Background: Bloodstream infections (BSIs) caused by Candida glabrata have increased substantially. Candida glabrata is often associated with resistance to fluconazole therapy. However, to our knowledge, risk factors for fluconazole-resistant C glabrata BSIs have not been studied.

Methods: A case-control study was conducted at 3 hospitals from January 1, 2003, to May 31, 2007. The 2 case groups included patients with fluconazole-resistant C glabrata BSIs (minimum inhibitory concentration ≥16 µg/mL) and patients with fluconazole-susceptible C glabrata BSIs (minimum inhibitory concentration ≤8 µg/mL). Hospitalized patients without C glabrata BSIs were randomly selected for inclusion in the control group and were frequency matched to cases on the basis of time at risk. Two case-control studies were performed using this shared control group. The primary risk factor of interest, previous fluconazole use, was evaluated at multivariate analyses, adjusting for demographic data, comorbid conditions, and antimicrobial exposures.

Results: We included 76 patients with fluconazole-resistant C glabrata BSIs, 68 patients with fluconazole-susceptible C glabrata BSIs, and 512 control patients. Previous fluconazole use (adjusted odds ratio [95% confidence interval], 2.3 [1.3-4.2]) and linezolid use (4.6 [2.2-9.3]) were independent risk factors for fluconazole-resistant C glabrata BSIs; previous cefepime use (2.2 [1.2-3.9]) and metronidazole use (2.0 [1.1-3.5]) were independent risk factors for fluconazole-susceptible C glabrata BSIs.

Conclusions: Previous fluconazole use is a significant risk factor for health care-associated fluconazole-resistant C glabrata BSIs. Future studies will be needed to evaluate the effect of decreasing fluconazole use on rates of fluconazole-resistant C glabrata BSIs.


ORIGINAL INVESTIGATION

Risk Factors for Fluconazole-Resistant Candida glabrata Bloodstream Infections

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Study Design and Setting

This study was conducted at 3 hospitals in the University of Pennsylvania Health System: the Hospital of the University of Pennsylvania, a 625-bed academic tertiary- and quaternary-care medical center; Penn Presbyterian Medi-
Case subjects were identified through the Hospital of the University of Pennsylvania Clinical Microbiology Laboratory, which began susceptibility testing of all Candida glabrata bloodstream isolates from the 3 involved hospitals in January 1, 2003. Candida glabrata was identified by macroscopic and microscopic morphologic features in addition to a positive reaction using the Rapid Assimilation of Trehalose Test (Hardy Diagnostics, Santa Maria, California).17 Fluconazole susceptibility was performed using Sensititre YeastOne (TREK Diagnostic Systems, Inc, Cleveland, Ohio) in accord with criteria from the Clinical Laboratory Standards Institute.18 Patients in whom C glabrata bloodstream isolates were detected between January 1, 2003, and May 31, 2007, with minimal inhibitory concentration (MIC) of 16 µg/mL or greater were eligible for inclusion in the fluconazole-resistant C glabrata case group. Patients with isolates with MIC of 8 µg/mL or less were eligible for the fluconazole-susceptible C glabrata case group.19 Dose-dependent susceptible isolates (MIC of 16−32 µg/mL), which have reduced fluconazole susceptibility and are, therefore, treated with higher fluconazole doses or different antifungal agents than are used to treat C albicans or fluconazole-susceptible C glabrata BSIs, were included in the fluconazole-resistant C glabrata case group.

Inclusion was limited to health care–associated BSIs, defined as C glabrata BSIs that developed after at least 48 hours of hospitalization or within 48 hours in patients who fulfilled at least 1 of the following criteria: (1) receipt within the previous 30 days of intravenous treatment, home health care services, or outpatient hemodialysis or (2) residence for at least 2 of the previous 90 days in a hospital, nursing home, or long-term care facility.19 Each patient was included only once, and only the initial episode of C glabrata BSI was reviewed. Patients admitted with outpatient blood cultures positive for C glabrata were excluded.

Hospitalized patients without C glabrata BSIs were eligible for inclusion in the control group. Control subjects were selected using a computer-generated random-number table and were frequency matched to case subjects by quartiles on the basis of time at risk. Time at risk was defined as the number of days from admission to a blood culture positive for C glabrata in the case groups and the number of days from admission to discharge in the control group. The number of control subjects selected was approximately 4-fold the total number of case subjects.

STUDY POPULATION

We identified 76 patients with fluconazole-resistant C glabrata BSIs and 68 patients with fluconazole-susceptible C glabrata BSIs. The control group included 512 patients without C glabrata BSIs. Of patients with C glabrata BSIs, half were from the Hospital of the University of Pennsylvania, where 45% of the isolates were fluconazole-resistant and one-fourth each were from Pennsylvania Presbyterian Medical Center and Pennsylvania Hospital, where 60% to 62% of isolates were fluconazole-resistant.

Results at bivariate analyses are given in Table 1 and Table 2. Patients with fluconazole-resistant C glabrata BSIs were more likely to have previously used fluconazole (unadjusted OR [95% CI], 4.6 [2.6−8.0]; P < .001), less likely to have been hospitalized at the Hospital of the University of Pennsylvania (0.6 [0.3−0.9]; P = .02), and had significantly longer median time at risk (23 vs 17 days;
Previous fluconazole use was also significantly associated with fluconazole-susceptible C. glabrata BSIs (unadjusted OR [95% CI], 2.0 [1.0-3.9]; \( P = .02 \)). There was no effect modification by year, hospital, oncologic status, or chemotherapy status found in either of the case-control studies.

At multivariate analyses, previous fluconazole use (adjusted OR, 2.3 [1.3-4.2]; \( P = .007 \)) and linezolid use (4.6...
The difference between the present study and previous studies in general inpatient populations may be related to case group selection. Although previous studies focused on *C. glabrata* because of its association with fluconazole resistance, susceptibility testing was typically absent. Both patients with fluconazole-resistant and fluconazole-susceptible isolates were included in the case group. This may have decreased the ability to detect risk factors for fluconazole-resistant *C. glabrata*, particularly given the results of this study, which found that previous fluconazole use was significantly associated with fluconazole-resistant *C. glabrata* BSIs but not with fluconazole-susceptible *C. glabrata* BSIs. High rates of fluconazole use in patients with cancer, however, may have resulted in higher rates of resistance in this population, enabling the investigators to find a strong association.

Linezolid use was also identified as an independent risk factor for fluconazole-resistant *C. glabrata* BSIs. Linezolid has broad gram-positive coverage that could alter skin and possibly gastrointestinal flora such as *Enterococcus* species, enabling colonization and subsequent infection with fluconazole-resistant *C. glabrata*. Lin et al.\(^1\) found vancomycin, another antibiotic with broad gram-positive coverage, to be an independent risk factor for *C. glabrata* and *C. krusei* BSIs.

Cefepime use and metronidazole use were found to be independent risk factors for fluconazole-susceptible *C. glabrata* BSIs. Lin et al.\(^2\) identified piperacillin-tazobactam, an antimicrobial agent with both gram-negative and anaerobic coverage, as a significant risk factor for *C. glabrata* and *C. krusei* BSIs. Animal models have suggested that *C. glabrata* may have fewer virulence factors.\(^2\) If *C. glabrata* is less pathogenic than *C. albicans*, *C. glabrata* may require selection pressure from antecedent antibiotic use for colonization and infection. Previous studies have also suggested that *Candida* infections may occur via horizontal transfer, and this mode of transmission may be particularly important in *C. glabrata* infections, the incidence of which increases with age.\(^2\)

There are several potential limitations of the present study. Misclassification of risk factors is possible because data were not collected prospectively (ie, the database may be missing comorbid conditions not identified via International Classification of Diseases, Ninth Revision, coding and medications prescribed outside of the University of Pennsylvania Health System). However, the percentage of missing data is unlikely to be dissimilar between groups, and this nondifferential misclassification would bias results toward null. In addition, the study was conducted in 3 hospitals in the same city. Geographic and hospital-associated differences in the susceptibility patterns of *C. glabrata* have been previously demonstrated.\(^2\)

To our knowledge, the present study is the first to evaluate independent risk factors for fluconazole-resistant *C. glabrata* BSIs. We found that previous fluconazole use and linezolid use were independent risk factors for fluconazole-resistant BSIs. Previous cefepime use and metronidazole use were independent risk factors for fluconazole-susceptible *C. glabrata* BSIs.

Previous fluconazole use could promote either de novo resistance by 1 or more mechanisms including upregulating efflux pumps or resistance by changing a patient’s endogenous flora, enabling colonization and infection with fluconazole-resistant *C. glabrata*.\(^9\) Our results are similar to those of 2 previous studies in patients with cancer that identified previous fluconazole use as a risk factor for invasive *C. glabrata* infections (OR, 5-11).\(^1\) However, subsequent studies that broadened the study population to include the general inpatient population did not find this association. Several ecologic studies did not enable identification of significant increases in *C. glabrata* BSIs despite significant increases in fluconazole use.\(^13,14\) A case-control study by Lin et al.\(^1\) found that previous fluconazole use was not a risk factor for *C. glabrata* and *Candida krusei* BSIs at bivariate or multivariate analyses. Malani et al.\(^2\) reported no difference in fluconazole-resistance rates between patients with and without previous fluconazole exposure. Limitations of the study by Malani et al, however, include that multivariate analysis was not performed and that the study may not have been powered to detect this difference.

**Table 3. Adjusted Risk Factors for *Candida glabrata* Bloodstream Infections**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fluconazole-Resistant</th>
<th>Fluconazole-Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>C. glabrata</em> Case Group</td>
<td><em>C. glabrata</em> Case Group</td>
</tr>
<tr>
<td>Time at risk</td>
<td>1.0 (1.0-1.0)</td>
<td>1.02 (1.0-1.0)</td>
</tr>
<tr>
<td>Therapy</td>
<td>Cefepime</td>
<td>1.6 (0.9-2.9)</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>2.3 (1.3-4.2)</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>4.6 (2.2-9.3)</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>1.5 (0.8-2.6)</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>1.3 (0.7-2.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; ellipses, variable not included in the multivariate model.

Both case groups were independently compared with the control group.

[2.2-9.3]; *P* < .001) were independent risk factors for fluconazole-resistant *C. glabrata* BSIs (Table 3). In the subgroup analysis, in which fluconazole-resistant *C. glabrata* was limited to those isolates with MIC greater than or equal to 64 µg/mL (n = 19), previous fluconazole use (5.2 [1.8-15.6]; *P* = .003), linezolid use (6 [1.4-14.5]; *P* = .01), and time at risk (1.02 [1.01-1.04]; *P* = .009) were independent risk factors. Previous cefepime use (adjusted OR [95% CI], 2.2 [1.2-3.9]; *P* = .007) and metronidazole use (2.0 [1.1-3.5]; *P* = .02) were independent risk factors for fluconazole-susceptible *C. glabrata* BSIs (Table 3).

**COMMENT**

To our knowledge, the present study is the first to evaluate independent risk factors for fluconazole-resistant *C. glabrata* BSIs. We found that previous fluconazole use and linezolid use were independent risk factors for fluconazole-resistant *C. glabrata* BSIs. Previous cefepime use and metronidazole use were independent risk factors for fluconazole-susceptible *C. glabrata* BSIs.

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To our knowledge, the present study is the first to evaluate independent risk factors for fluconazole-resistant *C. glabrata* BSIs and to identify previous fluconazole use as a significant risk factor for resistance in the general inpatient population. Future studies will be needed to identify the effect of decreasing fluconazole use on the rates of fluconazole-resistant *C. glabrata* BSIs.

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Author Contributions: Dr Lee had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lee, Fishman, Zaoutis, and Lautenbach. Acquisition of data: Lee, Weiner, Synnestvedt, and Nachamkin. Analysis and interpretation of data: Lee, Morales, and Lautenbach. Drafting of the manuscript: Lee and Lautenbach. Critical revision of the manuscript for important intellectual content: Lee, Fishman, Zaoutis, Morales, Weiner, Synnestvedt, Nachamkin, and Lautenbach. Statistical analysis: Lee, Morales, and Lautenbach. Obtained funding: Lee. Administrative, technical, and material support: Lee, Weiner, Synnestvedt, and Nachamkin. Study supervision: Fishman, Zaoutis, and Lautenbach.

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REFERENCES