JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2008, p. 2902–2905 Vol. 46, No. 9
0095-1137/08/$08.00+0 doi:10.1128/JCM.00937-08

Trends in Species Distribution and Susceptibility of Bloodstream Isolates of *Candida* Collected in Monterrey, Mexico, to Seven Antifungal Agents: Results of a 3-Year (2004 to 2007) Surveillance Study▽

Gloria M. González,[1]* Mariana Elizondo,[1] and Jacobo Ayala[2]

Departamento de Microbiología, Facultad de Medicina, Universidad Autónoma de Nuevo León,[1] and Unidad de Vigilancia Epidemiológica, Hospital San José-Tec. de Monterrey, Instituto Tecnológico y de Estudios Superiores de Monterrey,[2] Monterrey, Mexico

Received 15 May 2008/Returned for modification 5 June 2008/Accepted 7 July 2008

During a 3-year surveillance program (2004 to 2007) in Monterrey, Mexico, 398 isolates of *Candida* spp. were collected from five hospitals. We established the species distribution and in vitro susceptibilities of these isolates. The species included 127 *Candida albicans* strains, 151 *C. parapsilosis* strains, 59 *C. tropicalis* strains, 32 *C. glabrata* strains, 11 *C. krusei* strains, 5 *C. guilliermondii* strains, 4 *C. famata* strains, 2 *C. utilis* strains, 2 *C. zeylanoides* strains, 2 *C. rugosa* strains, 2 *C. lusitaniae* strains, and 1 *C. boidinii* strain. The species distribution differed with the age of the patients. The proportion of candidemias caused by *C. parapsilosis* was higher among infants ≤1 year old, and the proportion of candidemias caused by *C. glabrata* increased with patient age (>45 years old). MICs were calculated following the criteria of the Clinical Laboratory Standards Institute reference broth macrodilution method. Overall, *C. albicans*, *C. parapsilosis*, and *C. tropicalis* isolates were susceptible to fluconazole and amphotericin B. However, 31.3% of *C. glabrata* isolates were resistant to fluconazole (MIC ≥ 64 μg/ml), 43.3% were resistant to itraconazole (MIC ≥ 1 μg/ml), and 12.5% displayed resistance to amphotericin B (MIC ≥ 2 μg/ml). Newer triazoles, namely, voriconazole, posaconazole, and ravuconazole, had a notable in vitro activity against all *Candida* species tested. Also, caspofungin was active against *Candida* sp. isolates (MIC_{90} ≤ 0.5 μg/ml) except *C. parapsilosis* (MIC_{90} = 2 μg/ml). It is imperative to promote a national-level surveillance program to monitor this important microorganism.

Candida is the agent most frequently implicated in invasive fungal infections, and it now ranks as the fourth most common cause of nosocomial bloodstream infections (BSI), accounting for 8% of all hospital-acquired BSI in the United States (7, 9, 20, 28). Candidemia is associated with an extremely high rate of mortality (3, 8, 25, 29). Several surveillance programs have produced data documenting this increase as well as species distribution and antifungal susceptibility trends (2, 4, 10, 19, 22). Some considerable variations have been shown to occur among hospitals or countries with respect to the incidence of *C. albicans* and other *Candida* species as etiologic agents of BSI (16, 17, 18, 26). For developed countries, there are a great deal of data confirming the magnitude of *Candida*'s role in BSI along with *Candida* species distribution and antifungal susceptibilities, but this is not the case for Latin America. Some studies addressing these concerns are limited either to individual institutions or in terms of time. The largest candidemia study conducted in this region was done in Brazil and showed the considerable morbidity and mortality of the disease in that country. *C. albicans* was the most common species isolated, followed by *C. tropicalis* and *C. parapsilosis*. In addition, the study revealed that antifungal resistance was rare (5).

In Mexico, national or local surveillance programs of BSI due to *Candida* spp. have been limited to date. As a result, the species of *Candida* involved in BSI in tertiary-care hospitals in Mexico is basically unknown. During 2004 to 2007, we conducted this study for *Candida* BSI in Monterrey, Mexico, to determine the distribution of species involved in these infections, antifungal susceptibility profiles to seven agents, and the percentages of antifungal drug resistance among the isolates.

MATERIALS AND METHODS

Data collection. The data were collected in the course of a 3-year surveillance program from July 2004 through July 2007. The study included five tertiary-level teaching hospitals representative of the public and private health systems in Monterrey, Mexico. Two were private hospitals and three were public hospitals. The participant hospitals are listed in Acknowledgments. We evaluated all *Candida* sp. BSI from patients admitted to the hospitals between July 2004 and July 2007. A case of candidemia was defined as the isolation of any species of *Candida* from bloodstream culture. We defined an incident case with nosocomial candidemia as the first isolation during the surveillance period of any *Candida* species from blood at least 48 h after admission. Each participant hospital also contributed with demographic data recorded on a special form.

Identification of strains. Organisms were identified at the medical institutions by the routine in use at each laboratory. These isolates were immediately submitted to the Microbiology Department, Medical School, Autonomous University of Nuevo León, Monterrey, Mexico. The isolates were subcultured onto Sabouraud agar (Difco, Detroit, MI) for further corroboration and susceptibility testing. Confirmation of species identification was performed with API 20C AUX strips (bioMérieux, Mexico) and for standard morphological methods as germ tube assays and microscopic evaluation on cornmeal-Tween 80 agar. Isolates were stored as suspensions in water at room temperature and on agar slants at −20°C until needed. Prior to testing, each isolate was passaged at least twice on Sabouraud agar to check the purity and viability of all yeast cultures.

Antifungal agents. Fluconazole (FLC) and voriconazole (VRC) (Pfizer, Inc., New York, NY), itraconazole (ITC) (Janssen Pharmaceutica, Beerse, Belgium), amphotericin B (AMB) and ravuconazole (RVC) (Bristol-Myers Squibb, Prince-

* Corresponding author. Mailing address: Facultad de Medicina, Universidad Autónoma de Nuevo León, Departamento de Microbiología, Madero y Dr. Eduardo A. Pequeño s/n, Colonia Mitras Centro, Monterrey, NL, México 64460. Phone: (5281) 8329 4166. Fax: (5281) 8348 5477. E-mail: gmglez@yahoo.com.mx.

▽ Published ahead of print on 16 July 2008.

TABLE 1. Species distribution of 398 *Candida* bloodstream isolates in Monterrey, Mexico, separated into three phases (2004 to 2007)

Species	No. of isolates (%) from:			Total no. (%)
	Phase 1	Phase 2	Phase 3	
C. *albicans*	42 (35)	49 (32.5)	36 (28.3)	127 (31.9)
C. *parapsilosis*	42 (35)	61 (40.4)	48 (37.8)	151 (37.9)
C. *tropicalis*	15 (12.5)	18 (11.9)	26 (20.4)	59 (14.8)
C. *glabrata*	15 (12.5)	10 (6.6)	7 (5.5)	32 (8.0)
C. *krusei*	2 (1.6)	3 (1.9)	6 (4.7)	11 (2.7)
C. *guilliermondii*	1 (0.8)	2 (1.3)	2 (1.6)	5 (1.3)
Other *Candida* spp.	3[a] (2.5)	8[b] (5.3)	2[c] (1.6)	13 (3.3)
Total	120	151	127	398

[a] *C. zeylanoides* ($n = 1$), *C utilis* ($n = 2$).
[b] *C. zeylanoides* ($n = 1$), *C. famata* ($n = 3$), *C. rugosa* ($n = 2$), *C. lusitaniae* ($n = 1$), *C. boidinii* ($n = 1$).
[c] *C. famata* ($n = 1$), *C. lusitaniae* ($n = 1$).

TABLE 2. Species distribution of 398 *Candida* bloodstream isolates in various age groups

Species	% Isolates in indicated age group [yr of age (no. of isolates found)]					
	≤1 (170)	>1–14 (67)	15–24 (10)	25–44 (49)	45–64 (62)	>65 (40)
C. *albicans*	27.6	26.8	30	46.9	41.9	30
C. *parapsilosis*	52.3	40.2	40	22.4	16.1	22.5
C. *tropicalis*	12.3	23.8	0	16.3	12.9	10
C. *glabrata*	0.6	2.9	10	10.2	22.5	25
C. *krusei*	1.7	2.9	10	4.0	3.2	2.5
C. *guilliermondii*	2.4	1.4	0	0	0	0
Other *Candida* spp.[a]	2.9	1.4	10	0	3.2	10

[a] *C. zeylanoides* ($n = 1$), *C. utilis* ($n = 2$), *C. zeylanoides* ($n = 1$), *C. famata* ($n = 3$), *C. rugosa* ($n = 2$), *C. lusitaniae* ($n = 1$), *C. boidinii* ($n = 1$), *C. famata* ($n = 1$), *C. lusitaniae* ($n = 1$).

ton, NJ), posaconazole (PSC) (Schering-Plough, Kenilworth, NJ), and caspofungin (CAS) (Merck, Rahway, NJ) were obtained in reagent-grade powder form from their respective manufacturers.

Susceptibility testing. Serial twofold dilutions of each antifungal agent were prepared as outlined in document M27-A2 of the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS) (13). Final dilutions were made in antibiotic medium 3 (Difco, Detroit, MI) for AMB and RPMI 1640 with L-glutamine and buffered with 165 mM morpholinepropanesulfonic acid (MOPS; Hardy Diagnostics) for FLC, ITC, VRC, PSC, RVC, and CAS. The final concentrations of the antifungal agents ranged from 0.03 to 64 μg/ml for FLC and CAS and from 0.015 to 8 μg/ml for AMB, ITC, VRC, PSC, and RVC. Yeast inocula were prepared spectrophotometrically and further diluted in order to obtain concentrations ranging from 1.0×10^3 to 5.0×10^3 CFU/ml. The tubes were incubated at 35°C and read after 24 h for CAS (23) and after 48 h for the rest of the antifungal agents. The MIC endpoint for AMB was considered to be the lowest tested drug concentration able to prevent any visible growth. The MIC endpoint for azoles was defined as the lowest tested drug concentration causing a growth reduction of ≥80% compared to the growth of the drug-free control (13). The MIC endpoint for CAS was measured as the lowest concentration of drug that produced a significant decrease (≥50%) in growth compared to the growth of the drug-free control (23).

C. parapsilosis ATCC 22019 and *C. krusei* ATCC 6258 were included as the control organisms in all experiments.

The interpretative MIC breakpoints for FLC and ITC were those suggested by the CLSI M27-A2 document (13). Isolates with MICs of ≤8 μg/ml for FLC and of ≤0.125 μg/ml for ITC were considered susceptible. Isolates with MICs of 16 to 32 μg/ml for FLC and of 0.25 to 0.5 μg/ml for ITC were considered as susceptible in a dose-dependent manner. MICs of ≥64 μg/ml for FLC and of ≥1 μg/ml for ITC were considered resistant. For the purposes of this study, we determined that isolates with MICs of ≤1 μg/ml for AMB were classified as susceptible and those with MICs of ≥2 μg/ml as resistant (15). In the case of VRC, we considered a susceptible MIC breakpoint of ≤1 μg/ml, with susceptibility in a dose-dependent manner at 2 μg/ml and resistance at ≥4 μg/ml (24). Due to the lack of interpretative breakpoints for PSC, RVC, and CAS, a definite designation was not made.

This study was divided annually in three different phases: July 2004 to July 2005 (phase 1), July 2005 to July 2006 (phase 2), and July 2006 to July 2007 (phase 3).

Statistical analyses. The chi-square test for trend was utilized to test for changes in the incidence of candidemia by year of surveillance and in the species distribution by patient age.

RESULTS

Demographic data. A total of 398 isolates of *Candida* spp. were evaluated, and each represented an individual infectious episode. The number of isolates referred for testing each year was 120 in the first year, 151 in the second year, and 127 in the third year. These were diagnosed in 211 male (53%) and 187 female (47%) patients ranging in age from 1 day to 92 years. Of note is that 170 case patients (42.7%) were children of ≤1 year of age. Seventy-three cases were from private institutions (18.3%) and 325 patients were from public hospitals (81.6%). Ninety-one patients were under systemic antifungal regimens prior to the first reporting of positive blood culture results (FLC, 71 patients [17.8%]; VRC, 4 patients [1.5%]; CAS, 14 patients [3.5%]).

Distribution of *Candida* spp. The species distribution of *Candida* involved in BSI is shown in Table 1. *C. parapsilosis* was the most common species (151 cases; 37.9%), followed by *C. albicans* (127 cases; 31.9%), *C. tropicalis* (59 cases; 14.8%), and *C. glabrata* (32 cases; 8%). These four species correspond to 92.6% of the isolates. *C. krusei* comprised only 11 cases, *C. guilliermondii* comprised only 5 cases, and 13 cases (3.3%) were with unusual species with ≤3 isolates each (*C. zeylanoides*, *C. utilis*, *C. famata*, *C. rugosa*, *C. lusitaniae*, and *C. boidinii*). All candidemia episodes were caused by a single *Candida* sp. Overall, the species distributions of *Candida* during the 3-year period were relatively similar except for the six isolates of *C. krusei* during the third year of this surveillance program, which were obtained from patients in a single institution. On the other hand, there appears to be a slight decrease for both *C. albicans* and *C. glabrata* over the 3-year period. In general, the rank orders of *Candida* sp. distribution were basically the same in the five hospitals.

The distribution of *Candida* spp. according to age varied considerably (Table 2). The rank order for the groups for those of ≤1 and of >1 to 14 years of age was as follows: *C. parapsilosis* more than *C. albicans* more than *C. tropicalis* more than *C. glabrata*. Meanwhile, the situation was opposite for the older groups, namely, those of 45 to 64 and of >65 years of age: *C. albicans* more than *C. glabrata* more than *C. parapsilosis* more than *C. tropicalis*. The *P* value was 0.005 for the trend of increased frequency of *C. glabrata* with increasing age.

Antifungal susceptibility testing. Table 3 summarizes the in vitro susceptibility testing of the four most frequent *Candida* species (369 isolates) from BSI to AMB, FLC, ITC, VRC, PSC, RVC, and CAS. The results are reported as MIC_{50} and MIC_{90} ranges and as percentages of *Candida* spp. resistant to antifungal compounds according to the CLSI method (13), the work of Nguyen et al. (15), and the work of Pfaller et al. (24).

TABLE 3. In vitro susceptibilities of the seven antifungal agents against the most frequent *Candida* spp. isolated, surveillance program in Monterrey, Mexico, 2004 to 2007

Species (no. of isolates)	Antifungal compound	MIC (μg/ml)			% Resistant[a]
		Range	50%	90%	
C. albicans (127)	AMB	0.06–1	0.25	1	0
	FLC	0.25–64	1	2	0.78
	ITC	0.06–4	0.125	1	1.6
	VRC	0.015–1	0.06	0.06	0.78
	PSC	0.015–1	0.06	0.06	
	RVC	0.015–1	0.06	0.125	
	CAS	0.015–0.125	0.03	0.06	
C. parapsilosis (151)	AMB	0.125–1	1	1	0
	FLC	0.25–8	2	4	0
	ITC	0.015–2	0.125	1	0
	VRC	0.015–1	0.06	0.06	0
	PSC	0.015–1	0.06	0.06	
	RVC	0.015–1	0.06	0.06	
	CAS	0.06–2	0.25	2	
C. tropicalis (59)	AMB	0.06–1	0.5	1	0
	FLC	0.5–32	2	8	0
	ITC	0.03–4	0.06	1	1.6
	VRC	0.03–1	0.06	0.125	0
	PSC	0.015–1	0.06	0.125	
	RVC	0.03–1	0.06	0.125	
	CAS	0.015–0.125	0.03	0.125	
C. glabrata (32)	AMB	0.125–4	1	4	12.5
	FLC	1–>64	8	>64	31.25
	ITC	0.125–4	0.5	4	43.3
	VRC	0.03–1	0.125	0.25	0
	PSC	0.015–1	0.125	0.25	
	RVC	0.03–1	0.25	0.5	
	CAS	0.015–0.5	0.03	0.125	

[a] Resistance breakpoints were as follows: the FLC MIC was ≥64 μg/ml; the ITC MIC was ≥1 μg/ml; the AMB MIC was ≥2 μg/ml; and the VRC MIC was ≥4 μg/ml.

Nearly all strains (97.57%) were susceptible to AMB (MIC ≤ 1 μg/ml). Most strains (97.02%) were also susceptible to FLC. Almost all *C. albicans* BSI isolates collected during the 3-year surveillance program were inhibited by FLC, with FLC MICs of ≤8 μg/ml. Only one isolate was reported as resistant, with an MIC of 64 μg/ml. On the other hand, 10 *C. glabrata* isolates (31.25%) were resistant to FLC (≥64 μg/ml) and 5 isolates (15.6%) had decreased FLC susceptibility (16 to 32 μg/ml), while 53.12% were susceptible to FLC. The percentages of yeast isolates with resistance and decreased susceptibility to FLC were similar during the three phases. We did not find FLC resistance among isolates of *C. parapsilosis* and *C. tropicalis*. ITC resistance was observed for 4.60% of all *Candida* isolates evaluated and was also highest among *C. glabrata* isolates (43.75% resistance); 37.5% of the isolates were reported as susceptible in a dose-dependent manner, and 18.7% were susceptible. With regard to AMB, we found nine *C. glabrata* isolates with MICs of ≥2 μg/ml. Among newer triazoles VRC, PSC, and RVC, all were highly effective against all species tested from all age groups. Only one isolate of *C. albicans* showed a VRC MIC of 4 μg/ml and was resistant to FLC (MIC = 64 μg/ml) and ITC (MIC = 1 μg/ml). In addition, one *C. glabrata* isolate that was resistant to FLC (MIC > 64 μg/ml) and resistant to ITC (MIC = 4 μg/ml) had a VRC MIC of 2 μg/ml (susceptible in a dose-dependent manner).

On the other hand, CAS inhibited all *Candida* sp. isolates with MICs of ≤0.5 μg/ml, except *C. parapsilosis* (MIC_{90}, 2 μg/ml).

DISCUSSION

Over the past 30 years, numerous investigators have reported that the frequency of severe infections caused by yeasts, especially *Candida* spp., has increased dramatically (7, 9, 20). Because of the lack of data in our country about the trends in species distribution and antifungal susceptibilities among *Candida* isolates causing BSI, we decided to promote a local-level surveillance program to monitor this crucial microorganism. A total of 398 *Candida* isolates from blood were documented during the course of this surveillance program. Our data show three findings. First, the species distribution in our study is notable. Even though *C. albicans* has been reported as the most commonly isolated species causing candidemia in other countries (6, 14, 16, 22, 25, 26, 27), in this study we found that the frequency of candidemic episodes due to non-*C. albicans* species represented 68% of all *Candida* isolates. *C. parapsilosis* was the most frequent *Candida* species recovered, accounting for 37.9% of all isolates followed in order by *C. tropicalis* (14.8%) and *C. glabrata* (8%). We cannot explain the reason for this species distribution of *Candida* in causing BSI, but numerous medical circumstances may influence the risk of developing candidemia due to non-*C. albicans* spp. It has been suggested that the higher prevalence of *C. parapsilosis* in some institutions might be related to poor catheter care or infection control practices (11). *C. tropicalis* and *C. glabrata* are associated with cancer patients and previous exposure to azoles, respectively (12, 28, 30). This increased prominence of non-*C albicans* spp. causing BSI has been extensively noted in many studies (1, 5, 6, 14, 22). It is noteworthy that the 11 episodes of candidemia due to *C. krusei* were obtained from a single hospital over 3 years of surveillance, raising the possibility that this species may be associated with nosocomial outbreaks. Clinically, this organism is of particular importance due to its well-known resistance to FLC and its decreased susceptibility to AMB. It is recognized that BSI due to *C. krusei* is associated with a high crude mortality (80%), which is probably associated with its poor response to conventional therapy. Continued monitoring of these isolates is comprehensively urgent.

Second, the association of patient age with the rank order of *Candida* spp. producing BSI has been previously reported (6, 21, 27). Our study established the high proportion of *C. parapsilosis* and *C. albicans* and the lack of *C. glabrata* as etiologic species of candidemia in the neonatal and pediatric age groups. It is worth mentioning that only one isolate of *C. glabrata* was obtained from the ≤1-year-old age group and the isolate showed high susceptibility to all antifungal compounds tested. Nevertheless, the contrary was found in the age groups of 45 to 64 and >65 years of age, for which *C. glabrata* was the second most common etiologic agent of *Candida* BSI. We obtained 31 isolates of *C. glabrata* from these age groups, and 4 isolates showed resistance to AMB (MICs of ≥2 μg/ml), 10 displayed resistance to FLC (MICs of ≥64 μg/ml), and 14 isolates were resistant to ITC (MICs of ≥1 μg/ml). The majority of the isolates categorized as resistant to FLC were very susceptible to VRC, PSC, and RVC. *C. glabrata* was susceptible to the fungicidal activity of CAS.

Third, this study suggests that antifungal resistance is not a relevant factor among isolates of *C. albicans* from Monterrey. Contrary to *C. albicans*, *C. glabrata* exhibited resistance to

FLC, ITC, and AMB. These data confirm the importance of *C. glabrata* as a problem in hospitals, particularly for patients of ≥65 years of age. On the other hand, *C. parapsilosis* and *C. tropicalis* together accounted for 52.7% of *Candida* BSI presenting high susceptibility to all antifungal drugs tested.

The new triazoles tested (VRC, PSC, and RVC) displayed excellent and similar in vitro potencies against all *Candida* spp. CAS inhibited all *Candida* sp. isolates with MICs of ≤0.5 μg/ml, except *C. parapsilosis* (MIC_{90}, 2 μg/ml).

In conclusion, although our data may not exactly reflect the trends in species distribution and antifungal susceptibilities among *Candida* species BSI in other medical institutions of this country, these local findings should enhance the need to establish a permanent nationwide surveillance program. This paper is the first to provide local-level information about species distribution and antifungal susceptibility profiles of *Candida* BSI isolates from Monterrey, Mexico. It is the most representative study and to our knowledge is the only prospective study of candidemia ever reported for Mexican hospitals. Previous reports in other states of our country were based only on a single hospital or on particular groups of hospitalized patients, and none included data about in vitro susceptibility testing.

ACKNOWLEDGMENTS

We thank all participants. Hospitals and individuals contributing to the study included Hospital Universitario Dr. Jose Eleuterio Gonzalez (Jorge Canizales), Hospital San José-Tec de Monterrey (Claudia Guajardo), Instituto de Seguridad y Servicio Social de los Trabajadores del Estado Regional Hospital (Teresa Ávalos), Instituto Mexicano del Seguro Social Specialty Hospital no. 25 (Norma Garza), and Hospital Christus Muguerza (Beatriz Aguilar). We also thank Sergio Lozano for his review of the manuscript.

REFERENCES

1. **Abi-Said, D., E. Anaissie, O. Uzun, I. Raad, H. Pinzcowski, and S. Vartivarian.** 1997. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin. Infect. Dis. **24:**1122–1128.
2. **Berrouane, Y. F., L. A. Herwaldt, and M. A. Pfaller.** 1999. Trends in antifungal use and epidemiology of nosocomial yeast infections in a university hospital. J. Clin. Microbiol. **37:**531–537.
3. **Blumberg, H. M., W. R. Jarvis, J. M. Soucie, J. E. Edwards, J. E. Patterson, M. A. Pfaller, M. S. Rangel-Frausto, M. G. Rinaldi, L. Saiman, R. Todd Wiblin, R. P. Wenzel, and NEMIS Study Group.** 2001. Risk factors for candidal bloodstream infections in surgical intensive care units patients: The NEMIS prospective multicenter study. Clin. Infect. Dis. **33:**177–186.
4. **Boschman, C. R., U. R. Bodnar, M. A. Tornatore, A. A. Obias, G. A. Noskin, K. Englund, M. A. Postelnick, T. Suriano, and L. R. Peterson.** 1998. Thirteen-year evolution of azole resistance in yeast isolates and prevalence of resistant strains carried by cancer patients at a large medical center. Antimicrob. Agents Chemother. **42:**734–738.
5. **Colombo, A. L., M. Nucci, B. J. Park, S. A. Nouér, B. Arthington-Skaggs, D. A. da Matta, D. Warnock, and J. Morgan for the Brazilian Network Candidemia Study.** 2006. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. J. Clin. Microbiol. **44:**2816–2823.
6. **Diekema, D. J., S. A. Messer, A. B. Rueggemann, S. L. Coffman, G. V. Doern, L. A. Herwaldt, and M. A. Pfaller.** 2002. Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. J. Clin. Microbiol. **40:**1298–1320.
7. **Edmond, M. B., S. E. Wallace, D. K. McClish, M. A. Pfaller, R. N. Jones, and R. P. Wenzel.** 1999. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin. Infect. Dis. **29:**239–244.
8. **Gudlaugsson, O., S. Gillespie, K. Lee, J. Vande Berg, J. Hu, S. Messer, L. Herwaldt, M. Pfaller, and D. Diekema.** 2003. Attributable mortality of nosocomial candidemia, revisited. Clin. Infect. Dis. **37:**1172–1177.
9. **Hajjeh, R. A., A. N. Sofair, L. H. Harrison, G. M. Lyon, B. A. Arthington-Skaggs, S. A. Mirsa, M. Phelan, J. Morgan, W. Lee-Yang, M. A. Ciblak, L. E. Benjamin, L. T. Sanza, S. Huie, S. F. Yeo, M. E. Brandt, and D. W. Warnock.** 2004. Incidence of bloodstream infections due to *Candida* species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. J. Clin. Microbiol. **42:**1519–1527.
10. **Laupland, K. B., D. B. Gregson, D. L. Church, T. Ross, and S. Elsayed.** 2005. Invasive *Candida* species infections: a 5 year population-based assessment. J. Antimicrob. Chemother. **56:**532–537.
11. **Levy, I., L. G. Rubin, S. Vasishtha, V. Tucci, and S. K. Sood.** 1998. Emergence of *Candida parapsilosis* as the predominant species causing candidemia in children. Clin. Infect. Dis. **26:**1086–1088.
12. **Marr, K. A., K. Seidel, T. C. White, and R. A. Bowden.** 2000. Candidemia in allogenic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J. Infect. Dis. **181:**309–316.
13. **National Committee for Clinical Laboratory Standards.** 2002. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard M27–A2, 2nd ed. National Committee for Clinical Laboratory Standards, Wayne, PA.
14. **Nguyen, M. H., J. E. Peacock, A. J. Morris, D. C. Tanner, M. L. Nguyen, D. R. Snydman, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am. J. Med. **100:**617–623.
15. **Nguyen, M. H., C. J. Clancy, V. L. Yu, Y. C. Yu, A. J. Morris, D. R. Snydman, D. A. Sutton, and M. G. Rinaldi.** 1998. Do *in vitro* susceptibility data predict the microbiologic response to amphotericin B? Results of a prospective study of patients with *Candida* fungemia. J. Infect. Dis. **177:**425–430.
16. **Pfaller, M. A., R. N. Jones, G. V. Doern, H. S. Sader, R. J. Hollis, and S. A. Messer for the Sentry Participant Group.** 1998. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the sentry program. J. Clin. Microbiol. **36:**1886–1889.
17. **Pfaller, M. A., R. N. Jones, S. A. Messer, M. B. Edmond, and R. P. Wenzel.** 1998. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn. Microbiol. Infect. Dis. **31:**327–332.
18. **Pfaller, M. A., R. N. Jones, S. A. Messer, M. B. Edmond, R. P. Wenzel, and the SCOPE Participant Group.** 1998. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn. Microbiol. Infect. Dis. **30:**121–129.
19. **Pfaller, M. A., S. Messer, R. J. Hollis, R. N. Jones, G. V. Doern, M. E. Brabdt, and R. A. Hajjeh.** 1999. Trends in species distribution and susceptibility to fluconazole among blood stream isolates of *Candida* species in United States. Diagn. Microbiol. Infect. Dis. **33:**217–222.
20. **Pfaller, M. A., and D. J. Diekema.** 2002. Role of sentinel surveillance of candidemia: trends in species distribution and antifungal susceptibility. J. Clin. Microbiol. **40:**3551–3557.
21. **Pfaller, M. A., S. A. Messer, L. Boyken, S. Tendolkar, R. J. Hollis, and D. J. Diekema.** 2003. Variation in susceptibility of bloodstream isolates of *Candida glabrata* to fluconazole according to patient age and geographic location. J. Clin. Microbiol. **41:**2176–2179.
22. **Pfaller, M. A., and D. J. Diekema for the International Fungal Surveillance Participant Group.** 2004. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*. Clin. Microbiol. Infect. **10**(Suppl. 1)**:**11–23.
23. **Pfaller, M. A., S. A. Messer, L. Boyken, C. Rice, S. Tendolkar, R. J. Hollis, and D. J. Diekema.** 2004. Further standardization of broth microdilution methodology for in vitro susceptibility testing of caspofungin against *Candida* species by use of an international collection of more than 3,000 clinical isolates. J. Clin. Microbiol. **42:**3117–3119.
24. **Pfaller, M. A., D. J. Diekema, J. H. Rex, A. Espinel-Ingroff, E. M. Johnson, D. Andes, V. Chaturvedi, M. A. Ghannoum, F. C. Odds, M. G. Rinaldi, D. J. Sheehan, P. Troke, T. J. Walsh, and D. W. Warnock.** 2006. Correlation of MIC with outcome for *Candida* species tested against voriconazole: analysis and proposal for interpretive breakpoints. J. Clin. Microbiol. **44:**819–826.
25. **Puzniak, L., S. Teutsch, W. Powderly, and L. Polish.** 2004. Has the epidemiology of nosocomial candidemia changed? Infect. Control Hosp. Epidemiol. **25:**628–633.
26. **Rangel-Fraustro, S. M., T. Wiblin, H. M. Blumberg, L. Saiman, J. Patterson, M. Rinaldi, M. Pfaller, J. E. Edwards, W. Jarvis, J. Dawson, R. P. Wenzel, and the NEMIS Study Group.** 1999. National epidemiology of mycoses survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. Clin. Infect. Dis. **29:**253–258.
27. **Sandven, P., L. Bevanger, A. Digranes, H. H. Haukland, T. Mannsåker, P. Gaustad, and the Norwegian Yeast Study Group.** 2006. Candidemia in Norway (1991 to 2003): results from a nationwide study. J. Clin. Microbiol. **44:**1977–1981.
28. **Trick, W. E., S. K. Fridkin, J. R. Edwards, R. A. Hajjeh, and R. P. Gaynes.** 2002. Secular trend of hospital-acquired candidemia among intensive care unit patients in the Unites States during 1989–1999. Clin. Infect. Dis. **35:**627–630.
29. **Wey, S. B., M. Mori, M. A. Pfaller, R. F. Woolson, and R. P. Wenzel.** 1988. Hospital acquired candidemia: attributable mortality and excess length of stay. Arch. Intern. Med. **148:**2642–2645.
30. **Wingard, J. R.** 1995. Importance of *Candida* species other than *C. albicans* as pathogen in oncology patients. Clin. Infect. Dis. **20:**115–125.