Effect of pH on in vitro susceptibility of Candida glabrata and Candida albicans to eleven antifungal agents – Implications for clinical use

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Running Title: Reduced anti-Candida drug activity at vaginal pH

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Abstract:

The treatment of vulvovaginal candidiasis (VVC) due to *Candida glabrata* is challenging with limited therapeutic options. Unexplained disappointing clinical efficacy has been reported with systemic and topicalazole antifungal agents in spite of *in vitro* susceptibility. Given that vaginal pH of patients with VVC is unchanged at 4 - 4.5, we studied the effect of pH on the *in vitro* activity of eleven antifungal agents against 40 *C. glabrata* isolates and compared activity against 15 fluconazole sensitive, and 10 fluconazole reduced-susceptibility *C. albicans* strains. *In vitro* susceptibility to flucytosine, fluconazole, voriconazole, posaconazole, itraconazole, ketoconazole, clotrimazole, miconazole, ciclopiroxolamine, amphotericin B and caspofungin was determined using CLSI method for yeast susceptibility testing. Test media were buffered to a pH of 7, 6, 5 and 4. In conditions of reduced pH, *C. glabrata* isolates remained susceptible to caspofungin and flucytosine, however there was a dramatic increase in the MIC$_{90}$ for amphotericin B and everyazole drugs tested. Although susceptible to otherazole drugs tested at pH 7, *C. albicans* strains with fluconazole reduced-susceptibility also demonstrated reduced susceptibility to amphotericin B and all azoles at pH 4. In contrast, fluconazole sensitive *C. albicans* isolates remained susceptible at lowpH to azoles in keeping with clinical observations. In selecting agents for treatment of recurrent *C. glabrata* vaginitis, clinicians should recognize the limitations of *in vitro* susceptibility utilizing pH 7.0.
Vulvovaginal candidiasis (VVC) accounts for up to one third of all vaginitis cases presenting to gynecologists.1-3 VVC is most commonly caused by *Candida albicans*, but can also be caused by non-*albicans* *Candida* species, with *Candida glabrata* being the most common.24,26 Symptomatic *C. glabrata* vaginitis poses a significant problem for clinicians because effective treatment and eradication of *C. glabrata* from the vagina has proven difficult.23,25,26 The organism has variable intrinsic resistance to azole drugs.23,25,26 *C. glabrata* vaginitis has been moderately successfully treated with boric acid, yet this is not curative in one third of patients.8,23,25,26 Other therapies have been advocated such as topical flucytosine, oral itraconazole, and nystatin suppositories.8,18 Amphotericin B suppositories in patients with non-*albicans* *Candida* resistant to azoles were studied by Phillips, and found to be promising, however symptomatic *C. glabrata* vaginitis is often unresponsive to these regimens.11,18 VVC is also occasionally caused by fluconazole resistant *C. albicans*, posing a similar treatment dilemma in that susceptibility of these organisms to other azole and non-azole drugs is not clinically predictive.26

Drug treatment of vaginal infections may be unique in that the normal pH of the vagina is 4 to 4.5, which remains unchanged during VVC.13 Previous studies have found that the test medium pH in *in vitro* susceptibility testing can alter the azole minimum inhibitory concentration (MIC) for *Candida* species, and that an acidic pH tends to increase the MICs of fluconazole for selected *Candida* species.16 However, it was concluded that more acidic conditions did not change the designation of the isolates from susceptible to resistant neither were clinical implications evident. The purpose of this study was to determine whether a change in test media pH had an effect on *in vitro* susceptibility of *C. glabrata* and both fluconazole-susceptible and reduced-susceptibility *C. albicans* to 7 azole and 4 non-azole antifungal agents, in order to explain frequent in vivo failure of these agents in women with vaginitis caused by *C. glabrata.*
Materials and Methods:

Vaginal isolates of *C. glabrata* and *C. albicans* were chosen from the Wayne State Vaginitis Clinic microbiology laboratory organism bank. The definition of fluconazole susceptible *C. albicans* was a MIC ≤ 2 µg/mL, and MIC > 4 µg/mL for reduced susceptibility isolates. Vaginal isolates were randomly chosen from the years 2000-2010, and plated on CHROMagar to verify purity of culture. These plates were incubated for 48 hours at 37ºC in ambient air. Susceptibility testing was then performed using a broth microdilution method, according to CLSI document M27-A3 (2008) guidelines utilizing pH 7. Antifungals and concentrations tested were flucytosine and fluconazole (at MIC ranges 0.125 – 64 µg/mL), and voriconazole, posaconazole, itraconazole, ketoconazole, clotrimazole, miconazole, ciclopiroxolamine, amphotericin B and caspofungin (all with MIC ranges 0.03 – 16 µg/ml). *C. albicans* isolates known to be fluconazole susceptible (MIC < 2 µg/mL) were not tested against itraconazole, ketoconazole, clotrimazole and miconazole. A 0.1 ml yeast inoculum of 1.5 (± 1.0) x10^3 cells/ml in RPMI 1640 medium was added to each microdilution well. The trays were then incubated at 35 º C for 48 hours in ambient air. The MICs were read as the lowest antifungal concentration with substantially lower turbidity (80% growth reduction) compared to growth in the antifungal-free growth well for all agents. Testing known ATCC strains of *Candida parapsilosis* and *Candida krusei* ensured quality control. Antifungal susceptibility testing was carried out for each isolate at pH 6, 5 and 4 using a MOPS (Sigma-Aldrich) buffer solution and MIC range, median, MIC_{50} and MIC_{90} were compared.

Results:

A total of 40 vaginal strains of *C. glabrata*, 15 fluconazole-sensitive and 10 fluconazole-reduced susceptibility *C. albicans* strains were studied and MICs recorded at pH levels 7, 6, 5,
and 4 for each antifungal tested. Table 1 outlines MIC\textsubscript{50} and MIC\textsubscript{90} susceptibility results including ranges of antifungal agents tested for each pH value for both \textit{C. glabrata} and \textit{C. albicans}.

\textbf{C. glabrata}

At pH 7, all \textit{C. glabrata} isolates were susceptible to flucytosine, amphotericin B, caspofungin and ciclopiroxolamine. In contrast, a range of \textit{in vitro} activity was present for the various azole agents. The MIC\textsubscript{90} for fluconazole was 32 ug/mL (range 2 to >64 ug/ml) with considerably lower MIC’s for all other azoles tested. Notably low MICs were documented for posaconazole and voriconazole at 0.5ug/mL. Itraconazole and ketoconazole were highly active at pH 7 and the topical agents clotrimazole and miconazole were similarly active.

With progressive reduction in pH, MIC\textsubscript{90} values for 5-FC and caspofungin were unchanged, however an increase in MIC was evident for amphotericin B and to a less extent ciclopiroxolamine. A dramatic increase in MIC\textsubscript{90} was evident for all azoles tested to drug levels achievable in the vagina with systemic azole use, although pharmacologic data are not available. The trends observed for MIC\textsubscript{90} was also reflected in MIC\textsubscript{50} values.

\textbf{C. albicans}

At pH 7, fluconazole-susceptible strains of \textit{C. albicans} were predictably susceptible to all antifungal agents tested. With decrease in pH, a significant increase in MIC was evident only with amphotericin B and ciclopiroxolamine. Azole activity at the lower pH was maintained in the fluconazole susceptible isolates.

At pH 7, 10 vaginal isolates of fluconazole- reduced susceptibility \textit{C. albicans} were evaluated. MIC range for fluconazole activity was 4 to >64 ug/mL, with MIC\textsubscript{90} being 4ug/mL. These isolates remained susceptible to all other azole drugs tested, but demonstrated a
moderately higher MIC to flucytosine (MIC 2ug/mL). In contrast, lower pH tested, dramatic
increases in MIC were seen with testing for flucytosine, amphotericin B, fluconazole,
posaconazole, voriconazole, itraconazole and ketoconazole.

**Discussion:**

The results of this study reveal that different classes of antifungals and the two species of
*Candida* studied *in vitro* behaved differently with decrease in pH. The results confirm the
susceptibility of fluconazole sensitive *C. albicans* isolates to all azoles and *C. glabrata*’s variable
resistance to fluconazole, and may also offer insight as to why some antifungal medications may
not be as effective *in vivo* with a more acidic physiologic vaginal pH. Previous studies similarly
found that the medium pH can alter azole MICs for *Candida* species, and specifically an acidic
pH was reported to increase the MICs of fluconazole for selected *Candida* species. The clinical
implications of this observation were not, however, recognized.

*C. glabrata* vaginal infection is by no means infrequent, but case numbers are insufficient
to perform a randomized controlled trial in order to establish optimal treatment. The
resistance of *C. glabrata* to fluconazole, at all pH levels, observed in the present study is
consistent with numerous *in vitro* studies, reflects experience when treating vulvovaginal
candidiasis and blood stream infections. Posaconazole and voriconazole are frequently
but not invariably active against fluconazole resistant *C. glabrata*. The Candida surveillance
study demonstrated that resistance to fluconazole was highly predictive for resistance to
voriconazole. Sabatelli et al studied 1218 *C. glabrata* isolates and their resistance to different
azoles and amphotericin B, concluding that isolates with elevated MICs to one azole were
generally less susceptible to all azoles. An important new finding in the present study reveals
that *C. glabrata* isolates resistant to fluconazole but susceptible to posaconazole and
voriconazole at pH 7 are unlikely to be effectively treated in vivo given the dramatic increases in MIC to these drugs at pH 4 and 5.

Topical agents miconazole and clotrimazole which achieve high local concentrations are similarly likely to be ineffective. This conclusion is strongly supported by clinical experience. In contrast flucytosine maintained activity at low pH and supports experience in successfully treating *C. glabrata* affected woman with symptomatic vaginitis.

Topical amphotericin B has in small studies demonstrated effectiveness for treatment of *non-albicans Candida* vaginitis, but emerging resistance to this antifungal has been documented. Topical amphotericin B has also been used in combination with other antifungals, such as flucytosine. If flucytosine is as effective as previously described and stable at a low pH, perhaps it is contributing much more than amphotericin B to successful treatment.

In the present study that for both *Candida* species, amphotericin B activity was profoundly affected by pH with at least a 16-fold increase in MIC90 with decrease in pH.

Ciclopiroxolamine is an agent applied topically and well known for its potency against dermatophytes, and has been suggested as an antifungal for resistant VVC. It is a synthetic topical agent, widely used to treat onychomycosis, tinea pedis, pityriasis versicolor and seborrheic dermatitis. Its use in treating vaginal candidiasis has also been studied, with limited success, and has shown clinical promise against azole-resistant *Candida* species, including *C. glabrata*. It has demonstrated good topical and systemic tolerance in rats and rabbits when vaginal tissue was examined, and has been studied in setting with lower pH. However, in this study, a 4-fold rise in MIC90 from 0.5 to 2 ug/mL with a decrease in pH was seen. One factor that limits the clinical application of this data is that the break point of ciclopiroxolamine is unknown and the clinical relevance of increased MIC’s is questionable.
Caspofungin is an echinocandin that has demonstrated activity against *Candida* species both *in vitro* and *in vivo*, for systemic infections. None of the echinocandins are available as topical agents and have not yet been studied for vulvovaginal candidiasis, or at decreased pH levels. Results from this study demonstrated stable MICs with a decrease in pH with all *C. albicans* isolates having an MIC$_{90}$ of less than 2 ug/mL, and continued activity against *C. glabrata* isolates at lower pH. Additional studies would need to be performed to evaluate echinocandin response *in vivo* as a topical compound.

This *in vitro* study demonstrates the potential limitations of conventional *in vitro* testing in predicting antifungal clinical success when faced with the challenge of treating recurrent vulvovaginal *C. glabrata* infections as well as fluconazole refractory *C. albicans* vaginitis. Although the importance of media pH in standardizing susceptibility testing is widely recognized in recommending routine testing at pH 7, the profound effect of pH on *C. glabrata* susceptibility has not been appreciated, but is probably only relevant to patients with yeast vaginitis. The exact mechanism of pH induced reduced susceptibility has not been established. In contrast, fluconazole susceptible *C. albicans* strains responsible for the majority of vaginitis episodes are less vulnerable to the pH influence. Finally, *C. albicans* vaginal isolates already demonstrating reduced azole sensitivity at pH 7 are further compromised by lowering pH, resembling the effect seen with *C. glabrata*. This study also emphasizes the need for new alternate agents for treatment of *C. glabrata* vaginitis as well as to consider measuring *C. glabrata* drug susceptibility *in vitro* at pH 4 to 5 before recommending antimycotic therapy, however, validation studies are essential.
References:


2) American College of Obstetricians and Gynecologists. 2009 Vulvar Disorders. ACOG Clinical Updates in Women’s Health Care. VIII, number 2, pg 36


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**Fluconazole resistant C. albicans**

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**Fluconazole sensitive C. albicans**

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**Fluconazole sensitive C. glabrata**

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<td>8</td>
<td>0.03</td>
<td>0.03</td>
<td>0.06</td>
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<tr>
<td>Range</td>
<td>0.125 - 0.5</td>
<td>0.5 - 16</td>
<td>8 - 16</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03 - 0.06</td>
<td>1</td>
<td></td>
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</table>

5FC = flucytosine, AMB = Amphotericin B, CASPO = caspofungin, CPO = ciclopiroxolamine, FLU = fluconazole, VORI = voriconazole, POSA = posaconazole, ITRA = itraconazole, KTZ = ketoconazole, CLO = clotrimazole, MIC = miconazole