

Prospective, Multicenter Surveillance Study of *Candida glabrata*: Fluconazole and Itraconazole Susceptibility Profiles in Bloodstream, Invasive, and Colonizing Strains and Differences between Isolates from Three Urban Teaching Hospitals in New York City (*Candida* Susceptibility Trends Study, 1998 to 1999)

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Since the 1990s, the substantial increase in the rate of *Candida glabrata* infections has become a serious problem. As most *C. glabrata* infections arise from the host's endogenous microflora, the present prospective, multicenter analysis included all clinical isolates associated with colonization and with systemic and hematogenous candidiasis. Among 347 *C. glabrata* isolates, the overall rates of resistance to fluconazole (MIC \geq 64 μ g/ml) and itraconazole (MIC \geq 1 μ g/ml) were 10.7 and 15.2%, respectively, although for half ($n = 148$) of the itraconazole-susceptible isolates the MICs (0.25 to 0.5 μ g/ml) were in the susceptible—dependent upon dose range. Fluconazole resistance was more common among *C. glabrata* isolates obtained from centers caring for patients with cancer (MICs at which 90% of isolates are inhibited [MIC_{90s}] = 32 μ g/ml) or AIDS (MIC_{90s} > 64 μ g/ml) than among *C. glabrata* isolates from a community-based university medical center (MIC_{90s} = 16 μ g/ml) ($P = 0.001$). Thirty-three bloodstream isolates and those obtained from other body sites had similar in vitro susceptibility profiles. The fluconazole MIC_{90s} (\leq 16 μ g/ml) for *C. glabrata* yeast isolates from the gastrointestinal tract were lower than those (\geq 64 μ g/ml) for *C. glabrata* isolates from respiratory and urinary tract samples ($P = 0.01$). A similar discrepancy for itraconazole was not significant ($P > 0.5$). We did not observe differences in fluconazole or itraconazole susceptibility profiles among *C. glabrata* isolates associated with either hematogenous dissemination or colonization. The significant discrepancy in antifungal susceptibility among *C. glabrata* organisms isolated from hospitals in the same geographic region emphasizes the significance of periodic susceptibility surveillance programs for individual institutions, especially those providing care to patients at risk.

Rates of systemic infections due to *Candida* species have steadily increased over the past four decades, and such infections represent an important cause of morbidity for severely ill hospitalized patients (4, 9, 21, 24, 31). This rise in the rate of fungal infections is exacerbated by the increasing population of immunocompromised patients such as those with AIDS or cancer (1, 2, 8, 10, 21, 31, 33). In recent years, increases in the prevalences of *Candida glabrata* isolates with reduced susceptibilities to triazole antifungals and *Candida krusei*, which is intrinsically resistant to fluconazole and itraconazole, have heightened concerns regarding the empirical use of triazole-based drugs, especially in patients at risk of systemic invasion (1, 2, 13, 17, 28, 30a, 31, 33–35).

Surveillance studies have indicated the importance of knowing geographic variations in the distributions of *Candida* species and differences in the prevalence of triazole resistance among clinical isolates of *Candida albicans* (3, 18–20). The va-

riations in the rates of antifungal susceptibility among *C. glabrata* isolates from patients at hospitals within a geographic area are not known, however. In addition, since systemic *C. glabrata* yeast infections frequently arise from the host's endogenous microflora, mainly that in the orointestinal and genitourinary tracts (21, 25, 26), we thought that it was important to assess the antifungal susceptibility profiles of both colonizing *C. glabrata* strains and those associated with systemic disease. During a 12-month period, *C. glabrata* organisms isolated from patients receiving treatment at three urban teaching hospitals in New York City were evaluated prospectively.

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Study design. All clinical isolates that were submitted to the mycology laboratories at Memorial Sloan-Kettering Cancer Center (center I), New York Weill Cornell Medical Center (center II), and Beth Israel Medical Center (center III) in New York City were screened for *C. glabrata* from 1 November 1998 to 31 October 1999. All clinical isolates of *C. glabrata* recov-

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ered during the 12-month period were included in this study. More than one isolate from a single patient was included if different *C. glabrata* strains were identified or specimens were obtained from separate body sites. All specimens were initially processed at the microbiology laboratories of centers I, II, and III. Reconfirmation of species (under code) and determination of susceptibility to a panel of antifungal agents were conducted by the New York State Department of Health Mycology Laboratory. All molecular genotyping (data not shown) was carried out at The Public Health Research Institute, New York, N.Y., by methods described in previous reports (27).

C. glabrata identification. Identification of organisms as *Candida* species and species determination were performed by previously described methods (26). Five to 10 colonies were obtained from the primary culture and transported on Trypticase agar slants (Becton Dickinson Microbiology Systems, Cockeysville, Md.) to a central laboratory for species reidentification and antifungal susceptibility testing (under code).

Antifungal susceptibility. All samples positive for *Candida* isolates were maintained on Sabouraud dextrose agar plates (Becton Dickinson Microbiology Systems) at ambient temperature. A broth microdilution method was performed according to the proposed guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) (15). Antifungal drugs (amphotericin B, flucytosine, ketoconazole, fluconazole, and itraconazole) were obtained from their respective manufacturers. Quality control was performed by testing designated strains from the American Type Culture Collection. The interpretive criteria for susceptibility and the breakpoints used for the antifungal drugs were those described by the NCCLS (15).

Antifungal prophylaxis. Prophylactic fluconazole was routinely given to patients undergoing bone marrow transplantation or those receiving treatment for lymphoreticular malignancy (center I). Patients with AIDS at center III received fluconazole for extended periods for recurrent oropharyngeal candidiasis and/or following *Cryptococcus neoformans* infection. Triazole-derived drugs were not routinely used to prevent invasive mycosis in nonimmunosuppressed patients receiving treatment in medical or surgical critical care units at center II.

Statistical analysis. The association between categorical variables was determined by the chi-square test. A two-sided *P* value of less than 0.05 was considered statistically significant.

Isolates. During the 12 months of the study, 347 *C. glabrata* isolates were obtained from three urban teaching medical centers in New York City. Thirty-three (9.5%) were bloodstream isolates (50% were taken from an indwelling central venous catheter), and 314 were obtained from other body sites (Table 1). Among the nonbloodstream *C. glabrata* isolates, 121 (38.5%) were recovered from urine, 45 (14.3%) were recovered from bronchial wash or lavage specimens, 29 (9.2%) were recovered from sputum, 21 (6.7%) were recovered from oropharyngeal specimens, 19 (6.1%) were recovered from deep wounds, 17 (5.4%) were recovered from intra-abdominal infections, and 17 (5.4%) were isolated from stool specimens from patients with a paucity or absence of normal bacterial flora (Table 1).

The overall MIC ranges, the MICs at which 50% of isolates are inhibited (MIC₅₀s), and the MIC₉₀s for 347 *C. glabrata* isolates are presented in Table 2. The MIC₅₀s of fluconazole and itraconazole were 4.0 and 0.25 µg/ml, respectively. Rates

TABLE 1. Characteristics of 314 non-blood *C. glabrata* isolates recovered during 1998 and 1999

Source of specimens	No. (%) of isolates
Genitourinary tract.....	125 (39.8)
Urine.....	121
Catheterized.....	62
Voided.....	53
Nephrostomy.....	5
Ureter.....	1
Vagina.....	4
Respiratory tract.....	9 (29)
Bronchus.....	45
Bronchial wash.....	35
Bronchoalveolar lavage.....	10
Sputum.....	29
Tracheal aspirate.....	4
Lung.....	6
Postmortem.....	3
Pleura.....	7
fluid.....	6
Biopsy specimen.....	1
Gastrointestinal tract.....	46 (14.6)
Stool.....	17
Intra-abdominal.....	17
Abscess.....	10
Drains.....	4
Deep wound.....	3
Peritoneal fluid.....	8
Pelvis.....	2
Colon biopsy specimen.....	1
Bile.....	1
Head and neck.....	24 (7.6)
Oropharynx.....	21
Ear.....	2
Nose.....	1
Others.....	28 (8.9)
Deep wounds.....	19
Abscesses.....	4
Tissue biopsy.....	3
Cyst.....	1
Central venous catheter tip.....	1

of resistance to fluconazole (MIC ≥ 64 µg/ml) and itraconazole (MIC ≥ 1 µg/ml) were 10.7% (*n* = 37) and 15.2% (*n* = 53), respectively. Among susceptible isolates, 9.8% were susceptible—dependent upon dose (S-DD) to fluconazole (MICs = 16.0 to 32.0 µg/ml), whereas half (*n* = 148) of the itracon-

TABLE 2. Antifungal susceptibility profiles for clinical *C. glabrata* isolates

Characteristic	No. of isolates	MIC range or MIC ₅₀ /MIC ₉₀ (μg/ml)				
		Fluconazole	Itraconazole	Ketoconazole	Flucytosine	Amphotericin B
MIC range	347	0.06–>64.0	0.03–>16.0	0.03–4.0	0.03–16.0	0.12–2.0
Total isolates	347	4.0/32.0	0.25/1.0	0.12/1.0	0.06/0.12	0.5/1.0
Center I	168	4.0/32.0	0.25/1.0	0.12/0.5	0.06/0.12	0.5/1.0
Center II	121	4.0/16.0	0.25/1.0	0.5/0.5	0.06/0.12	0.5/1.0
Center III	58	8.0/>64.0	0.5/4.0	0.5/2.0	0.12/0.25	1.0/1.0
Blood	33	4.0/32.0	0.5/1.0	0.25/0.5	0.12/0.25	0.5/1.0
Other body sites	314	4.0/32.0	0.25/1.0	0.12/1.0	0.06/0.12	0.5/1.0
Respiratory tract ^a	113	4.0/>64.0	0.25/>1.0	0.12/1.0	0.06/0.12	0.5/1.0
Urinary tract	121	8.0/>64.0	0.25/>1.0	0.12/1.0	0.06/0.12	0.5/1.0
Gastrointestinal tract	46	4.0/8.0	0.25/0.5	0.12/0.25	0.06/0.12	0.5/1.0

^a Respiratory tract includes 21 oropharyngeal isolates, 1 nasal culture isolate, and isolates from the 91 respiratory tract specimens indicated in Table 1.

azole-susceptible *C. glabrata* isolates were S-DD (MICs = 0.25 to 0.5 μg/ml) (Fig. 1). The amphotericin B MIC₅₀ and MIC₉₀ were 0.5 and 1.0 μg/ml, respectively. A significant difference was observed in the profiles of susceptibility to azole-derived agents of the *C. glabrata* isolates from the patients at the three hospitals. *C. glabrata* isolates from center I had drug resistance profiles similar to those of the *C. glabrata* isolated from patients receiving care at center II. In contrast, 58 isolates from center III showed significantly higher rates of resistance to fluconazole (MIC₉₀s > 64 μg/ml) and itraconazole (MIC₉₀s = 4.0 μg/ml) ($P = 0.001$).

The profiles of susceptibility to a panel of five antifungals among *C. glabrata* isolates obtained from various body sites were compared (Table 2). Four (1.2%) individual isolates from an abdominal abscess, a patient with polymicrobial peritonitis,

an oropharyngeal specimen, and a stool specimen showed in vitro resistance to amphotericin B. The susceptibilities of the *C. glabrata* isolates to ketoconazole varied, with the MIC₅₀s ranging from 0.12 to 0.25 and the MIC₉₀s ranging from 0.25 to 1.0 μg/ml. The amphotericin B MIC₅₀ (0.5 μg/ml) and MIC₉₀ (1.0 μg/ml) were identical for *C. glabrata* organisms isolated from blood, other sites of systemic infection, and patients who were colonized. The profiles of susceptibility to triazole-derived antifungal drugs among isolates from the bloodstream and other body sites showed no differences: fluconazole MIC₅₀, 4.0 μg/ml; itraconazole MIC₅₀, 0.25 to 0.5 μg/ml; fluconazole MIC₉₀, 32.0 μg/ml; itraconazole MIC₉₀, 1.0 μg/ml. The MIC₉₀ of fluconazole was significantly different for respiratory tract (>64 μg/ml) and urinary tract (>64.0 μg/ml) isolates compared with those for gastrointestinal tract (≤8.0 μg/

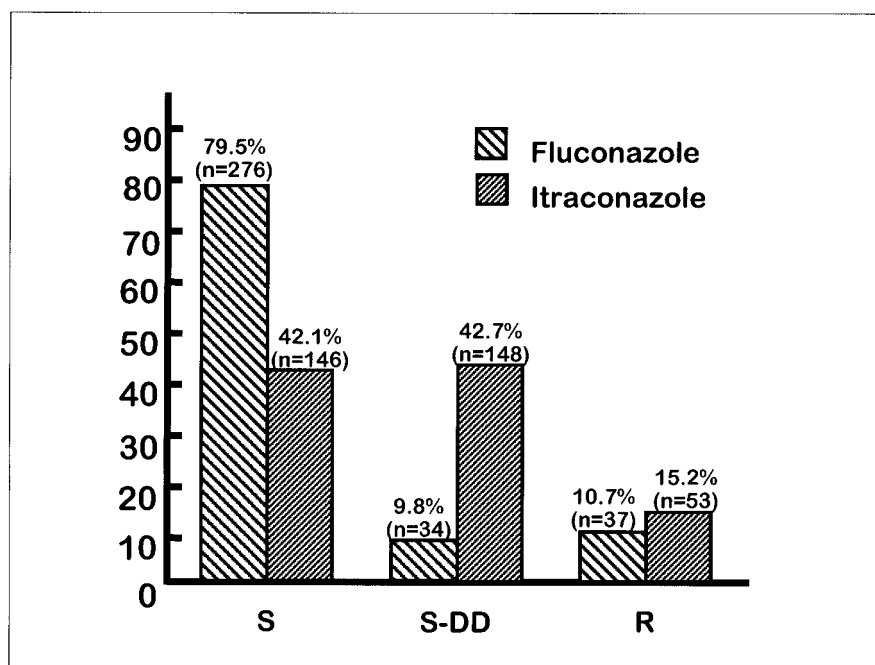


FIG. 1. Distribution of percentage of *C. glabrata* isolates susceptible to triazole-derived antifungals among 347 clinical isolates. The abbreviations (MIC breakpoints) used are as follows: for fluconazole, S, susceptible (MIC ≤ 8.0 μg/ml); S-DD, susceptible—dependent upon dose (MICs = 16.0 to 32.0 μg/ml); and R, resistant (MIC ≥ 64.0 μg/ml); for itraconazole, S, susceptible (MIC ≤ 0.125 μg/ml); S-DD, susceptible—dependent upon dose (MICs = 0.25 to 0.5 μg/ml); and R, resistant (MIC ≥ 1.0 μg/ml).

ml) isolates ($P = 0.01$). Similar differences in the itraconazole susceptibility profiles were not significant ($P > 0.5$) (Table 2).

Since 1990, with the introduction of fluconazole in the United States, a decline in the prevalence of *C. albicans* infections has occurred, with *C. albicans* accounting for just over 50% of all yeast isolates from blood during the last decade (2, 4, 16, 18–20, 26). Among the non-*C. albicans* group of *Candida* organisms, however, a change has also been recognized, as *C. glabrata* has emerged as the most common species other than *C. albicans* in fungemic patients from North America (18, 30a). Patients with cancer are at increased risk of systemic candidiasis (24), and we have recently reported that nearly half of non-*C. albicans* *Candida* isolates in this group of patients are *C. glabrata* (46%) (26). Similar trends have emerged from multicenter studies of patients with fungemia in the United States (18). *Candida* species other than *C. albicans* were identified in 45% of patients with hematogenous candidiasis from 1997 to 1998 in a study that included 32 medical centers nationwide; of these, *C. glabrata* was the most common (18). This *Candida* species distribution was echoed in the results of the Surveillance and Control of Pathogens of Epidemiologic Importance surveillance program, conducted by the same group (18), that included 50 medical centers throughout the United States evaluated during 1995 and 1996.

The emergence of *C. glabrata* as the principal non-*C. albicans* species was not surprising given its ability to develop resistance to azole-based drugs and expand under the selection pressure provided by the common use of fluconazole and itraconazole (11, 12, 23, 28, 30, 31, 32, 35) for prophylaxis, preemptive therapy, and empirical therapy, discriminately or indiscriminately, in high-risk settings. Alternatively, this rise in the rate of occurrence of *C. glabrata* infections may be related to its ability to rapidly acquire drug resistance due to the haploid nature of the microorganism and its ability to mutate rapidly following exposure to triazole-derived agents (6). However, prior antifungal exposure may not be necessary for the development of de novo resistance in clinical isolates of *C. glabrata* (33). This was supported by a prospective epidemiological analysis of triazole resistance in *C. glabrata*. We observed no genetic evidence of either clustering or the presence of a single dominant resistant strain in hospitalized patients with cancer (27).

The present study was an extension of the *Candida* Susceptibility Trends (CST) study (26) and aimed to provide an understanding of the prevalence of fluconazole and itraconazole resistance among *C. glabrata* isolates in patients at teaching hospitals in New York City during 1998 and 1999. Reports from medical centers caring for human immunodeficiency virus (HIV)-seropositive patients during the past two decades have shown an increasing prevalence of recalcitrant oropharyngeal and vaginal candidiasis that for the most part has resulted from antimicrobial agent-resistant *Candida* species, including *C. glabrata* (5, 7, 8, 29). The high frequencies of in vitro resistance to fluconazole ($MIC_{90S} > 64.0 \mu\text{g/ml}$) and itraconazole ($MIC_{90S} = 4.0 \mu\text{g/ml}$) among *C. glabrata* organisms isolated from patients at a hospital with a substantial population of HIV-infected individuals (center III) were significant in our study ($P < 0.001$) (Table 2). In contrast, rates of triazole-derived antifungal resistance were minimal among isolates from patients at a community-based university medical

center (center II; fluconazole $MIC_{90S} = 16.0 \mu\text{g/ml}$), and while they were less susceptible (fluconazole $MIC_{90S} = 32.0 \mu\text{g/ml}$), *C. glabrata* isolates were obtained from patients at a comprehensive care cancer center (center I) (Table 2).

The overall rates of resistance of *C. glabrata* isolates to fluconazole (10.7%) and itraconazole (15.2%) were comparable (Fig. 1). However, a marked distinction was noticed within the susceptible yeast population. For nearly 80% ($n = 276$) of all fluconazole-susceptible *C. glabrata* isolates, the fluconazole MIC was $\leq 8.0 \mu\text{g/ml}$. However, the MICs of itraconazole for a vast majority of isolates ($n = 148$) were higher (0.25 to 0.5 $\mu\text{g/ml}$) and the isolates are considered S-DD for mucosal candidiasis, as recommended by the Subcommittee on Antifungal Susceptibility Testing of the NCCLS (22). This observation may be significant in determining strategies for the treatment of systemic mycoses due to *C. glabrata*, and even for infections caused by triazole-susceptible isolates, therapy with oral itraconazole must be approached with caution.

The proportion of resistant yeast isolates may change in relation to the site of colonization. There has been a concern that susceptible *C. glabrata* isolates are more likely to be associated with bloodstream invasion, in contrast to yeast colonization of the respiratory, orointestinal, and genitourinary tracts. We observed no difference in the fluconazole susceptibilities among 33 blood-borne *C. glabrata* isolates ($MIC_{90S} = 32.0 \mu\text{g/ml}$) compared with those isolated from other body sites ($MIC_{90S} = 32.0 \mu\text{g/ml}$) (Table 2). Interestingly, the MIC_{90S} for *C. glabrata* isolates from 46 gastrointestinal tract specimens were lower (8.0 $\mu\text{g/ml}$) than those for isolates from the respiratory tract ($n = 113$) and the urinary tract ($n = 121$) ($MIC_{90S} > 64 \mu\text{g/ml}$) (Table 2). This observation was statistically significant ($P < 0.01$). The potential of yeasts associated with candiduria to cause disease in asymptomatic nonimmunocompromised patients remains unclear. The proportions of *C. glabrata* isolates have increased not only among fungemic isolates and/or isolates that cause mucocutaneous candidiasis in immunocompromised individuals but also among yeasts isolated from urine specimens (14). The clinical relevance of candiduria in asymptomatic immunocompromised individuals is uncertain, and only a small minority (1.3%) of such individuals have developed hematogenous dissemination in this setting (14).

In conclusion, our observation that the prevalence of azole resistance in clinical *C. glabrata* isolates may be stratified according to the patient population and sites of infection or colonization may provide critical information in the development of prophylactic and therapeutic guidelines. Due to increasing MICs (S-DD), itraconazole must be used with caution for the treatment of invasive candidiasis due to *C. glabrata*. Centers caring for patients with HIV infection and/or with an underlying malignancy may have higher frequencies of fluconazole- and itraconazole-resistant *C. glabrata* strains associated with either colonization or invasive disease. Periodic analysis is critical in determining the rapidly evolving susceptibility trends among *Candida* species, especially at centers caring for patients at risk.

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