 3 when HVSs were taken again for demonstration of yeast by direct microscopy and fungal culture. All the HVSs were of the same color and size and sent to the mycological laboratory in identical containers labeled with a numerical identity. The plan of block randomization, patients' treatment assignments, the pre- and post-nature of the specimen and clinical findings were not disclosed to the mycologist and the laboratory staff who performed fungal culture and species identification till the completion of the 2-year study.

### Efficacy outcomes

The primary objective was to test the hypothesis that diabetic patients with *C. glabrata* VVC when treated with boric acid vaginal suppositories (600 mg/day) for 14 days show a higher mycological cure rate in comparison with a single oral dose of 150 mg fluconazole. Mycological cure was defined as the absence of *Candida* growth on the HVS culture on the 15th day of therapy. The primary efficacy outcome was the mycological cure in patients with *C. glabrata* VVC in the two treatment arms. The secondary efficacy outcomes were mycological cure in *C. albicans* VVC, overall mycological cure irrespective of the type of *Candida* species isolated, presence of yeast on direct microscopy, and frequency of clinical symptoms and signs of VVC on the 15th day in the two treatment arms.

### Adverse effects

Treatment-emergent adverse events were defined as those occurring after receiving the first dose of treatment.

### Sample size and power calculations

Sample size estimation for the assessment of primary efficacy outcome was based on our previously published mycological cure rate of 18.7% in diabetic patients with *C. glabrata* VVC after a single oral dose of 150 mg fluconazole therapy (8). The sample size was calculated using a statistical program (EPI-Info 2002; Centers for Disease Control and Prevention, Atlanta, GA), assuming the persistence of the above trend and three times higher response rate (56.1%) with boric acid therapy. Calculations revealed that 30 subjects with *C. glabrata* infection in each of the two treatment arms would be required to give a study power of 80% at 95% CI. With a 54.1% prevalence rate of *C. glabrata* infection, as observed in our previous study in diabetic subjects with VVC (8), a sample size of 112 diabetic patients with VVC was estimated to give us 60 subjects with *C. glabrata* VVC.

### Statistical analysis

Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed as efficacy analyses. Patients included in the ITT analysis included all those who were assigned to the two treatment arms and in whom at least baseline HVS culture showed *Candida* growth. To be included in the PP analysis, patients also had to comply with the assigned treatment regimen and follow-up as per the study protocol on day 15 (visit 3). For determination of the primary and secondary efficacy outcomes in the ITT analysis, missing data were imputed by explicit allocation of poor outcome in both treatment arms. The differences in the mean age, BMI, and A1C between patients in

**Table 1—*Baseline clinical characteristics, symptoms, and signs and type of* Candida *species in the ITT and PP groups***

| | ITT analysis | | | PP analysis | | |
|---|---|---|---|---|---|---|
| Parameters | Fluconazole | Boric acid | *P* value | Fluconazole | Boric acid | *P* value |
| *n* | 55 | 56 | | 49 | 50 | |
| Age (years) | 40.2 ± 10.7 | 41.2 ± 11.3 | 0.63 | 40.2 ± 9.8 | 40.8 ± 11.5 | 0.78 |
| BMI (kg/m$^2$) | 24.4 ± 5.4 | 24.9 ± 4.5 | 0.64 | 24.6 ± 5.6 | 24.7 ± 4.7 | 0.88 |
| A1C (%) | 9.36 ± 2.5 | 8.5 ± 1.6 | 0.04 | 9.35 ± 2.8 | 8.5 ± 1.7 | 0.05 |
| Postmenopausal | 21 (38.1) | 17 (30.3) | 0.50 | 19 (38.8) | 14 (28.0) | 0.35 |
| Use of commercial sanitary napkins during menstruation | 14 (41.2) | 22 (56.4) | 0.28 | 13 (43.3) | 22 (61.1) | 0.23 |
| VVC symptoms for >1 month | 50 (90.9) | 47 (83.9) | 0.41 | 44 (89.8) | 41 (82.0) | 0.40 |
| Vulval pruritus | 45 (81.8) | 41 (73.2) | 0.39 | 40 (81.6) | 35 (70.0) | 0.26 |
| Vulval edema | 5 (9.0) | 13 (23.2) | 0.08 | 5 (10.2) | 9 (18.0) | 0.40 |
| Vaginal congestion | 39 (70.9) | 43 (76.7) | 0.62 | 33 (67.3) | 37 (74.0) | 0.61 |
| Direct microscopy positivity | 35 (63.6) | 30 (53.5) | 0.37 | 29 (59.2) | 24 (48.0) | 0.36 |
| *C. glabrata* | 35 (63.6) | 33 (58.9) | 0.75 | 30 (61.2) | 29 (58.0) | 0.90 |
| *C. albicans* | 14 (25.4) | 18 (32.1) | 0.95 | 13 (26.5) | 16 (32.0) | 0.92 |
| Other *Candida* species | 6 (10.9) | 5 (8.9) | 0.97 | 6 (12.2) | 5 (10.0) | 0.97 |

Data are means ± SD for age, BMI, and A1C and *n* (%) for other indices in the two treatment arms in ITT and PP groups. *P* values test differences in the means or proportions observed in the two treatment arms.

the two treatment arms were analyzed using Student's *t* test. Logistic regression analysis, with mycological cure as the dependent variable and treatment group and A1C as the independent variable, was used to determine the significance of difference in the primary and secondary efficacy outcomes in the two treatment groups. The differences in the parametric and nonparametric indexes between subjects who grew *C. albicans* and *C. glabrata* on HVS culture were compared using a Student's *t* test and $\chi^2$ test, respectively. All *P* values calculated were two tailed, and $P < 0.05$ was considered significant. SPSS 7.5.1 statistical package was used for analysis.

**RESULTS** — Of 112 subjects randomized to the two treatment arms, 111 were included in the ITT analysis and 99 were analyzed in the PP analysis. One patient was excluded from the ITT analysis because she fell into exclusion criteria (sexually inactive, in whom a HVS was not taken). Twelve patients were dropped for PP analysis because of the following reasons: two stopped boric acid therapy due to vaginal burning sensation appearing on the 7th day of therapy, two did not come for follow-up because of diabetic foot and pulmonary consolidation (fluconazole arm), and eight patients were lost to follow-up for unknown reasons (four in each of the two treatment arms).

The most common species isolated in the cohort of 111 patients included in the ITT analysis was *C. glabrata* ($n = 68$, 61.3%), followed by *C. albicans* ($n = 32$, 28.8%) and *C. tropicalis* ($n = 4$, 3.6%). The baseline demographic and clinical characteristics, including the proportion of patients with type 1 and type 2 diabetes, frequencies of *C. glabrata* and *C. albicans* species isolated on HVS culture, number of postmenopausal women, and those using commercially available protective sanitary napkins, were comparable in both the treatment arms in the ITT and PP analyses groups (Table 1). Only two women were on oral contraceptive pills (one in each of the two treatment arm). The mean A1C value at baseline was lower in the boric acid treatment arm than in the fluconozaole arm in the ITT as well as in the PP analyses group. The primary and secondary efficacy outcomes were, therefore, adjusted for A1C at baseline (Table 2).

The mycological cure rate in patients with *C. glabrata* VVC was significantly higher in the boric acid treatment arm compared with the fluconazole arm in both the ITT and PP analyses (*P* values = 0.01 for both after adjustment for baseline A1C). The odds in favor of mycological cure with boric acid vaginal suppositories in diabetic patients with *C. glabrata* VVC was 4.0 (95% CI 1.4–11.6). The goodness of fit of the logistic regression model was assessed by Nagelkerke $R^2$. Although the Nagelkerke $R^2$ value for primary outcome was only 15.3%, the model should not be interpreted as inadequate (23). No significant difference in mycological cure was observed in the two treatment arms in subjects with *C. albicans* VVC. The overall mycological cure on the 15th day, when analyzed irrespective of the type of *Candida* species isolated at baseline HVS culture, tended to be higher in those receiving boric acid in the ITT ($P = 0.07$) and PP ($P = 0.06$) analyses. The improvement in vaginal pruritus, discharge, and other clinical signs and symptoms was comparable in the two treatment arms in the ITT or PP analyses.

The duration of different symptoms and signs related to VVC, yeast positivity on direct microscopy, and mean A1C values were comparable in diabetic subjects who grew *C. albicans* and *C. glabrata* in the ITT and PP analyses groups. The mean A1C tended to be higher in subjects who continued to grow *Candida* on repeat HVS culture compared with those who did not grow *Candida* in the ITT (9.3 ± 2.0% vs. 8.6 ± 2.1%; $P = 0.11$) and PP groups (9.5 ± 2.2% vs. 8.6 ± 2.1%; $P = 0.06$).

### Adverse effects

Two of the patients in the boric acid treatment arm who stopped the treatment due to vaginal burning sensation were considered to demonstrate the adverse effect, as this improved after stopping the drug.

**CONCLUSIONS** — The 59.9% prevalence of *C. glabrata* infection observed in the current study confirms the findings of our earlier studies that non-*albicans* VVC is frequent in diabetic women (4,8). de Leon et al. (6) observed the 54% vaginal carriage rate of *C. glabrata* in type 2 diabetes. The comparable frequency of clinical symptoms and signs between diabetic

**Table 2—*Primary and secondary efficacy outcomes in the two treatment arms in the ITT and PP groups***

| Parameters | ITT analysis | | | | | PP analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Fluconazole ($n$ = 55) | Boric acid ($n$ = 56) | Odds ratio (95% CI) | $P$ value | Nagelkerke-$R^2$ | Fluconazole ($n$ = 49) | Boric acid ($n$ = 50) | Odds ratio (95% CI) | $P$ value | Nagelkerke $R^2$ |
| Primary outcome | | | | | | | | | | |
| Mycological cure in *C.glabrata* VVC | 10/35 (28.6) | 21/33 (63.6) | 4.4 (1.6–12.1) | 0.005 | 0.159 | 10/30 (33.3) | 21/29 (72.4) | 5.3 (1.7–16.0) | 0.003 | 0.194 |
| As above (adjusted for A1C) | As above | As above | 4.0 (1.4–11.6) | 0.01 | 0.153 | As above | As above | 4.5 (1.4–14.4) | 0.01 | 0.191 |
| Secondary outcomes | | | | | | | | | | |
| Mycological cure in *C.albicans* VVC | 12 (85.7) | 11 (61.1) | 0.3 (0.04–1.5) | 0.13 | 0.110 | 12 (92.3) | 11 (68.8) | 0.1 (0.02–1.8) | 0.14 | 0.138 |
| Overall mycological cure | 25 (45.4) | 37 (66.1) | 2.1 (0.9–4.5) | 0.07 | 0.069 | 25 (51.0) | 37 (74.0) | 2.3 (0.97–5.5) | 0.06 | 0.096 |
| Yeast on direct microscopy | 21 (38.2) | 13 (23.2) | 0.5 (0.2–1.2) | 0.10 | 0.034 | 15 (30.6) | 7 (14.0) | 0.4 (0.13–1.1) | 0.07 | 0.053 |
| Vulval pruritus | 11 (20.0) | 7 (12.5) | 0.5 (0.2–1.4) | 0.20 | 0.038 | 5 (10.2) | 1 (2.0) | 0.15 (0.02–1.4) | 0.09 | 0.117 |
| Vulval edema | 6 (10.2) | 7 (12.5) | 1.1 (0.3–3.4) | 0.91 | 0.007 | — | 1 (2.0) | NA | 0.89 | NA |
| Vaginal congestion | 34 (61.8) | 25 (44.6) | 0.5 (0.2–1.1) | 0.09 | 0.059 | 28 (57.1) | 19 (38.0) | 0.48 (0.2–1.1) | 0.09 | 0.075 |

Data are odds ratio (95% CI) or $n$ (%) in two treatment arms in ITT and PP groups. $P$ values test differences in the proportions observed in the two treatment arms in the ITT and PP groups for primary and secondary outcomes (after adjustment for A1C at baseline). Patients with mixed infection and non-*albicans* candidiasis other than *C. glabrata* were excluded in the analysis because of the limited numbers.

women with *C. glabrata* or *C. albicans* infection is similar to that reported by Geiger et al. (24) in nondiabetic women.

Increased prevalence of *C. glabrata* infection in diabetic women has clinical relevance because poor therapeutic response and innate resistance to azoles has been reported for *C. glabrata* VVC in nondiabetic women (10–13). Similar information is lacking in diabetic subjects, as they are often excluded in antifungal efficacy studies (8,10,25–27). Poor mycological cure in diabetic women with *C. glabrata* VVC to single-dose oral 150-mg fluconazole, observed in the current study, is in accordance with our earlier case-control study (8). Mechanisms implicated for resistance of *C. glabrata* to fluconazole include increased fungal ergosterol synthesis and up to eightfold higher expression of azole efflux pump protein coded by CgCDR1 transporter genes (26,28). Diabetic patients with VVC also respond poorly to itraconazole and ketoconazole (29,30)

In the current study, the higher mycologoical cure (72.4%) to boric acid therapy in diabetics with *C. glabrata* VVC is similar to that reported in nondiabetic individuals (10,14–18). In 1974, Swate and Weed (16) first reported boric acid to be a "safe, effective and inexpensive form of therapy" for VVC. Sobel and Chaim (14) reported clinical improvement in 81% and mycological cure in 77% of nondiabetic patients with symptomatic *C. glabrata*/Torulopsis vaginitis treated with vaginal boric acid. There are also reports of better therapeutic response to boric acid compared with topical nystatin and miconazole in nondiabetic women with *C. albicans* VVC (17,18). Otero et al. (31) have reported a greater in vitro susceptibility of *C. albicans* to boric acid compared with *C. glabrata*.

Boric acid or boracic [$B(OH)_3$] is a weak acid, and its mode of antifungal action is not clear. Shiohara and Tasker (15) proposed that its acidic properties lead to disruption of the fungal cell wall. The pH of boric acid–Sabourauds's broth (5.0–5.09) required for in vitro inhibition of *C. albicans* growth has been reported to be similar to the vaginal pH in untreated *Candida* vaginitis, indicating that the effect of boric acid is not specific to its acidic properties (17). Alkaline compound (i.e., $Na_2B_4O_3$ [borax]) also has antiseptic properties (32). The doses of the boric acid used to treat VVC have ranged from 600 mg daily for 7 days (16) to twice daily for 14 days (18). We used 600 mg boric

acid daily for 14 days because >90% mycological cure has been reported with this schedule in nondiabetic patients with symptomatic *C. albicans* (17) or *C. glabrata* VVC (14).

Boric acid therapy (600 mg/day for 14 days) has been found to be safe (14,17), except for local burning sensation and vestibular erythema in occasional patients (14,17,18). Two of our patients also reported this side effect. Improvement in clinical features of VVC was comparable in two treatment arms. However, we cannot exclude an element of bias in the analysis of this secondary outcome, as the same investigator carried out the clinical examination following treatment.

In our previous studies, poor glycemic control was linked with *Candida* growth (4) but was unrelated to the type of species isolated or response to the fluconazole therapy (8). In the current study, there was a trend of higher mean A1C levels in those showing persistence of *Candida* growth following either of the two therapies. The cause of increased *C. glabrata* isolation in diabetic women is not clear but may involve frequent use of antifungal drugs leading to its reduced susceptibility to azoles (33) and consequent polarization/homing in diabetic women. Feng et al. (34) reported lesser susceptibility of *C. glabrata* in comparison with *C. albicans* to β-defensins, natural cationic antimicrobial/antifungal peptides expressed in human epithelia. In diabetic milieu, β-defensins expression is reduced (35). Reduced expression of defensins in association with resistance of *C. glabrata* to fungicidal activity of drugs like fluconazole may also explain the high prevalence of *C. glabrata* VVC in diabetic women.

One of the relevant findings in this study is the importance of species identification of *Candida* isolates for proper management of VVC in diabetic women. It is emphasized that conventional inexpensive testing procedures, though time consuming, are good enough to identify *Candida* up to species level and would help in the management of diabetic women with VVC. As an alternative, boric acid therapy could be considered as the frontline therapy for treating VVC in diabetic women because it is effective against both *C. albicans* and *C. glabrata* compared with fluconazole, which is effective against *C. albicans* only.

**Acknowledgments**— The authors are thankful to the financial support by ICMR, New Delhi, for this study.

**References**


1. Sonck CE, Somersalo O: The yeast flora of anogenital region in diabetic girls. *Arch Dermatol* 83:214–220, 1963
2. Reed BD: Risk factors for Candida vulvo vaginitis. *Obstet Gynecol Surv* 47:551–560, 1992
3. Peer AK, Hoosen AA, Seedat MA, van den Ende J, Omar MA: Vaginal yeast infections in diabetic women. *S Afr Med J* 83: 727–729, 1993
4. Goswami R, Dadhwal V, Tejaswi S, Datta K, Paul A, Haricharan RN, Banerjee U, Kochupillai NP: Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. *J Infect* 41:162–166, 2000
5. Bohannon NJ: Treatment of vulvovaginal candidiasis in patients with diabetes. *Diabetes Care* 21:451–456, 1998
6. de Leon EM, Jacober SJ, Sobel JD, Foxman B: Prevalence and risk factors for vaginal Candida colonization in women with type 1 and type 2 diabetes. *BMC Infect Dis* 2:1, 2002
7. Jurevic RJ, Bai M, Chadwick RB, White TC, Dale BA: Single-nucleotide polymorphisms (SNPs) in human beta-defensin 1: high-throughput SNP assays and association with Candida carriage in type I diabetics and nondiabetic controls. *J Clin Microbiol* 41:90–96, 2003
8. Goswami D, Goswami R, Banerjee U, Dadhwal V, Miglani S, Lattif AA, Kochupillai N: Pattern of Candida species isolated from patients with diabetes mellitus and vulvovaginal candidiasis and their response to single dose oral fluconazole therapy. *J Infect* 52:111–117, 2006
9. Corsello S, Spinillo A, Osnengo G, Penna C, Guaschino S, Beltrame A, Blasi N, Festa A: An epidemiological survey of vulvovaginal candidiasis in Italy. *Eur J Obstet Gynecol Reprod Biol* 110:66–72, 2003
10. Redondo-Lopez V, Lynch M, Schmitt C, Cook R, Sobel JD: Torulopsis glabrata vaginitis: clinical aspects and susceptibility to antifungal agents. *Obstet Gynecol* 76: 651–655, 1990
11. vanden Bossche H, Marichal P, Odds FC, Le Jeune L, Coene MC: Characterization of an azole-resistant Candida glabrata isolate. *Antimicrob Agents Chemother* 36: 2602–2610, 1992
12. Fidel PL Jr, Vazquez JA, Sobel JD: Candida glabrata: review of epidemiology, pathogenesis, and clinical disease with comparison to C. albicans. *Clin Microbiol Rev* 12:80–96, 1999
13. Vermitsky JP, Edlind TD: Azole resistance in Candida glabrata: coordinate upregulation of multidrug transporters and evidence for a Pdr1-like transcription factor. *Antimicrob Agents Chemother* 48:3773–3781, 2004
14. Sobel JD, Chaim W: Treatment of Torulopsis glabrata vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 24:649–652, 1997
15. Shinohara YT, Tasker SA: Successful use of boric acid to control azole-refractory Candida vaginitis in a woman with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 16:219–220, 1997
16. Swate TE, Weed JC: Boric acid treatment of vulvovaginal candidiasis. *Obstet Gynecol* 43:893–895, 1974
17. Van Slyke KK, Michel VP, Rein MF: Treatment of vulvovaginal candidiasis with boric acid powder. *Am J Obstet Gynecol* 141: 145–148, 1981
18. Jovanovic R, Congema E, Nguyen HT: Antifungal agents vs. boric acid for treating chronic mycotic vulvovaginitis. *J Reprod Med* 36:593–597, 1991
19. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
20. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK: Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol* 92:757–765, 1998
21. Fotedar R, Banerjee U: Changing pattern of Candida species in a bone marrow transplant patient. *J Infect* 32:243–245, 1996
22. *Guidelines on Standard Operating Procedures for Laboratory Diagnosis of HIV-Opportunistic Infection.* Kumari S, Ed. New Delhi, World Health Org. Regional Office for South East Asia
23. Hosmer DW Jr, Lemeshow S: *Applied Logistic Regression*. New York, John Wiley & Sons, 1989
24. Geiger AM, Foxman B, Sobel JD: Chronic vulvovaginal candidiasis: characteristics of women with Candida albicans, C glabrata and no candida. *Genitourin Med* 71: 304–307, 1995
25. Horowitz BJ, Edelstein SW, Lippman L: Candida tropicalis vulvovaginitis. *Obstet Gynecol* 66:229–232, 1985
26. Odds FC: Resistance of yeasts to azole-derivative antifungals. *J Antimicrob Chemother* 31:463–471, 1993
27. Dennerstein GJ: Depo-Provera in the treatment of recurrent vulvovaginal candidiasis. *J Reprod Med* 31:801–803, 1986
28. Sanglard D, Ischer F, Calabrese D, Majcherczyk PA, Bille J: The ATP binding cassette transporter gene CgCDR1 from Candida glabrata is involved in the resistance of clinical isolates to azole antifungal agents. *Antimicrob Agents Chemother* 43:2753–2765, 1999

29. Gonzalez Ortiz M, Martinez Abundis E: Itraconazole in the treatment of Candida vulvovaginitis in patients with type II diabetes mellitus (non-insulin dependent) *Ginecol Obstet Mex* 63:15–18, 1995
30. Balbi C, D'Ajello M, Balbi GC: Treatment with ketoconazole in diabetic patients with vaginal candidiasis. *Drugs Exp Clin Res* 12:413–414, 1986
31. Otero L, Fleites A, Mendez FJ, Palacio V, Vazquez F: Susceptibility of Candida species isolated from female prostitutes with vulvovaginitis to antifungal agents and boric acid. *Eur J Clin Microbiol Infect Dis* 18:59–61, 1999
32. Carey H: Double blind clinical trial of Borax and Candida in the treatment of vaginal discharge. *Comm Br Homoeopath Res Grp* 15:12–14, 1986
33. Ruhnke M: Epidemiology of Candida albicans infections and role of non-Candida-albicans yeasts. *Curr Drug Targets* 7:495–504, 2006
34. Feng Z, Jiang B, Chandra J, Ghannoum M, Nelson S, Weinberg A: Human beta-defensins: differential activity against candidal species and regulation by Candida albicans. *J Dent Res* 84:445–450, 2005
35. Froy O, Hananel A, Chapnik N, Madar Z: Differential effect of insulin treatment on decreased levels of beta-defensins and Toll-like receptors in diabetic rats. *Mol Immunol* 44:796–802, 2007