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Variation in Susceptibility of Bloodstream Isolates of *Candida glabrata* to Fluconazole According to Patient Age and Geographic Location in the United States in 2001 to 2007[▽]

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We examined the susceptibilities to fluconazole of 642 bloodstream infection (BSI) isolates of *Candida glabrata* and grouped the isolates by patient age and geographic location within the United States. Susceptibility of *C. glabrata* to fluconazole was lowest in the northeast region (46%) and was highest in the west (76%). The frequencies of isolation and of fluconazole resistance among *C. glabrata* BSI isolates were higher in the present study (years 2001 to 2007) than in a previous study conducted from 1992 to 2001. Whereas the frequency of *C. glabrata* increased with patient age, the rate of fluconazole resistance declined. The oldest age group (≥80 years) had the highest proportion of BSI isolates that were *C. glabrata* (32%) and the lowest rate of fluconazole resistance (5%).

Candidemia is without question the most important of the invasive mycoses (6, 33, 35, 61, 65, 68, 78, 86, 88). Treatment of candidemia over the past 20 years has been enhanced considerably by the introduction of fluconazole in 1990 (7, 10, 15, 28, 29, 31, 40, 56–58, 61, 86, 90). Because of its widespread usage, concern about the development of fluconazole resistance among *Candida* spp. abounds (2, 6, 14, 32, 47, 53, 55, 56, 59, 60, 62, 80, 86). Despite these concerns, fluconazole resistance is relatively uncommon among most species of *Candida* causing bloodstream infections (BSI) (5, 6, 22, 24, 33, 42, 54, 56, 65, 68, 71, 86). The exception to this statement is *Candida glabrata*, of which more than 10% of BSI isolates may be highly resistant (MIC ≥ 64 μg/ml) to fluconazole (6, 9, 15, 23, 30, 32, 36, 63–65, 71, 87, 91). Suboptimal fluconazole dosing practices (low dose [<400 mg/day] and poor indications) may lead to an increased frequency of isolation of *C. glabrata* as an etiological agent of candidemia in hospitalized patients (6, 17, 29, 32, 35, 41, 47, 55, 60, 68, 85) and to increased fluconazole (and other azole) resistance secondary to induction of CDR efflux pumps (2, 11, 13, 16, 43, 47, 50, 55, 69, 77, 83, 84) and may adversely affect the survival of treated patients (7, 10, 29, 40, 59, 90). Among the various *Candida* species, *C. glabrata* alone has increased as a cause of BSI in U.S. intensive care units since 1993 (89). Within the United States, the proportion of fungemias due to *C. glabrata* has been shown to vary from 11% to 37% across the different regions (west, midwest, northeast, and south) of the country (63, 65) and from <10% to >30% within single institutions over the course of several years (9, 48). It has been shown that the prevalence of *C. glabrata* as a cause of BSI is potentially related to many disparate factors in addition to fluconazole exposure, including geographic characteristics (3, 6, 63–65, 71, 88), patient age (5, 6, 25, 35, 41, 42, 48, 63, 82, 92), and other characteristics of the patient population studied (1, 32, 35, 51). Because *C. glabrata* is relatively resistant to fluconazole, the frequency with which it causes BSI has important implications for therapy (21, 29, 32, 40, 41, 45, 56, 57, 59, 80, 81, 86, 90).

Previously, we examined the susceptibilities to fluconazole of 559 BSI isolates of *C. glabrata* and grouped the isolates by patient age and geographic location within the United States over the time period from 1992 to 2001 (63). In the present study we build upon this experience and report the fluconazole susceptibilities of 642 BSI isolates of *C. glabrata* collected from sentinel surveillance sites throughout the United States for the time period from 2001 through 2007 and stratify the results by geographic region and patient age. The activities of voriconazole and the echinocandins against this contemporary collection of *C. glabrata* isolates are also reported.

MATERIALS AND METHODS

Organisms. Between 2001 and 2007, a total of 2,536 BSI isolates of *Candida* spp. from 24 sentinel surveillance sites in the United States were submitted to the University of Iowa College of Medicine (Iowa City, IA) for identification and antifungal susceptibility testing with fluconazole, voriconazole, anidulafungin, caspofungin, and micafungin. The isolates represent consecutive incident isolates from patients with candidemia treated at hospitals within the four major regions of the United States (Table 1). Patient ages were provided for 642 (89%) of the 718 BSI isolates of *C. glabrata*. These 642 isolates constitute the study set described herein.

All *C. glabrata* isolates were identified using Vitek and API products (bioMérieux, Dunham, NC), the results of which were supplemented by conventional methods as required, and stored as water suspensions until they were used. Prior to testing, each isolate was passaged on potato dextrose agar (Remel, Lenexa, KS) and CHROMagar (Becton Dickinson, Sparks, MD) to ensure purity and viability.

Susceptibility test methods. Fluconazole (Pfizer), voriconazole (Pfizer), anidulafungin (Pfizer), caspofungin (Merck), and micafungin (Astellas) were all obtained from their respective manufacturers as reagent grade powders. Broth microdilution testing was performed exactly as described in Clinical and Labo-

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TABLE 1. Temporal and geographic trends in the frequency of isolation and fluconazole resistance among BSI isolates of *C. glabrata* in the United States

Region	Time period	Total no. of *Candida* BSI isolates	% of *C. glabrata* isolates:	
			Among all isolates	Resistant to fluconazole
West	1992–2001[a]	700	17	7
	2001–2007	61	34	10
Midwest	1992–2001[a]	678	23	7
	2001–2007	1,420	28	12
Northeast	1992–2001[a]	819	21	11
	2001–2007	897	19	17
South	1992–2001[a]	1,486	15	11
	2001–2007	619	21	11
Total	1992–2001[a]	3,683	18	9
	2001–2007	2,536	25	14

[a] Data were compiled from Pfaller et al. (63).

ratory Standards (CLSI) document M27-A3 (19). The interpretive criteria for each agent were those published by Pfaller et al. (66, 67, 73) and in CLSI document M27-S3 (20): for fluconazole, an isolate for which the MIC is ≤8 μg/ml is susceptible, an isolate for which the MIC is 16 to 32 μg/ml is dose dependently susceptible, and an isolate for which the MIC is ≥64 μg/ml is resistant; for voriconazole, the corresponding MICs are ≤1 μg/ml (susceptibility), 2 μg/ml (dose-dependent susceptibility), and ≥4 μg/ml (resistance); and for anidulafungin, caspofungin, and micafungin, the corresponding MICs are ≤2 μg/ml (susceptible) and >2 μg/ml (nonsusceptible).

Quality control. Quality control was accomplished by testing the following strains on each day of testing: *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258 (20).

RESULTS AND DISCUSSION

Overall, *C. glabrata* accounted for 25% of all *Candida* sp. BSI isolates and was the second most common species isolated. The frequency of *C. glabrata* as a cause of candidemia in the United States ranged from 19% in the northeast to 34% in the west (Table 1). By comparison with our previous survey encompassing the years 1992 to 2001 (63), the proportion of *Candida* sp. BSI isolates that were *C. glabrata* increased in three of the four regions and decreased only slightly in the northeast (from 21% to 19%).

As seen in our previous survey, the fluconazole susceptibilities of *C. glabrata* BSI isolates varied by region (Table 1). Notably, the rates of fluconazole resistance among the *C. glabrata* isolates from 2001 to 2007 increased compared to those from 1992 to 2001 in all regions except for the south, where the rate was unchanged. Furthermore, the region with the highest prevalence of *C. glabrata* (west; 34%) had the lowest frequency of resistance (10%). Overall, 14% of the 2001 to 2007 U.S. *C. glabrata* isolates were resistant to fluconazole compared with only 9% in 1992 to 2001.

Given the increasing resistance to fluconazole among U.S. BSI isolates of *C. glabrata*, it is important to examine the activity of possible alternatives to fluconazole in the treatment of these infections. Voriconazole and the echinocandins are now available for the treatment of candidemia and other forms of invasive candidiasis (26, 56, 57, 61, 70–72, 86). All three echinocandins showed excellent activity against *C. glabrata* isolates from all four regions, with 99 to 100% of isolates susceptible at the CLSI breakpoint of ≤2 μg/ml (Table 2). Although 85% to 91% of isolates were susceptible to voriconazole (Table 2), it is notable that the region with the lowest susceptibility to fluconazole (northeast; 46%) also had the lowest susceptibility to voriconazole, a pattern consistent with previously demonstrated cross-resistance (70, 71).

Consistent with previous observations (25, 48, 63), very few

TABLE 2. Regional variation in susceptibility of BSI isolates of *C. glabrata* to azoles and echinocandins, 2001 to 2007

Region	Antifungal agent	No. tested	MIC (μg/ml)[a]			% of isolates that were[b]:	
			Range	50%	90%	S	R
West	Fluconazole	21	2–>128	8	16	76	10
	Voriconazole	21	0.06–8	0.25	0.5	91	5
	Caspofungin	21	0.03–0.12	0.03	0.06	100	0[c]
Midwest	Fluconazole	368	1–>128	8	64	61	12
	Voriconazole	368	0.015–8	0.25	2	90	7
	Anidulafungin	200	0.015–0.5	0.06	0.12	100	0[c]
	Caspofungin	345	0.015–4	0.03	0.06	99	0.3[c]
	Micafungin	178	0.007–0.12	0.015	0.015	100	0[c]
Northeast	Fluconazole	162	0.5–>128	16	128	46	17
	Voriconazole	161	0.015–>8	0.25	2	85	10
	Anidulafungin	78	0.015–0.25	0.06	0.12	100	0[c]
	Caspofungin	160	0.015–0.5	0.03	0.06	100	0[c]
	Micafungin	75	0.007–0.06	0.015	0.015	100	0[c]
South	Fluconazole	120	1–>128	8	64	54	11
	Voriconazole	120	0.007–8	0.25	2	89	11
	Anidulafungin	45	0.03–0.25	0.06	0.12	100	0[c]
	Caspofungin	118	0.015–0.5	0.03	0.25	100	0[c]
	Micafungin	29	0.007–0.25	0.015	0.03	100	0[c]

[a] 50% and 90%, MICs encompassing 50% and 90% of isolates tested, respectively.
[b] S, susceptible; R, resistant. Breakpoints are according to CLSI document M27-S3.
[c] Isolates for which echinocandin MICs exceed 2 μg/ml are considered nonsusceptible.

TABLE 3. Frequency of isolation and fluconazole resistance of BSI isolates of *C. glabrata* by patient age group

Patient age group (yrs)	Total no. of *Candida* BSI isolates (%[a])	No. of *C. glabrata* isolates tested (% of total)	% of *C. glabrata* isolates resistant to fluconazole
<1	21 (0.8)	1 (5)	0
1–9	103 (4.1)	4 (4)	25
10–19	70 (2.8)	6 (9)	33
20–29	128 (5.0)	25 (20)	28
30–39	184 (7.3)	32 (17)	22
40–49	372 (14.7)	80 (22)	23
50–59	483 (19.0)	146 (30)	14
60–69	481 (18.9)	141 (29)	9
70–79	449 (17.7)	128 (29)	8
>80	245 (9.7)	79 (32)	5
All ages	2,536 (100)	642 (25)	14

[a] % of total BSI isolates.

BSI due to *C. glabrata* in the pediatric and adolescent age groups (≤19 years) were reported (Table 3). Only 11 *C. glabrata* BSI isolates from patients who were ≤19 years of age were submitted. In contrast to the percentage of resistant isolates observed in 1992 to 2001 for isolates from this age group (7%) (63), 27% of the current isolates were resistant to fluconazole. This increased resistance may reflect the increased use of fluconazole prophylaxis and treatment in these groups of younger patients (12, 27, 49, 57, 58).

Whereas the proportion of BSI isolates of *Candida* that were *C. glabrata* increased with patient age, the rate of fluconazole resistance declined (Table 3). Thirty percent of *Candida* BSI in patients who were ≥60 years of age were due to *C. glabrata*; however, only 8% of the isolates were resistant to fluconazole compared to 18% of the isolates from patients 20 to 59 years of age (Table 3). The oldest age group (≥80 years) had the highest proportion of BSI isolates that were *C. glabrata* (32%) and the lowest rate of fluconazole resistance (5%).

These results confirm and extend the previous findings that we and others have reported concerning the increasing prevalence of *C. glabrata* as a cause of BSI in the United States both over time and as a function of patient age (1, 2, 25, 32, 33, 35, 37, 41, 47, 48, 55, 63, 68, 89). The variation in frequency of *C. glabrata* as a cause of BSI across clinical services has clearly been shown by Horn et al. (35) and by Hachem et al. (32). Horn et al. (35) found that patients with *C. glabrata* fungemia were more likely than other patients with candidemia to be older and to have received a solid organ transplant, whereas Hachem et al. (32) found that antifungal prophylaxis with fluconazole was a predisposing risk factor for *C. glabrata* BSI among cancer patients.

Important new findings in this survey are the apparent increase in fluconazole resistance among *C. glabrata* BSI isolates from pediatric and adolescent patients as well as the very low rate of fluconazole resistance among BSI isolates from older patients (Table 3). Although earlier studies of fluconazole prophylaxis in infant and pediatric patients have not shown emergence of fluconazole resistance, most were not conducted over a period long enough to demonstrate such a change (39).

Population-based studies have shown that the highest incidence of *Candida* BSI occurs at the extremes of age (3, 6, 8, 33, 37, 74, 82, 93). Older individuals are not only at high risk of *Candida* BSI and associated mortality but are also at higher risk of infection with *C. glabrata* (5, 6, 25, 30, 35, 41, 42, 48, 82). Importantly, in this study we show that, despite a high frequency of *C. glabrata* BSI, those isolates infecting the older patient age groups are considerably less likely to exhibit resistance to fluconazole (Table 3). This may reflect the fact that, although older individuals may have more frequent contact with the health care environment, they are less likely than younger individuals to undergo hematologic stem cell transplantation or solid organ transplantation and thus less likely to receive fluconazole prophylaxis (38). Furthermore, it is now apparent that colonization with *C. glabrata* is much more common among older individuals irrespective of exposure to the health care environment (34, 44, 46, 76, 77). Such colonization likely reflects a change in the ecology of *Candida* colonization with age rather than selection by drug exposure (44, 46, 75). Such colonizing strains are more likely to be fluconazole naive and thus less likely to have acquired resistance to fluconazole (69).

Perhaps one of the greatest values of surveys such as this is the demonstration of the continued and widespread emergence of this potentially azole-resistant species among patients of all age groups throughout the United States. Similar surveillance efforts should also be undertaken within individual institutions in order to provide knowledge of local epidemiological trends when selecting initial empirical therapy for *Candida* BSI (7, 21, 29, 56, 59, 80). Delays in administering effective antifungal therapy (right drug and right dose) directly influence mortality (28, 29, 52, 59), and such local epidemiological data provide the best way to optimize early initial antifungal therapy (21, 56, 59, 80). In an institution with high rates of infection from fluconazole-resistant *C. glabrata*, an echinocandin should be recommended as the initial treatment of choice (Table 2) (56–58, 80). In institutions that have lower rates of infection with *C. glabrata* or in patients for whom infection due to fluconazole-resistant *C. glabrata* is less likely, fluconazole may still be appropriate as initial therapy for patients who are not critically ill and do not have prior fluconazole exposure (56–58, 80). In such settings, however, it is important to pay strict attention to the appropriate utilization of fluconazole (10, 18, 29, 41, 59, 90).

Inappropriate antifungal therapy can occur due to omission of antifungal treatment, incorrect antifungal dosages, or administration of an antifungal agent to which the infecting organism was resistant (21, 29, 40, 41, 59, 85, 90). Previous Infectious Diseases Society of America (IDSA) guidelines recommend that, if fluconazole is used in the treatment of a *C. glabrata* BSI, a dose of 12 mg/kg of body weight/day (usually ≥800 mg/day) should be administered, while a dose of 6 mg/kg/day (usually 400 mg/day) is sufficient for *Candida albicans*, *C. parapsilosis*, and *Candida tropicalis* (57, 58). Unfortunately, fluconazole has been shown to be the antifungal agent that is most likely to be used inappropriately (either wrong dose or resistant organism) (28, 29, 41, 59). Garey et al. (29) have shown in a retrospective analysis that 78% of patients with *C. glabrata* BSI were treated with a dose of fluconazole less than that recommended by the IDSA. Likewise Klevay et al. (41) found that, in contrast to patients with *C. albicans* BSI, those

with *C. glabrata* infection were less likely to receive an adequate dose of fluconazole as empirical therapy (12% versus 52%; $P < 0.05$) and that time to receipt of adequate therapy was longer for patients infected with *C. glabrata* than for those infected with *C. albicans* ($P < 0.001$). Although Wilson et al. (90) found that fluconazole was a viable therapy for *C. glabrata* fungemia, they noted that higher doses of fluconazole (>400 mg/day) were more likely to achieve fungemia eradication than lower doses (≤400 mg/day) among patients who received only fluconazole (91% versus 50%, respectively [$P = 0.042$]). Finally, Sendid et al. (85) found that the emergence of *C. glabrata* as a cause of BSI in a French university hospital was linked to low-dose (50- to 100-mg/day) fluconazole usage, whereas the prevalence of *C. glabrata* decreased with an institutional shift to higher doses (>200 mg/day) of fluconazole concomitant with the introduction of voriconazole and caspofungin.

IDSA guidelines also suggest that, once *Candida* infection is confirmed, species level identification is in most cases an effective method for prediction of antifungal susceptibility (56–58). However, as shown in the present study, resistance to fluconazole among isolates of *C. glabrata* is not predictable, and therefore antifungal susceptibility testing is needed to ensure optimal antifungal treatment of *C. glabrata* BSI (7, 21, 29, 59). Indeed, several authors have now demonstrated the importance of the relationship between the daily dose of fluconazole and the in vitro susceptibility of the organisms to fluconazole as a predictor of therapeutic success or failure (4, 10, 18, 29). Baddley et al. (10) recently demonstrated that a fluconazole area under the concentration curve-to-MIC ratio of <11.5 or a MIC of ≥64 mg/ml was associated with increased mortality among patients with candidemia treated with fluconazole. Parkins et al. (59) reported that empirical therapy of candidemia with an adequate antifungal agent (isolate susceptible in vitro) was associated with a significant reduction in all-cause mortality (27% versus 46%; $P = 0.02$). Notably, empirical therapy with fluconazole was more likely to be deemed inadequate. Thus, both accurate and timely identification of *Candida* BSI isolates to species level and MIC testing may be more important than previously recognized in the successful management of candidemia (7).

The rising cost of novel antifungal agents, in conjunction with an increase in available therapies, increasing fluconazole resistance, local variation in the prevalence of *C. glabrata*, and growing evidence that inappropriate or delayed therapy increases mortality associated with candidemia, has made therapeutic decision making more complex, requiring more mycological data and clinical expertise (7). Given the variability in incidence and fluconazole resistance among *C. glabrata* isolates, the newly released IDSA guidelines recommend that patients with *C. glabrata* BSI be empirically treated with an echinocandin, with de-escalation to fluconazole only after the patient is stable and the organism is known to be susceptible (21, 45, 56–58, 79). Collins et al. (21) have shown that the timely use of fluconazole susceptibility testing of *C. glabrata* BSI isolates can facilitate de-escalation from a costly echinocandin to fluconazole, resulting in lower overall treatment costs in patients with documented *C. glabrata* fungemia. Increasingly, antifungal susceptibility testing appears to be a necessity in today's world of resistant organisms and expensive agents (21, 56–58, 79).

In summary, we provide further documentation of the emerging frequency of *C. glabrata* as a cause of BSI in patients of all ages throughout the United States. The variable frequencies of occurrence and resistance to fluconazole associated with this species underscore the need for both prompt identification and antifungal susceptibility testing of bloodstream isolates in order to optimize antifungal therapy. The overall decreased susceptibility of *C. glabrata* to fluconazole makes proper dosing of this agent essential to its optimal use in the treatment of *C. glabrata* and other candidal infections. Antifungal susceptibility testing can be used in an efficient and cost-effective manner in guiding de-escalation from costly echinocandins to fluconazole in the treatment of *C. glabrata* infections.

The relatively small number of isolates from certain regions and age groups limits this study. In addition we could not obtain complete data on several patient-related factors that might have influenced the risk of *C. glabrata* or the risk for fluconazole resistance (e.g., severity of illness, device use, underlying disease, and antifungal use). Regardless, the overall size of this collection of *C. glabrata* BSI isolates does provide useful descriptive information. Such information will continue to be useful as a basis for comparison for future studies regarding the prevalence and antifungal susceptibility of *C. glabrata* as a BSI pathogen in the United States.

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