Epidemiology of Candidemia: 3-Year Results from the Emerging Infections and the Epidemiology of Iowa Organisms Study

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Bloodstream infections due to *Candida* species cause significant morbidity and mortality. Surveillance for candidemia is necessary to detect trends in species distribution and antifungal resistance. We performed prospective surveillance for candidemia at 16 hospitals in the State of Iowa from 1 July 1998 through 30 June 2001. Using U.S. Census Bureau and Iowa Hospital Association data to estimate a population denominator, we calculated the annual incidence of candidemia in Iowa to be 6.0 per 100,000 of population. *Candida albicans* was the most common species detected, but 43% of candidemias were due to species other than *C. albicans*. Overall, only 3% of *Candida* species were resistant to fluconazole. However, *Candida glabrata* was the most commonly isolated species other than *C. albicans* and demonstrated some resistance to azoles (fluconazole MIC at which 90% of the isolates tested are inhibited, 32 µg/ml; 10% resistant, 10% susceptible dose dependent). *C. glabrata* was more commonly isolated from older patients ($P = 0.02$) and caused over 25% of candidemias among persons 65 years of age or older. The investigational triazoles posaconazole, ravuconazole, and voriconazole had excellent in vitro activity overall against *Candida* species. *C. albicans* is the most important cause of candidemia and remains highly susceptible to available antifungal agents. However, *C. glabrata* has emerged as an important and potentially antifungal resistant cause of candidemia, particularly among the elderly.

Candida bloodstream infections cause significant morbidity and mortality (8, 20), and *Candida* species are now the fourth most common cause of hospital-acquired bloodstream infection in the United States (5). *Candida albicans* is the most common cause of candidemia, and in general has remained susceptible in vitro to both amphotericin B and fluconazole (11, 12). As the use of fluconazole increases (1), however, it is important to monitor for any increase in azole resistance among bloodstream isolates of *C. albicans* or any increase in frequency of bloodstream infection due to *Candida* species other than *C. albicans*, which have a higher incidence of in vitro azole resistance (e.g., *C. glabrata* and *Candida krusei*) (3).

Surveillance studies have provided important information about the epidemiology of candidemia, including Centers for Disease Control and Prevention (CDC) population-based surveillance (8), the National Epidemiology of Mycoses Survey (NEMIS) (2, 13, 15, 18), the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) study (5), and the SENTRY program (4, 11, 12). These studies often are done in large tertiary care hospitals and/or urban areas. We present data from the first statewide, longitudinal surveillance study of bloodstream infections caused by *Candida* species.

The Emerging Infections and the Epidemiology of Iowa Organisms (EIEIO) surveillance program was begun in July 1998 to monitor trends in antimicrobial resistance in the State of Iowa. As part of this study, we conducted prospective sur-

veillance for candidemia at 16 hospitals. The hospitals participating in EIEIO were selected based upon geographic region and size, in order to evaluate isolates from all regions and hospital sizes and types (e.g., rural, rural referral, and urban) (7). Our surveillance program can, therefore, provide insight into the incidence, species distribution, and antifungal susceptibility of *Candida* species causing bloodstream infections in a rural state.

MATERIALS AND METHODS

Surveillance. The EIEIO surveillance network included 15 laboratories representing 17 medical centers distributed throughout the State of Iowa. Fourteen of these participating laboratories, representing 16 medical centers, submitted consecutive unique patient blood culture isolates of *Candida* species. Duplicate patient isolates were not accepted. All isolates were saved on agar slants and were sent to the University of Iowa College of Medicine (Iowa City) for storage and further characterization by reference identification and susceptibility testing methods. All isolates of *Candida* species causing bloodstream infection at these 16 medical centers during the 3-year period from 1 July 1998 to 30 June 2001 were evaluated.

Organism identification. All *Candida* species blood culture isolates were identified at the participating institution by the routine methodology in use at each laboratory. Upon receipt at the University of Iowa, the isolates were subcultured onto potato dextrose agar not containing antibiotics (Remel, Lenexa, Kans.) and CHROMagar *Candida* medium (Hardy Laboratories, Santa Maria, Calif.) to ensure viability and purity. All green colonies on CHROMagar were presumptively identified as *C. albicans* after screening by differential growth at 35 and 43°C for *Candida dubliniensis* (6). Other *Candida* species identifications were confirmed with the Vitek YBC system (bioMérieux, St. Louis, Mo.). Isolates were stored as suspensions in sterile distilled water at ambient temperature prior to susceptibility testing, which was performed within 2 weeks of receipt of all isolates.

Susceptibility testing. Antifungal susceptibility testing was performed by the reference broth microdilution method exactly as described by the National Committee for Clinical Laboratory Standards (NCCLS) document M27-A (10). Ref-

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TABLE 1. Characteristics of patients with candidemia in the EIEIO program, 1 July 1998 to 30 June 2001

Characteristic	n (%)
Age (yr)	
<1.....	24 (9)
1–18.....	15 (6)
19–49.....	43 (17)
50–64.....	53 (21)
>64.....	117 (46)
Gender	
Male.....	149 (59)
Female.....	105 (41)
Location at time of candidemia:	
Intensive care unit.....	101 (40)
General ward.....	142 (56)
Outpatient setting.....	10 (4)

erence powders of amphotericin B (Sigma), flucytosine (5-FC; Sigma), fluconazole (Pfizer), voriconazole (Pfizer), itraconazole (Janssen), posaconazole (Schering Plough), and ravuconazole (Bristol Myers Squibb) were obtained from their respective manufacturers. Serial twofold dilutions were prepared as outlined in the NCCLS document (10) and final dilutions were made in RPMI 1640 medium buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (Sigma). Aliquots (0.1 ml) of each antifungal agent at a 2× final concentration were dispensed into the wells of plastic microdilution trays with a Quick Spense II system (Dynatech Laboratories, Chantilly, Va.). The trays were sealed and frozen at –70°C until needed.

Prior to testing, each isolate was passaged at least twice on potato dextrose agar (Remel) to ensure optimal growth characteristics. A 0.1-ml yeast inoculum (concentration of 0.5×10^3 to 2.5×10^3 cells/ml) was added to each well of the microdilution trays. The trays were incubated in air at 35°C, and MIC endpoints were read after 48 h of incubation. Drug- and yeast-free controls were included on each tray. Following incubation, the broth microdilution trays were examined with a reading mirror, and the growth in each well was compared with that in the growth control well. The MIC of amphotericin B was defined as the lowest concentration resulting in 100% growth inhibition compared with the growth control. The MICs of each triazole and of 5-FC were defined as the lowest concentrations resulting in a prominent inhibition of growth (~50%) compared with the growth control (10). The data reported represent concentrations of each antifungal agent necessary to inhibit 50% (MIC₅₀) and 90% (MIC₉₀) of the isolates tested. The interpretive susceptibility criteria for fluconazole, itraconazole, and 5-FC were those published by Rex et al. (16) and the NCCLS (10).

Quality control was performed by testing *Candida parapsilosis* ATCC 22091 and *C. krusei* ATCC 6258.

Statistical analyses. The Chi-square test for trend was used to test for changes in the incidence of candidemia by year of surveillance and in the species distribution by patient age. Alpha was set at 0.05, and all reported *P* values are two tailed.

Crude overall incidence rates were calculated with U.S. Bureau of Census and Iowa Hospital Association data (7). The 16 EIEIO hospitals accounted for 47.9% of all acute care discharges in the State of Iowa in CY2000. Assuming that the distribution of geographic region and hospital size was representative, we estimated the population denominator to be the same fraction of the total population of the State of Iowa in CY2000 for the purpose of estimating incidence rates.

RESULTS

A total of 254 bloodstream infections caused by *Candida* species were identified by EIEIO centers during the study period. Most candidemias occurred in adults older than 50 years of age (67%) (Table 1). More candidemias occurred among males (59%) than females and among patients hospitalized on general wards than in intensive care units (Table 1).

C. albicans (*n* = 148 [58%]) and *C. glabrata* (*n* = 51, 20%) were the most common species causing candidemia during the study period (Table 2). The proportion of *Candida* species other than *C. albicans* causing bloodstream infection did not change over time (data not shown). Two age-related trends

TABLE 2. Species distribution of *Candida* bloodstream isolates in the EIEIO program, 1998 to 2001

Species	n (%)
<i>C. albicans</i>	148 (58)
<i>C. glabrata</i>	51 (20)
<i>C. tropicalis</i>	28 (11)
<i>C. parapsilosis</i>	17 (7)
<i>C. krusei</i>	5 (2)
Other <i>Candida</i> spp. ^a	5 (2)

^a Includes two *C. lusitanae* and two *C. kefyr* isolates and *C. famata* one isolate.

were noted: (i) the percentage of candidemias caused by *C. parapsilosis* trended higher among infants less than 1 year of age (17%) than among all other age groups (6%, *P* = 0.06), and (ii) the percentage of candidemias caused by *C. glabrata* increased steadily with patient age (see Fig. 1 [*P* = 0.02] for trend).

Based upon our estimated surveillance population, the mean annual incidence of candidemia was 6.0 per 100,000 of population. The incidence increased annually from 5.6 (1 July 1998 to 30 June 1999) to 5.9 (1 July 1999 to 30 June 2000) to 6.8 (1 July 2000 to 30 June 2001) per 100,000, but the change in incidence over time did not reach statistical significance.

Table 3 summarizes the in vitro susceptibility test results of these 254 *Candida* bloodstream isolates. Overall, the fluconazole resistance rate was low; three percent of all *Candida* species isolates were fluconazole resistant, with no fluconazole resistance detected among isolates of *C. albicans*, *C. parapsilosis*, or *Candida tropicalis*. Of 51 *C. glabrata* bloodstream isolates tested, 10% were fluconazole resistant (MIC, ≥64 µg/ml), and 10% were fluconazole susceptible dose dependent (MIC, 16 to 32 µg/ml). Itraconazole resistance was observed for 11% of all *Candida* isolates tested and was also highest among *C. glabrata* (53% resistant). For each species of *Candida* tested, the MIC₅₀s and MIC₉₀s for ravuconazole, posaconazole, and voriconazole were two- to fourfold lower than for itraconazole. Each of these investigational triazoles inhibited 98 to 99% of all *Candida* isolates tested at a MIC of ≤1 µg/ml, compared to 95% of isolates inhibited by itraconazole at a MIC of ≤1 µg/ml. Most *Candida* (87%) clustered at the amphotericin B MIC of 1 µg/ml—for only seven isolates (3%) were MICs of amphotericin B 2 µg/ml, including three of the five *C. krusei* isolates.

FIG. 1. Percentage of all candidemias due to *Candida glabrata* in each age group. *P* = 0.02 for trend of increased frequency of *C. glabrata* with increasing age.

TABLE 3. In vitro susceptibilities of bloodstream *Candida* spp. isolates in the EIEIO program, July 1998 to June 2001

Species (no. of isolates tested)	Antifungal agent	MIC ($\mu\text{g/ml}$) ^a			% Resistant ^b
		Range	50%	90%	
All <i>Candida</i> species (254)	Amphotericin B	0.25–2.0	1.0	1.0	
	5-FC	0.06–>128.0	0.12	1.0	3.6
	Fluconazole	0.12–128.0	0.25	8.0	2.8
	Itraconazole	0.007–>8.0	0.06	1.0	11.0
	Posaconazole	0.007–>8.0	0.03	0.5	
	Ravuconazole	0.007–8.0	0.007	0.25	
	Voriconazole	0.007–8.0	0.007	0.25	
<i>C. albicans</i> (148)	Amphotericin B	0.25–1.0	1.0	1.0	
	5-FC	0.06–>128.0	0.25	1.0	2.7
	Fluconazole	0.12–2.0	0.25	0.5	0
	Itraconazole	0.007–0.25	0.03	0.06	0
	Posaconazole	0.007–0.12	0.015	0.06	
	Ravuconazole	0.007–0.06	0.007	0.015	
	Voriconazole	0.007–0.25	0.007	0.015	
<i>C. glabrata</i> (51)	Amphotericin B	0.25–1.0	1.0	1.0	
	5-FC	0.06–16.0	0.12	0.12	0
	Fluconazole	1–28.0	8.0	32.0	9.8
	Itraconazole	0.06–>8.0	1.0	2.0	52.9
	Posaconazole	0.06–>8.0	0.5	1.0	
	Ravuconazole	0.03–8.0	0.25	1.0	
	Voriconazole	0.03–8.0	0.12	1.0	
<i>C. tropicalis</i> (28)	Amphotericin B	0.5–1.0	1.0	1.0	
	5-FC	0.06–>128.0	0.25	16.0	7.1
	Fluconazole	0.25–2.0	0.5	2.0	0
	Itraconazole	0.015–1.0	0.12	0.25	3.6
	Posaconazole	0.015–0.25	0.06	0.12	
	Ravuconazole	0.007–0.25	0.03	0.12	
	Voriconazole	0.007–0.12	0.03	0.06	
<i>C. parapsilosis</i> (17)	Amphotericin B	1.0–2.0	1.0	2.0	
	5-FC	0.06–0.25	0.12	0.25	0
	Fluconazole	0.25–1.0	0.5	1.0	0
	Itraconazole	0.015–0.25	0.12	0.25	0
	Posaconazole	0.015–0.12	0.06	0.12	
	Ravuconazole	0.007–0.03	0.015	0.03	
	Voriconazole	0.007–0.03	0.015	0.03	

^a 50% and 90%, MIC₅₀ and MIC₉₀, respectively.^b Percent resistant according to NCCLS breakpoints (10).

DISCUSSION

Candida albicans is the most common cause of candidemia, accounting for 58% of candidemias in Iowa hospitals surveyed. This is slightly higher than the 52 to 54% reported from surveillance studies performed in the U.S. by CDC (8), NEMIS (13), SCOPE (5) and SENTRY (11). Furthermore, our study suggests that antifungal resistance has not emerged among bloodstream isolates of *C. albicans* in Iowa, even with the widespread use of fluconazole. All of the *C. albicans* bloodstream isolates collected during this 3-year surveillance study were inhibited at fluconazole MICs of $\leq 2 \mu\text{g/ml}$. So although resistance to fluconazole has been reported among mucocutaneous isolates of *C. albicans* (16), such resistance does not often complicate bloodstream infections due to *C. albicans*.

Other than *C. albicans*, *C. glabrata* is the most common species causing bloodstream infection in Iowa hospitals. In contrast to *C. albicans*, *C. glabrata* did manifest resistance to azole antifungal agents. The fluconazole MICs for 20% of *C. glabrata* bloodstream isolates were $\geq 16 \mu\text{g/ml}$; 10% of the

isolates were in the susceptible dose-dependent (S-DD) category, while 10% were fully resistant to fluconazole. This 80% rate of susceptibility to fluconazole among *C. glabrata* isolates in Iowa compares favorably with data from SENTRY centers in North America, where fluconazole susceptibilities among *C. glabrata* isolates were 63% in 1998 and 83% in 1999 (11). For no *C. glabrata* isolates were amphotericin B MICs $> 1 \mu\text{g/ml}$. *C. glabrata* was also notable in EIEIO hospitals for being more common among older patients and absent among infants less than 1 year of age. These data are consistent with previous reports of the importance of *C. glabrata* as an emerging problem in the hospital, particularly in the elderly population (9, 11). Recent reports suggest that *C. glabrata* may also manifest resistance to amphotericin B (11, 17), although optimal in vitro methods for detecting such resistance are still being investigated (14).

C. tropicalis, *C. parapsilosis* and *C. krusei* together accounted for approximately 20% of *Candida* bloodstream infections in our study. We detected only five cases of *C. krusei* bloodstream

infection over 3 years of surveillance. Considered inherently resistant to currently available azole antifungal agents, *C. krusei* isolates are also frequently resistant to amphotericin B. The amphotericin B MICs for three of the five isolates identified in this study were 2 µg/ml. *C. tropicalis* and *C. parapsilosis* were uniformly susceptible in vitro to fluconazole. Interestingly, *C. tropicalis* had the highest rate of in vitro resistance to 5-FC among the *Candida* species.

Consistent with previous reports (4, 11), each of the investigational triazoles tested (posaconazole, ravuconazole, and voriconazole) demonstrated excellent in vitro potency against *Candida* species. Although the MICs of these agents were higher among fluconazole- and itraconazole-resistant isolates, they still demonstrated a two- to fourfold lower MIC than itraconazole for these strains. In vitro susceptibility breakpoints for these agents have not been established, nor has their role in the management of serious infections due to *Candida* species. Nonetheless, they may represent future options for prophylaxis or management of selected patients at risk for or infected with *Candida* species (19).

Our data confirm the important role of *Candida* species as a cause of bloodstream infection in the health care setting. The annual incidence of 6 cases per 100,000 population in the State of Iowa is an estimate, given that our study was not designed to be population based and therefore inclusive of all cases of candidemia in the State of Iowa during the surveillance period. Our incidence estimate may be biased toward a falsely high rate, since one participating hospital is the largest tertiary care referral center in Iowa. Even so, our estimated incidence is lower than the incidence of 8 per 100,000 reported by CDC surveillance in two large urban areas (Atlanta, Ga., and San Francisco, Calif.) in 1992 to 1993. Demographic differences between the rural, elderly population of Iowa and the urban population surveyed by the CDC may explain this finding. In particular, the highest incidence of candidemia in the CDC study was found among neonates (8), and 14% of the candidemias were reported in the 0- to 12-month age group. The population of Iowa is one of the most elderly in the United States, and fewer candidemias in our study population occurred among children younger than 1 year.

In summary, we report the results of the first longitudinal statewide surveillance of bloodstream infection due to *Candida* species. These results demonstrate the continued prominence of *C. albicans* as a cause of candidemia, as well as the preserved activity of azoles against contemporary isolates of *Candida* species. However, *C. glabrata* is emerging, particularly in older adults, as an important and potentially antifungal resistance cause of candidemia. Given an aging population, widespread use of azole antifungal agents, and increasing acuity of hospitalized patients with risk factors for candidemia, we suspect that *C. glabrata* will continue to emerge as an important cause of serious disease in the health care setting. Ongoing surveillance of serious infections caused by *Candida* species will be important for tracking changes in the epidemiology and in antifungal susceptibility among these important health care-associated pathogens.

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