Candida glabrata Fungemia: Experience in a Tertiary Care Center

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Background. During the past decade, Candida glabrata has emerged as an important cause of fungemia. We reviewed demographic data, risk factors, treatment, and outcomes associated with C. glabrata fungemia from 1995–2002 and performed susceptibility testing of isolates.

Methods. Data on all episodes of fungemia were prospectively recorded, and the associated isolates were saved. Medical records were reviewed retrospectively. Susceptibility testing was performed for fluconazole, itraconazole, and voriconazole.

Results. C. glabrata caused 103 (17%) of 609 fungemic episodes during the 8-year period that we studied. Medical records and isolates were available for 94 episodes that occurred in 91 patients. The patients included 42 men and 49 women. The mean age was 51 years. Thirty-four episodes (36%) occurred in patients ≥60 years old; only 3 episodes occurred in patients <1 year old. The most common predisposing factors were use of broad-spectrum antibiotics (in 86% of episodes), use of central venous catheters (77%), stay in an intensive care unit (48%), renal failure (46%), and receipt of parenteral nutrition (45%). Of the 94 episodes, 83 were treated with antifungal agents. The overall mortality rate at day 30 was 29%. For the 11 episodes that were not treated, the mortality rate was 64% (7 of 11 episodes). Outcome appeared to be unrelated to whether fluconazole or amphotericin B was administered. In vitro, 60% of isolates were resistant to fluconazole, 83% to itraconazole, and 44% to voriconazole. Susceptibility to these azoles did not change over the 8 years of the study.

Conclusion. C. glabrata fungemia was most often seen in older adults and was associated with a mortality rate of 29%. Outcomes appeared to be unrelated to in vitro susceptibility results and to the antifungal agent used.

Since 1995, Candida species have become the fourth most common cause of nosocomial bloodstream infection and are associated with a crude mortality rate of 39%, which is the highest mortality rate associated with any cause of nosocomial bloodstream infections. In intensive care units (ICUs), infection with Candida species is the third most frequent cause of nosocomial bloodstream infection and is associated with a crude mortality rate of 47% [1]. During the past decade, an increase in the incidence of bloodstream infections due to Candida species other than Candida albicans has been reported from individual medical centers as well as from multicenter studies assessing candidemia [2–16]. In many medical centers in the United States, the most common non-albicans species of Candida is Candida glabrata, which accounts for as many as one-quar-ter to one-third of all cases of fungemia [10–12]. The increase in the incidence of C. glabrata fungemia appears to be multifactorial. It has been shown that the prevalence of this organism is related to disparate factors, including geography [10], age [8, 15], patient population studied [4, 6, 7, 10], and use of fluconazole [4, 6]. Because this species is relatively resistant to fluconazole, the increasing proportion of fungemias due to C. glabrata has important implications for therapy.

We reviewed the demographic data, risk factors, treatment, and outcomes associated with C. glabrata fungemia at our institution during an 8-year period from 1995 through 2002. In addition, azole-susceptibility testing of C. glabrata isolates associated with fungemia was performed, changes in susceptibility patterns...
PATIENTS AND METHODS

Patients and setting. All episodes of *C. glabrata* fungemia that occurred during January 1995–December 2002 at the University of Michigan Health System (Ann Arbor, MI) were identified. All fungemias had been prospectively recorded, and the associated isolates had been saved in the Infectious Diseases Research Laboratory at the Veterans Affairs Medical Center (Ann Arbor, MI) since 1995. An episode of fungemia was defined as ≥1 blood culture yielding *C. glabrata*. A second episode of fungemia occurring in the same patient within 4 weeks of the first episode was counted as being the same episode. Episodes in which a central catheter tip (but not blood) yielded *C. glabrata* were excluded.

Medical records were reviewed to identify risk factors, treatment, complications, and outcomes. Clearance of fungemia was assessed at the end of therapy, and mortality was assessed at 30 and 90 days after the first positive blood culture result. Death was recorded as being associated with *C. glabrata* if the patient died within 48 h of the isolation of the organism from the blood and/or autopsy showed yeast invasion of viscera [9]. Death due to unrelated causes was defined as death occurring in a patient whose last positive blood culture result was obtained >48 h before death, whose symptoms and signs of fungal infection had resolved, and for whom another cause of death was obvious.

Susceptibility testing. *C. glabrata* isolates were stored at −70°C in Sabouraud dextrose broth with glycerol. Each isolate was retrieved from storage and plated twice in succession on Sabouraud dextrose agar before testing. Two control strains, *C. albicans* ATCC 24433 and *C. parapsilosis* ATCC 22019, were tested on each day that susceptibility tests were performed.

Voriconazole and fluconazole powders were obtained from Pfizer. The stock solution of voriconazole was made by dissolving the powder in dimethyl sulfoxide (DMSO); fluconazole was dissolved in sterile distilled water. Itraconazole powder was obtained from Janssen Research Foundation. The stock solution was made by dissolving the powder in DMSO. All stock solutions were stored at −70°C. The solutions were thawed and diluted to the proper concentrations in RPMI 1640.

The NCCLS broth macrodilution method, as outlined in the M27-A document [17], was used for susceptibility tests. Concentrations were 0.06–64 μg/mL for fluconazole, 0.006–6.4 μg/mL for itraconazole, and 0.008–8 μg/mL for voriconazole. The MIC was determined to be the lowest drug concentration at which visual turbidity was equal to or less than that of an 80% dilution of the control tube that did not have an antifungal agent added. The MIC<sub>50</sub> and MIC<sub>90</sub> values were calculated for the 3 antifungal agents. Susceptibility was determined for fluconazole and itraconazole according to NCCLS guidelines [17]. No breakpoints have been established for voriconazole; however, the proposed breakpoint of ≥4 μg/mL for resistance was used.

Statistical analysis. Data are expressed as mean (± SD). Categorical variables were assessed using χ² or Fisher exact tests.

RESULTS

Incidence and demographic data. There were a total of 609 fungemic episodes that occurred from 1 January 1995 through 31 December 2002, of which *C. glabrata* fungemias accounted for 103 episodes (17%). The proportion of fungemias due to *C. glabrata* ranged from 9%–29% per year (figure 1). Complete medical records and the initial *C. glabrata* isolate were available for 94 of these episodes, which occurred in 91 patients and form the basis of this review.
Table 1. Demographic and clinical characteristics of 91 patients with 94 episodes of Candida glabrata fungemia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C. glabrata fungemia episodes (n = 94)</th>
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<tbody>
<tr>
<td>Patient age, mean years ± SD</td>
<td>51 ± 21</td>
</tr>
<tr>
<td>Sex, male subjects/female subjects</td>
<td>42/49</td>
</tr>
<tr>
<td>Underlying conditiona</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>43 (46)</td>
</tr>
<tr>
<td>Solid-organ cancer</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>21 (22)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Hematological cancer</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Solid-organ transplant</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>6 (6)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Associated risk factorsa</td>
<td></td>
</tr>
<tr>
<td>Receipt of systemic antibiotics</td>
<td>81 (86)</td>
</tr>
<tr>
<td>Treatment with central venous catheter</td>
<td>72 (77)</td>
</tr>
<tr>
<td>Stay in an intensive care unit</td>
<td>45 (48)</td>
</tr>
<tr>
<td>Receipt of parenteral nutrition</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Receipt of immunosuppressive drugs</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Prior abdominal surgery</td>
<td>25 (27)</td>
</tr>
<tr>
<td>Neutropeniab</td>
<td>11 (12)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of episodes, unless otherwise indicated.

a Most episodes occurred in patients with >1 underlying condition or risk factor.

b Absolute neutrophil count, <500 cells/μL.

_C. glabrata_ fungemia occurred in 42 men (46% of subjects) and 49 women (54%). The mean age was 51 ± 21 years (range, 5 months to 87 years). Overall, 34 (36%) of the episodes occurred in patients ≥60 years old, and 21 (22%) occurred in those ≥70 years old; only 3 (3%) of the episodes occurred in children <1 year old (figure 2). One patient had 2 separate episodes that occurred 20 months apart, and a second patient had 3 separate episodes, with the second and third episodes occurring at 27 and 34 months after the initial episode.

**Risk factors.** The majority of patients had multiple underlying illnesses and other risk factors that have been associated with fungemia (table 1). For 58 episodes (62%), >4 risk factors were identified. The most common underlying illness and predisposing factors were use of broad-spectrum antibiotics (86%), use of central intravenous catheters (77%), stay in an ICU (48%), renal insufficiency (46%), and receipt of parenteral nutrition (45%). A total of 23 (24%) of the episodes were associated with receipt of an antifungal agent within 30 days before onset; for 20 of these episodes, this antifungal agent was fluconazole alone (17 episodes) or amphotericin B followed by fluconazole (3 episodes).

**Characteristics of fungemia.** Thirty-three (35%) of the episodes were characterized by fungemia of >1 day in duration; 26 (28%) were characterized by fungemia of ≥3 days in duration, and 20 (21%) were characterized by fungemia of ≥5 days in duration. The mean duration of fungemia was 3.5 days. The longest duration of fungemia was 33 days, in a patient who had end-stage liver disease and who had received a transjugular intrahepatic portosystemic shunt; he died with persistent_C. glabrata_ fungemia. Fifteen episodes (16%) had polymicrobial blood cultures that also yielded gram-negative bacilli (in 11 episodes), gram-positive cocci or bacilli (6), or a second yeast (2).

**Specific clinical syndromes.** No patient developed endophthalmitis, osteomyelitis, or CNS infection that was clinically evident during the follow-up period. Three patients had _C. glabrata_ endocarditis, 4 had intraabdominal abscesses or peritonitis, and 1 had an obstructing renal fungus ball.

All 3 patients with endocarditis had complicated hospital courses and endocarditis associated with indwelling vascular devices. Transesophageal echocardiographic examination revealed vegetations on the tricuspid valve in 2 patients and the mitral and aortic valves in 1 patient each. In all patients, after device removal, treatment was given with amphotericin B and flucytosine for 4–12 weeks followed by fluconazole suppression in 2 of the 3 patients. Three of the 4 patients with intraabdominal infection (liver, splenic, and pelvic abscesses in 3 patients and peritonitis in 1 patient) were liver transplant recipients. Another patient had an obstructing renal pelvis mycetoma that yielded _C. glabrata_ when removed endoscopically.

**Treatment and outcomes.** Of the 94 episodes, 83 (88%) were treated with an antifungal agent. Eleven episodes (22%) were not treated because of the death of the patient prior to or at the time that the diagnosis was established (7 patients), the discharge of the patient to comfort care (1 patient), or no reason was documented (3 patients). Of those 83 episodes for which an antifungal agent was used, 26 (31%) were treated with fluconazole alone. Twenty-seven (33%) were treated with fluconazole initially, and then therapy was switched to an amphotericin B formulation after the species was documented to be _C. glabrata_. A total of 21 episodes (25%) were treated with an amphotericin B formulation alone. For 6 (7%) of the episodes, treatment began with an amphotericin B formulation and was then changed to fluconazole. The remaining 3 episodes (4%) were treated with a variety of regimens that included caspofungin. The dosage of fluconazole was 50–800 mg daily. From 1995 to 1997, amphotericin B deoxycholate was primarily used; from 1998 to 2002, patients increasingly received lipid formulations of amphotericin B. In 2002, 3 patients received caspofungin, but none had this agent used as primary therapy.

For 22 (85%) of 26 episodes treated with fluconazole therapy alone, additional blood cultures yielded no yeasts by the end of therapy (table 2). The microbiological success rate for treat-
The mortality rate increased with increasing age; patients from which only C. glabrata had a higher mortality rate than did episodes with blood culture results. The mortality rate was 37% (31 of 83 patients with fungemia, and death due to other causes occurred in 15 episodes (0 of 3 episodes) in patients <1 year old, 20% (1 of 5 episodes) in patients 1–20 years old, and 0% (0 of 3 episodes) in patients >20 years of age had a mortality rate of 35% (12 of 34 episodes), compared with 28% (9 of 32 episodes) in patients >40 to 60 years old, 25% (5 of 20 episodes) in patients >20 to 40 years old, 20% (1 of 5 episodes) in patients 1–20 years old, and 0% (0 of 3 episodes) in patients <1 year old (P = .018). Death that occurred 22 (85) 18 (86) 31 (94) 2 (67) 3 (27) 22 (85) 18 (86) 31 (94) 2 (67) 3 (27) at 30 days All causes Candidemia b Other causes b

### Notes
- AmB, amphotericin B; AmB + Flu, amphotericin B before or after fluconazole; Caspo +, caspofungin plus other antifungal agents; Flu, fluconazole; none, no treatment.
- Includes patients who died <48 h after a blood culture yielded C. glabrata and/or had autopsy evidence of invasive yeast infection.
- Includes patients who died >48 h after a blood culture yielded C. glabrata, who had resolved all signs and symptoms of fungal infection, and who had another obvious cause of death.

### Table 3. Results of susceptibility studies of 94 Candida glabrata isolates recovered from 91 patients.

<table>
<thead>
<tr>
<th>Drug, incubation time</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;, g/mL</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, g/mL</th>
<th>Range, g/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>24 h</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>48 h</td>
<td>64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>24 h</td>
<td>0.4</td>
<td>&gt;6.4</td>
</tr>
<tr>
<td></td>
<td>48 h</td>
<td>3.2</td>
<td>&gt;6.4</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>24 h</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>48 h</td>
<td>2</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

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**DISCUSSION**

*C. glabrata* is reported with increasing frequency as a cause of fungemia and invasive candidiasis. This species is the second most common yeast isolated as part of normal human flora [18, 19]. Its role as other than a commensal yeast has been noted primarily in the past 2 decades [20–23]. During the 8-year period of this study, *C. glabrata* caused 9%–29% of cases of fungemia each year. At some institutions, the rate of fungemia due to *C. glabrata* has remained unchanged from a decade ago [24, 25], but others have noted an impressive rise in fungemias due to *C. glabrata* [2, 5, 26]. In a 2-year period during 1993–1995, the National Epidemiology of Mycoses Survey found that, in a surgical ICU in New York, 41% of fungemias were due to *C. glabrata*, whereas similar units in Oregon and California had an 8% rate of fungemia due to *C. glabrata* [27]. Medical centers in Central America (and some medical centers in Europe) rarely isolate *C. glabrata* from blood cultures [16, 28]. Cancer centers have reported a shift away from *C. albicans* towards *C. glabrata* as a cause of fungemia [4, 6, 26, 29, 30]. This is presumed to be related to the use of fluconazole for prophylaxis in these high-risk patient populations. The association of fluconazole use with increasing isolation of *C. glabrata* is strongest for cancer centers [4, 6, 30] and is less strong but still present in some individual nonspecialty hospitals [8].

As we and others have noted previously—and as we have verified again in the current study—*C. glabrata* fungemia is seen more often in older adults [8, 9, 15, 31, 32] and is uncommonly found in neonates and young children [8, 9, 33]. Higher rates of oropharyngeal colonization with *C. glabrata* have been found in older adults than in others [18, 34], but whether this has any relationship to fungemia is not clear. Older adults not only had an increased risk of fungemia due to *C. glabrata* but also appeared to have an increased risk of dying from the event, as noted by others [31].

Few studies have focused on fungemia due to *C. glabrata* [21, 22, 29, 30]. The majority of studies are from cancer centers [22, 29, 30]; thus, risk factors and outcomes may differ greatly from what is noted in a general hospital setting. In our population, the most common risk factors for *C. glabrata* fungemia were use of broad-spectrum antibiotics, use of central venous catheters, receipt of parenteral nutrition, and stay in an ICU, which are results similar to those noted previously in the few studies from institutions similar to ours [20, 21]. Among cancer patients, *C. glabrata* has emerged most prominently in those with hematological malignancies and stem cell transplants, compared with those with solid tumors [22].

There is concern over an increase in azole resistance among strains of *C. glabrata* [12, 27, 35, 36]. However, we noted no increase in MIC values when isolates from this study (those from 1995–2002) were compared with isolates from non–HIV-infected individuals treated at our institution in the 1980s and early 1990s [37, 38]. During the 8-year period of this study, at our institution, no increase in resistance to the 3 azoles that were studied was noted. There also was no difference between the fluconazole susceptibilities of isolates recovered from patients who had received fluconazole treatment before fungemia and those of isolates recovered from patients who had not received fluconazole.

The mortality rate at 30 days was 29%, and at 90 days, it was 33%. Others have noted mortality rates of 39%–83% associated with *C. glabrata* fungemia [7, 9, 20–22, 31]. The highest mortality rate, 83%, occurred in the mid-1980s [20]. Later series that included a larger number of *C. glabrata* fungemias collected during 1990–1997 and 1995–1997 noted 30-day mortality rates of 49% and 39%, respectively [9, 21].

Outcomes appeared to be unrelated to the antifungal agent used to treat the fungemia. Success rate, measured by clearance of *C. glabrata* from the blood and by mortality, was similar when episodes treated with amphotericin B were compared with episodes treated with fluconazole. Similar results have been reported for *C. glabrata* fungemia in several multicenter treatment trials that enrolled a relatively small number of patients with fungemia due to *C. glabrata* [39, 40]. One study of a large number of patients from a cancer center compared outcomes of fungemia due to *C. glabrata* and fungemia due to *C. albicans* and also found no difference in the response to either amphotericin B or fluconazole therapy [22]. A meta-analysis of prospective treatment trials that compared fluconazole therapy with amphotericin B therapy was unable to establish significant differences in the response rates to these 2 agents in patients who had fungemia due to *C. glabrata* [41]. In our study, as in others, patients who were not treated with an antifungal agent had the highest mortality rate [9, 21].

In vitro susceptibilities to fluconazole did not appear to predict the response to therapy with that agent. These results do not differ from several previous observations in which outcomes did not correlate with results of in vitro susceptibility studies [42, 43]. In several studies, the best predictor for death from candidiasis was the APACHE score at the time of fungemia [9, 28, 44], emphasizing the fact that patients who have *C. glabrata* fungemia are often seriously ill and have multiple underlying conditions that are responsible for the high mortality rates.

Our data do not show enhanced survival following treatment with antifungal agents that have better in vitro activity against *C. glabrata*. In spite of this finding, we agree with the guidelines for treatment of candidiasis published by the Infectious Diseases Society of America, which state that there is stronger evidence for treating serious *C. glabrata* infections with amphotericin B or caspofungin than with fluconazole [45].

There are several limitations to our study. Most prominent is the retrospective nature of the data collected. There likely
were biases in the selection of the antifungal agents used for various patients. Sicker patients were perhaps more likely to have been given amphotericin B formulations, and a sizeable proportion of very sick patients received no therapy because of early death due to fungemia. Another limitation is that this is a single-center experience and thus may not be broadly applicable to other institutions. Unfortunately, this is true of all of the studies that have focused on fungemia due to C. glabrata. Finally, the small sample size when various subsets were assessed in regards to mortality precludes meaningful statistical analysis of many of these factors.

Acknowledgments

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