JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2004, p. 1519–1527 Vol. 42, No. 4
0095-1137/04/$08.00+0 DOI: 10.1128/JCM.42.4.1519–1527.2004

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

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Received 27 October 2003/Returned for modification 15 December 2003/Accepted 7 January 2004

To determine the incidence of *Candida* bloodstream infections (BSI) and antifungal drug resistance, population-based active laboratory surveillance was conducted from October 1998 through September 2000 in two areas of the United States (Baltimore, Md., and the state of Connecticut; combined population, 4.7 million). A total of 1,143 cases were detected, for an average adjusted annual incidence of 10 per 100,000 population or 1.5 per 10,000 hospital days. In 28% of patients, *Candida* BSI developed prior to or on the day of admission; only 36% of patients were in an intensive care unit at the time of diagnosis. No fewer than 78% of patients had a central catheter in place at the time of diagnosis, and 50% had undergone surgery within the previous 3 months. *Candida albicans* comprised 45% of the isolates, followed by *C. glabrata* (24%), *C. parapsilosis* (13%), and *C. tropicalis* (12%). Only 1.2% of *C. albicans* isolates were resistant to fluconazole (MIC, ≥64 μg/ml), compared to 7% of *C. glabrata* isolates and 6% of *C. tropicalis* isolates. Only 0.9% of *C. albicans* isolates were resistant to itraconazole (MIC, ≥1 μg/ml), compared to 19.5% of *C. glabrata* isolates and 6% of *C. tropicalis* isolates. Only 4.3% of *C. albicans* isolates were resistant to flucytosine (MIC, ≥32 μg/ml), compared to <1% of *C. parapsilosis* and *C. tropicalis* isolates and no *C. glabrata* isolates. As determined by E-test, the MICs of amphotericin B were ≥0.38 μg/ml for 10% of *Candida* isolates, ≥1 μg/ml for 1.7% of isolates, and ≥2 μg/ml for 0.4% of isolates. Our findings highlight changes in the epidemiology of *Candida* BSI in the 1990s and provide a basis upon which to conduct further studies of selected high-risk subpopulations.

Candida species are the fourth most common cause of hospital-acquired bloodstream infections (BSI) in the United States (5, 9). These infections are associated with attributable mortality rates that have ranged from 38% between 1983 and 1986 (46) to 49% in the same institutions between 1997 and 2001 (13). Although the incidence of *Candida* BSI increased among intensive care unit (ICU) patients in hospitals participating in the National Nosocomial Infections Surveillance system during the 1980s (2), there was a significant decrease in the annual incidence of infections with *Candida albicans*, the most common cause of *Candida* BSI, in this group of patients in the 1990s (40). During the same time period, there was a significant increase in the incidence of *C. glabrata* BSI (40). Changes in the species distributions of bloodstream isolates in hospitalized patients outside the ICU setting have also been reported (1, 20, 30).

In the early 1990s, increasing usage of fluconazole to treat human immunodeficiency virus (HIV)-infected persons with recurrent oropharyngeal candidiasis led to changes in the prevalence of different *Candida* species and to the emergence of azole-resistant strains (37). Among the factors that led to this development were the selection of intrinsically less susceptible organisms, such as *C. glabrata* and *C. krusei*, and the acquisition of resistance by previously susceptible strains of *C. albicans* following long-term azole exposure. The potential effects of azole selective pressure in a broader patient population are less well understood. The reported decrease in the proportion of *Candida* BSI that were due to *C. albicans* and the reported increase in the proportion of *C. glabrata* BSI in the 1990s (1, 20, 30, 40) might have been mediated by one or more confounding risk factors in addition to selection for species that were less susceptible to azoles (37, 46).

In a prospective population-based active surveillance conducted in Atlanta, Ga., and San Francisco, Calif., between 1992 and 1993, *C. albicans* was found to account for 52% of *Candida* BSI. Antifungal drug susceptibility testing revealed minimal levels of azole resistance among bloodstream isolates of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* (16). Between 1998 and 2000, we conducted a prospective population-based surveillance for *Candida* BSI to determine the distributions of species involved in these infections and the proportions of antifungal drug resistance among the isolates. We report here the results of this surveillance and discuss the implications of recent changes in the epidemiology of *Candida* BSI for patient management.

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MATERIALS AND METHODS

Surveillance. The study was conducted in two locations: the entire state of Connecticut (population of 3.3 million and 33 hospitals) and Baltimore City/

Baltimore County, Md. (population of 1.4 million and 14 hospitals). The study was conducted for 2 years, from 1 October 1998 to 30 September 2000. An incident case was defined by the first isolation during the surveillance period of any *Candida* species from the blood of a resident in a surveillance area. A standardized data collection form was used to abstract medical records in order to gather information on demographic and clinical characteristics, underlying conditions, and outcome. For patients who had more than one episode of candidemia, the second episode was also defined as an incident case if it occurred at least 30 days after the previous episode. Outcome was defined as survival or death within 30 days after the incident candidemia episode. The number of days of hospitalization before the onset of candidemia (patient days) was calculated as the difference between the date of admission and the date of collection of a positive blood culture. Patients who developed positive blood cultures either prior to or on the first day of hospital admission were classified as representing outpatient-acquired candidemia cases.

Laboratory records of all hospitals and laboratories in the surveillance areas were audited every 6 to 12 months to estimate the completeness of reporting and to detect additional cases. Cases found after audits were added to the analysis, so that this surveillance captured all candidemia cases reported in the surveillance areas.

Statistical analysis and denominators. Statistical analysis was done by use of SAS for Windows version 8.2 (SAS Institute). The chi-square test was used to detect significant associations between defined variables. Univariable and multivariable analyses were performed by using the LOGISTIC procedure. For the multivariable analysis, logistic regression was done by use of backward elimination. All variables significant at a P value of ≤ 0.1 were included in the multivariable analysis model; the criterion for staying in the model was set at 0.05.

Incidence rates were standardized for age and race by using the 2000 population data from the U.S. Bureau of the Census (http://www.census.gov). Hospital-related denominators (hospitalization or patient days and number of discharges) for each surveillance area were also obtained from the Connecticut Health Information Management Exchange, Inc., and the Maryland Health Services Cost Review Commission databases. These databases are health care information systems which incorporate statewide clinical, financial, and patient demographic data.

Microbiological methods. Detection of candidemia and species identification of isolates were performed in the area laboratories according to their standard protocols. In describing their blood culture procedures, 34 of 51 responding laboratories (66%) used the BACTEC automated system (Becton Dickinson, Sparks, Md.), and 11 (21%) used the BacTAlert system (Organon Teknika Corp., Durham, N.C.). All available bloodstream isolates of *Candida* species from cases were sent to the Centers for Disease Control and Prevention (CDC), Atlanta, Ga., for confirmation of identification and antifungal drug susceptibility testing. Species identification was done by standard laboratory methods (44). *C. dubliniensis* was identified by PCR amplification of a region containing the novel *C. dubliniensis* group I intron (4). When CDC and submitting laboratory identifications differed, isolate identification was confirmed by use of a DNA probe-based PCR-enzyme immunoassay method (7, 10). The CDC final identification was used for the purpose of this analysis. In cases for which no isolates were sent to the CDC, the species identification provided by the referring laboratory was used.

Antifungal susceptibility testing. The MICs of flucytosine, fluconazole, and itraconazole were determined at the CDC by the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution method (19). For flucytosine, end points were determined visually following 48 h of incubation. To eliminate the effects of trailing growth, spectrophotometric end points for fluconazole and itraconazole were determined after 48 h. Visual and spectrophotometric end points were defined as the lowest drug concentrations that resulted in a prominent decrease in growth and a 50% reduction in optical density, respectively, compared to the data for the drug-free growth control well. The MICs of amphotericin B were determined by the E-test (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions with RPMI 1640 medium supplemented with 2% glucose (27, 43). E-test MICs were read at 48 h as the lowest drug concentrations at which the zone of complete growth inhibition intersected the scale on the antifungal test strip.

Interpretive breakpoints proposed by the NCCLS for fluconazole, itraconazole, and flucytosine were used (19). Isolates for which fluconazole MICs are ≤ 8 μg/ml are classified as susceptible, while those for which MICs are ≥ 64 μg/ml are classified as resistant. Isolates for which MICs are 16 to 32 μg/ml are classified as susceptible in a dose-dependent manner (S-DD). Isolates for which itraconazole MICs are ≤ 0.125 μg/ml are classified as susceptible, those for which MICs are 0.25 to 0.5 μg/ml are classified as S-DD, and those for which MICs are ≥ 1 μg/ml are classified as resistant. Isolates for which flucytosine MICs are ≤ 4 μg/ml are classified as susceptible, those for which MICs are 8 to 16 μg/ml are classified as intermediate, and those for which MICs are ≥ 32 μg/ml are classified as resistant. Interpretive breakpoints for amphotericin B have not been established by the NCCLS. However, when isolates that appeared to be resistant to amphotericin B in animal models were tested by the E-test with RPMI 1640 medium, MICs of ≥ 0.38 μg/ml were obtained (6, 22).

RESULTS

A total of 1,143 cases of *Candida* BSI were identified in Connecticut and Baltimore during the 2 years of surveillance (Table 1). A retrospective audit was used to identify 203 of these cases (18%). The average annual incidence of candidemia at the two sites combined, after adjusting for age and race (to the U.S. population), was 10 cases per 100,000 population. The average annual incidences differed significantly ($P = 0.004$) between the two sites: 24 cases per 100,000 in Baltimore and 7 cases per 100,000 in Connecticut. The majority of candidemia cases (821, or 72%) occurred among persons ≥ 45 years old. Significant differences in rates of disease by race and age groups were noted (Fig. 1), with the highest incidences of disease occurring among blacks, neonates, and older persons (persons >65 years old). There were no significant differences in incidence rates between males and females. For purposes of comparison with hospital-based surveillance studies, the incidence of candidemia in 1999 was 1.5 cases per 10,000 hospital days (1.7 in Baltimore and 1.3 in Connecticut) or 0.8 cases per 1,000 discharges (1 in Baltimore and 0.6 in Connecticut). A total of 409 patients died within 30 days of the diagnosis of candidemia, for an overall crude mortality rate of 36%.

Species distributions. *C. albicans* was present in 45% of cases and was the most common species recovered (Table 1). *C. glabrata* was recovered from 24% of cases, followed by *C. parapsilosis* (13%), *C. tropicalis* (12%), *C. krusei* (2%), *C. lusitaniae* (1%), *C. dubliniensis* (0.9%), and *C. kefyr* and *C. rugosa* (0.1% each).

The CDC received 935 isolates (from 82% of cases) for confirmation of identification. For 43 isolates with discrepant identifications, the results obtained by the PCR-enzyme immunoassay method matched the CDC species identification for all but 1 isolate, for which the identification was resolved by DNA sequencing (7). When species identifications from the submitting laboratory were compared to CDC identifications, the rate of misidentification was 4.6% (43 of 935 isolates). The most commonly misidentified species was *C. glabrata*. Fifteen *C. glabrata* isolates were misidentified as any of three different species, most commonly *C. albicans* (seven isolates). Conversely, seven isolates of three different species were submitted to the CDC as *C. glabrata*. Misidentifications were not linked to any particular submitting laboratory.

Antifungal susceptibility testing. All 935 available isolates were tested for antifungal susceptibility at the CDC, and the results are shown in Table 2. Data are reported as MIC ranges and as the concentrations of each antifungal agent necessary to inhibit 50% (MIC_{50}) and 90% (MIC_{90}) of isolates. Overall, fluconazole resistance (MIC, ≥ 64 μg/ml) was detected in 35 isolates (3.7%), with minimal resistance being seen in *C. albicans* (1.2% of all *C. albicans* isolates). Overall, 30 (5.9%) of 512 *Candida* isolates other than *C. albicans* showed resistance to fluconazole: all *C. parapsilosis* isolates were susceptible, but 7% of *C. glabrata* and 6% of *C. tropicalis* isolates were resistant

TABLE 1. Selected demographic and clinical characteristics and outcomes for persons with candidemia by species from 1998 to 2000 in Connecticut and Baltimore

Characteristic	No. (%) of isolates of:					
	C. albicans	Non-*C. albicans*	*C. glabrata*	*C. tropicalis*	*C. parapsilosis*	All species[a]
Site						
Baltimore	289 (56)	391 (62)	188 (68)	98 (70)	72 (47)	680 (59)
Connecticut	227 (44)	235 (38)	87 (32)	43 (30)	81 (53)	463 (41)
Sex						
Male	278 (54)	323 (52)	134 (49)	67 (48)	90 (59)	602 (53)
Female	236 (46)	302 (48)	141 (51)	73 (52)	63 (41)	538 (47)
Race						
White	293 (57)	313 (50)	136 (49)	60 (43)	91 (59)	606 (53)
Black	190 (37)	280 (45)	126 (46)	79 (56)	52 (34)	470 (41)
Other or unknown	33 (6)	33 (5)	13 (5)	2 (1)	10 (7)	67 (6)
Age (yr)						
<1	43 (8)	29 (5)	8 (3)	2 (1)	18 (12)	72 (7)
1–19	24 (5)	25 (4)	1 (<1)	7 (5)	5 (3)	49 (4)
20–44	88 (17)	113 (18)	42 (15)	28 (20)	26 (17)	201 (18)
45–64	129 (25)	178 (28)	82 (30)	42 (30)	41 (27)	307 (27)
>65	232 (45)	281 (45)	142 (52)	62 (44)	63 (41)	514 (45)
Died within 30 days of culturing	205 (40)	204 (33)	100 (36)	57 (40)	28 (18)	409 (36)
Malignancy	115 (23)	151 (25)	69 (25)	38 (29)	29 (20)	266 (24)
Neonate	37 (7)	25 (4)	8 (3)	0	17 (11)	62 (5)
Neutropenia	53 (11)	67 (10)	17 (6)	21 (16)	19 (13)	120 (11)
Transplant recipient	20 (4)	41 (7)	19 (7)	9 (6)	8 (5)	61 (5)
HIV infected[b]	36 (7)	49 (8)	25 (9)	11 (8)	8 (5)	85 (8)
Diabetes	132 (26)	190 (31)	102 (37)	38 (28)	36 (24)	322 (29)
Liver disease	122 (25)	113 (19)	45 (17)	31 (23)	25 (17)	235 (21)
Dialysis[c]	70 (14)	100 (16)	39 (14)	28 (21)	22 (15)	170 (15)
Renal failure	171 (34)	224 (37)	103 (38)	54 (40)	45 (30)	395 (35)
Autoimmune disease	26 (5)	39 (6)	18 (7)	7 (5)	10 (7)	65 (6)
Immunosuppressive therapy	212 (44)	261 (44)	120 (45)	66 (51)	53 (37)	473 (44)
Surgery in last 3 mo	273 (55)	275 (46)	127 (47)	60 (45)	64 (44)	548 (50)
Outpatient acquired[d]	117 (23)	208 (33)	83 (30)	48 (34)	58 (38)	325 (28)
ICU at time of diagnosis	204 (40)	205 (33)	98 (36)	43 (31)	49 (32)	409 (36)
CVC in place at time of diagnosis	388 (83)	464 (84)	197 (83)	109 (85)	116 (81)	852 (78)
Total	516 (45)	626 (55)	275 (24)	141 (12)	153 (13)	1,143

[a] All incident cases identified at both sites during the surveillance period.
[b] AIDS was diagnosed in 30 *C. albicans* cases (86%) and in 35 non-*C. albicans* cases (71%).
[c] Any patient who received any form of dialysis within 3 months prior to this candidemia episode.
[d] Positive blood culture either prior to or on the day of hospital admission.

to this agent. No statistically significant differences in the rates of fluconazole resistance were found between the two surveillance sites. An amphotericin B MIC of ≥1 μg/ml was demonstrated for 16 isolates (1.7%), and an amphotericin B MIC of ≥2 μg/ml was demonstrated for 4 isolates (0.4%). Antifungal susceptibility testing was performed by the referring hospital in 111 cases (10%) as part of medical management during hospitalization.

Clinical characteristics. The demographic and clinical characteristics and the distributions of the various underlying pa-

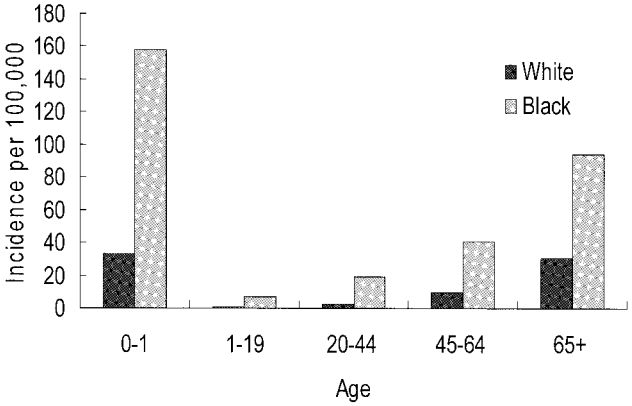

FIG. 1. Annual incidence of candidemia, by age (years) and race, in Connecticut and Baltimore from 1998 to 2000. Incidence rates were calculated by using population data from the U.S. Census 2000 and were adjusted to the U.S. population by age and race.

tient comorbidities and outcomes are summarized by species in Table 1. In 325 cases (28%), candidemia was diagnosed from blood cultures obtained for nonhospitalized individuals or patients within 24 h of hospitalization, indicating outpatient-acquired candidemia. Among the 1,080 patients (94%) hospitalized during this episode of candidemia, the median time between admission and date of positive blood culture for *Candida* species was 10 days (range, 0 to 312 days). The median duration of hospitalization overall was 23 days (range, 0 to 497 days). Although candidemia is often associated with ICU stay, only 409 patients (36%) were in an ICU when this episode of candidemia was diagnosed. A large proportion of patients (641, or 58%) had been hospitalized at least once within the 3 months prior to this episode of candidemia.

Among conditions known to be associated with candidemia, receiving immunosuppressive therapies was the most common (44%), followed by malignancies (24%). Only 11% of all patients were neutropenic, and 5% were transplant recipients (hematopoietic stem cell or solid organ transplants). Of note, 8% of all patients were HIV infected, and the majority of these patients (76%) were diagnosed with AIDS. The distributions of the various underlying conditions were similar for cases from Baltimore and Connecticut, except for HIV infection, which was more common for cases from Baltimore (11 versus 3%, respectively; $P < 0.0001$). Central venous catheters (CVCs) were in place in 852 patients (78%). Vascular catheters were often (83% of CVCs) changed after candidemia was diagnosed.

Candidemia in infants. A total of 64 cases (5.6%) occurred in infants ≤3 months old; 58% of them were black. Almost all were premature (median gestational age, 25 weeks; range, 23 to 40 weeks) and/or had very low birth weight (median birth weight, 793 g; range, 430 to 3,740 g). The majority of these infants were neonates (74% were 1 month old or younger at the time of candidemia diagnosis), with a median age of 16 days (range, 5 to 85 days) at diagnosis. *C. albicans* (60%) was the most common cause of candidemia, followed by *C. parapsilosis* (27%) and *C. glabrata* (13%). Eight infants (13%) died during this hospitalization.

***C. albicans* versus other *Candida* species.** As shown in Table 1, few differences between *C. albicans* and *Candida* species other than *C. albicans* were noted regarding the various demographic characteristics and distributions of the underlying conditions. Several points can be made, however. First, 38% of *C. parapsilosis* cases occurred in outpatients. Second, the 153 *C. parapsilosis* cases had significantly lower fatality rates than did cases of candidemia due to other species. Third, no significant differences were seen in patients over 65 years of age infected with *C. albicans* (232 cases) versus *C. glabrata* (142 cases) ($P = 0.28$). Fourth, 210 patients (19%) had received systemic antifungal drugs during the month prior to diagnosis; 147 of these patients (71%) had received fluconazole. Ninety-six patients (15%) with candidemia due to a *Candida* species other than *C. albicans* had received fluconazole; 51 patients (10%) with *C. albicans* candidemia had received fluconazole (relative risk, 1.5; 95% confidence interval, 1.1 to 2.1).

Predictors of fluconazole resistance. Upon univariable analysis, the following were found to be significantly associated with candidemia caused by a fluconazole-resistant isolate (MIC, ≥64 μg/ml): Black race, presence of neutropenia, transplant recipient, HIV infection, hospitalization required in the 3 months prior to this episode, outpatient-acquired candidemia, and administration of a systemic azole drug in the 3 months prior to this episode (Table 3). Upon multivariable analysis, the following were found to remain independently associated with an increased risk of fluconazole resistance: transplant recipient, HIV infection, and hospitalization required in the previous 3 months.

DISCUSSION

This report provides a population-based description of the burden of *Candida* BSI and its epidemiologic characteristics at the end of the 1990s. Although *C. albicans* continues to be the single most common species causing candidemia, results from this study confirm prior reports that, compared to the situation in the 1980s, a larger proportion of *Candida* BSI in the United States is now caused by *Candida* species other than *C. albicans* (20, 40). Furthermore, since fluconazole is being used more frequently in the management and prevention of invasive *Candida* infections, one of the most important findings of this study is that the incidences of azole resistance overall and of fluconazole resistance in particular remain quite low among bloodstream isolates of *C. albicans* and *Candida* species other than *C. albicans*.

Compared to the findings of an earlier population-based surveillance study in Atlanta and San Francisco (16), the overall incidence of candidemia was higher during this study. However, our data revealed significant differences in the incidences of candidemia between the two surveillance sites, suggesting that geographic differences may exist. The incidence of disease in Connecticut (7 cases per 100,000 population) is similar to the incidence in Atlanta and San Francisco during 1992 and 1993 (8 cases per 100,000) (16) as well as to the incidence determined in a population-based study conducted in Iowa between 1998 and 2001 (6 cases per 100,000) (8). We found a significantly higher incidence of candidemia in Baltimore (24 cases per 100,000) than in Connecticut. However, the incidences by hospital days or discharges were comparable be-

TABLE 2. In vitro susceptibilities of *Candida* isolates to amphotericin B, flucytosine, fluconazole, and itraconazole

Species (no. of isolates)	Antifungal agent	MIC (μg/ml)			No. (%) of resistant isolates[a]
		Range	MIC_{50}	MIC_{90}	
Candida albicans (423)	Amphotericin B	0.002–0.5	0.125	0.25	NA
	Flucytosine	≤0.125–>64	≤0.125	1	18 (4.3)
	Fluconazole	≤0.125–>64	≤0.125	0.5	5 (1.2)
	Itraconazole	≤0.015–>8	0.03	0.125	4 (0.9)
Candida glabrata (226)	Amphotericin B	0.002–12	0.25	0.5	NA
	Flucytosine	≤0.125–>8	≤0.125	≤0.125	0
	Fluconazole	≤0.125–>64	4	16	16 (7.1)
	Itraconazole	≤0.015–>8	0.25	1	44 (19.5)
Candida parapsilosis (123)	Amphotericin B	0.006–1.5	0.25	0.38	NA
	Flucytosine	≤0.125–>64	≤0.125	≤0.125	1 (<1)
	Fluconazole	≤0.125–>4	0.5	1	0
	Itraconazole	≤0.015–>1	0.06	0.25	1 (<1)
Candida tropicalis (118)	Amphotericin B	0.006–1	0.25	0.38	NA
	Flucytosine	≤0.125–>64	0.25	0.5	1 (<1)
	Fluconazole	≤0.125–>64	0.5	8	7 (6)
	Itraconazole	≤0.015–>8	0.125	0.5	7 (6)
Candida krusei (20)	Amphotericin B	0.125–4	0.75	2	NA
	Flucytosine	2–32	8	8	1 (5)
	Fluconazole	2–>64	32	64	7 (35)
	Itraconazole	0.125–>1	0.25	1	5 (25)
Candida dubliniensis (8)	Amphotericin B	0.047–0.25	0.064	0.25	NA
	Flucytosine	≤0.125	≤0.125	≤0.125	0
	Fluconazole	≤0.125	≤0.125	≤0.125	0
	Itraconazole	≤0.015–0.25	0.03	0.06	0
Candida lusitaniae (15)	Amphotericin B	0.002–1	0.125	0.25	NA
	Flucytosine	≤0.125–>64	≤0.125	16	1 (6.7)
	Fluconazole	≤0.125–1	0.5	1	0
	Itraconazole	≤0.015–0.5	0.06	0.25	0
Other *Candida* species[b] (2)	Amphotericin B	0.064–0.25	0.064	0.25	NA
	Flucytosine	≤0.125	≤0.125	≤0.125	0
	Fluconazole	1	1	1	0
	Itraconazole	0.06–0.25	0.06	0.25	0
All *Candida* species (935)	Amphotericin B	0.002–12	0.19	0.38	NA
	Flucytosine	≤0.125–>64	≤0.125	1	22 (2.4)
	Fluconazole	≤0.125–>64	0.5	8	35 (3.7)
	Itraconazole	≤0.015–8	0.06	0.5	61 (6.5)

[a] According to NCCLS breakpoints; no breakpoints have been established for amphotericin B.
[b] *Candida kefyr* ($n = 1$) and *Candida rugosa* ($n = 1$).

tween the two surveillance sites, suggesting that the higher population-based incidence in Baltimore may be related either to more prolonged hospitalization than in Connecticut or to a larger number of hospital admissions or discharges. Furthermore, when we used hospital-based denominators, candidemia rates found in this study among hospitalized patients continued to be relatively higher than rates previously reported in studies in which similar denominators were used (12, 39; reviewed in reference 36). This rate difference could be due to the population-based prospective design of our study, but it also suggests that the overall rate of candidemia in the United States is not declining. In certain hospital settings, such as ICUs or cancer wards, even higher rates of candidemia have been reported (36). Since specific denominators for such settings were not available to us, we could not calculate similar rates for our study.

In the early 1990s, increasing use of fluconazole to treat HIV-infected patients with recurrent oropharyngeal candidiasis resulted in the selection of *Candida* species intrinsically less susceptible to azoles and in the emergence of azole drug-resistant strains in these patients due to the acquisition of resistance by previously susceptible strains of *C. albicans* (reviewed in reference 37). This phenomenon has led to the concern that widespread fluconazole use in broader patient populations could lead to similar selection for species and strains possessing inherent or acquired azole resistance. A number of studies have attempted to determine the likelihood of such occurrences by quantifying shifts in species distribu-

TABLE 3. Predictors of resistance to fluconazole among all patients with candidemia[a]

Type of analysis and variable	No. (%) of patients with isolates that were:		Odds ratio	95% Confidence interval	*P*
	Resistant[b]	Susceptible[c]			
Univariable					
Black race	21 (60)	349 (39)	2.29	1.18–4.45	0.01
Neutropenia[d]	8 (24)	93 (11)	2.36	1.10–5.07	0.03
Transplant recipient	5 (15)	46 (5)	2.9	1.18–7.23	0.02
HIV infected	9 (26)	57 (6)	4.6	2.25–9.50	<0.0001
Required hospital admission in prior 3 mo	28 (82)	506 (58)	3.2	1.34–7.65	0.005
Received systemic azoles in prior 3 mo	8 (23)	108 (12)	2.1	1.0–4.5	0.05
Outpatient acquired[e]	16 (46)	261 (29)	2.0	1.0–3.8	0.03
Multivariable					
Transplant recipient			4.2	1.5–11.7	0.007
HIV infected			5.2	2.2–12.5	0.0002
Required hospital admission in prior 3 mo			2.9	1.2–7.1	0.02

[a] Antifungal susceptibility data were available for 935 isolates (35 resistant and 900 susceptible).
[b] MIC, ≥ 64 μg/ml.
[c] MIC, < 8 μg/ml.
[d] Presence of neutropenia at the time of candidemia diagnosis.
[e] Positive blood culture either prior to or on the day of hospital admission.

tions toward species less susceptible or resistant to azoles, such as *C. glabrata* and *C. krusei*, and increases in MICs toward resistant values in species usually susceptible to azoles, such as *C. albicans* and *C. tropicalis*.

Although many such studies are cross-sectional in nature and cannot fully address the question of shifts over time, several longitudinal studies have shed light on this issue. A report based on National Nosocomial Infections Surveillance system data from 1989 to 1999 documented a significant decrease in the incidence of *C. albicans* nosocomial BSI among ICU patients (from 8 per 10,000 CVC days in 1989 to 2 per 10,000 CVC days in 1999; $P < 0.001$) (40). A significant increase in *C. glabrata* BSI was also noted (from 0.2 per 10,000 CVC days in 1989 to 0.5 per 10,000 CVC days in 1999; $P = 0.05$), but there was no change in *C. krusei* infections (40). A multicenter prospective study conducted in four U.S. medical centers between 1990 and 1994 likewise showed that the proportion of *Candida* isolates other than *C. albicans* from blood had increased throughout the study period, although the species distribution by year was not given (20). Other population-based and sentinel surveillance studies of nosocomial candidiasis, although not longitudinal in design, also showed that the proportion of fungemia due to *C. albicans* remained almost constant throughout the 1990s at about 50% and that the proportion due to *Candida* species other than *C. albicans* ranged from 42 to 48% (8, 9, 16, 26; reviewed in reference 23). The proportion of *C. krusei* fungemia in these studies also remained constant, from 0 in the National Epidemiology of Mycoses Survey study of ICU infections (9) to 4% in a previous population-based study (16). A change in this proportion would have been expected had a shift to inherently azole-resistant species been occurring.

Geographic variations may be an important confounder in these data. The National Epidemiology of Mycoses Survey study demonstrated geographic variations in species distributions throughout the United States, with *C. albicans* ranging from 46% in the northeast to 70% in the southwest and *C. glabrata* ranging from 15% in the southwest to 26% in the northeast (9). *C. glabrata*, a species that easily acquires azole resistance, is represented during the 1990s in surveillance data at proportions ranging from 12 to 24% (23), which again may vary based on geographic differences. Our surveillance data reveal that this trend is continuing. In this study, *C. albicans* comprised 45% of all candidemia cases, and *C. glabrata* was the major component of infections caused by *Candida* species other than *C. albicans*, comprising 24% of all candidemia cases. These species proportions are very similar to those previously reported from the northeastern United States (9). Similar species distributions have been noted elsewhere in the United States (8, 24) but rarely in Europe (12, 25, 34, 42; reviewed in reference 36) or Latin America (25). Our species distribution data are also consistent with other data showing increases in the proportions of *C. glabrata* infections in the 1990s in the United States but not in other parts of the world (25, 36).

Our findings also confirm the low proportions of fluconazole resistance among *C. albicans* bloodstream isolates that were recently reported elsewhere (8, 24, 25; reviewed in references 33 and 37). When our two surveillance studies are compared, the MIC_{50}s of fluconazole and itraconazole for *C. albicans* have remained almost unchanged between 1992 to 1993 and 1998 to 2000. These findings have important implications for the management of *C. albicans* infections, especially given that fluconazole is commonly used for the treatment of uncomplicated candidemia (32). The negligible incidence of fluconazole resistance among *C. albicans* isolates during both population-based and sentinel surveillance programs supports the current practice that antifungal susceptibility testing should not be performed routinely for *C. albicans* but may be indicated for patients who fail to respond to initial therapy or who develop breakthrough candidemia while receiving fluconazole prophylaxis.

Our susceptibility results for *Candida* species other than *C. albicans* mirror those of a study by Kao et al. (16) and the results of other studies (25, 37) in showing a low level of in vitro azole resistance in *C. glabrata* and *C. tropicalis*, no resis-

tance in *C. parapsilosis* or the newly reported *C. dubliniensis*, and the expected high level of resistance in *C. krusei*. Nevertheless, in the initial management of fungemia caused by *Candida* species other than *C. albicans*, *C. glabrata* should receive special attention. Previous surveillance studies demonstrated resistance (MIC, ≥64 μg/ml) in *C. glabrata* varying from 7 to 15% (reviewed in reference 23). Although only 7% of the incident *C. glabrata* isolates in this study were resistant to fluconazole (MIC, ≥64 μg/ml), the MIC_{50} of 4 μg/ml for these isolates was higher than those for the other species tested, and the MIC_{90} was within the S-DD range at 16 μg/ml. Therefore, fluconazole may not be the initial therapy of choice for such infections until the results of susceptibility testing are known and may not be an appropriate choice at all in extremely ill patients. The use of chromogenic culture media (CHROMagar Candida or equivalent) (11, 15) in the laboratory can help distinguish *C. albicans* from several common *Candida* species other than *C. albicans* and can serve an important role in rapid species identification prior to the completion of antifungal susceptibility testing.

In a previous study (16), Kao et al. documented amphotericin B MICs ranging from 0.016 to 6 μg/ml, with 7% of isolates demonstrating potential resistance at concentrations of ≥2 μg/ml. In this study, we documented amphotericin B MICs ranging from 0.002 to 12 μg/ml, with MICs of ≥0.38 μg/ml for 10% of isolates, ≥1 μg/ml for 1.7%, and ≥2 μg/ml for 0.4%. The decreased susceptibility of *C. krusei* to amphotericin B (MIC_{90}, 2 μg/ml) is consistent with previous reports for this organism (16, 26). Pfaller et al. (28) recently reported the in vitro activities of flucytosine against more than 8,000 incident isolates of *Candida* spp. obtained from blood and other deep sites at more than 200 hospitals worldwide. Only 3% of *C. albicans* and 1% of *C. glabrata* isolates were resistant to this agent in vitro. In the present study, 4.3% of *C. albicans* isolates were resistant to flucytosine, compared with <1% of *C. parapsilosis* and *C. tropicalis* isolates and no *C. glabrata* isolates. Our results support the suggestion that this agent could be a useful adjunct in the treatment of serious *Candida* infections (28).

This study showed that patients who had received prophylactic fluconazole in the month prior to candidemia were slightly but significantly more likely to develop candidemia due to *Candida* species other than *C. albicans*. The effects of prior fluconazole use on the distribution of various *Candida* species causing BSI and, in particular, on the emergence of *C. glabrata* infections were previously demonstrated for patients with hematologic malignancies (1, 18), although other confounding risk factors have also been described (47, 48). Previous studies also showed a significant association between receipt of antifungal prophylaxis as well as acute leukemia and a higher incidence of candidemia caused by *Candida* species other than *C. albicans* (41). Taken as a whole, these results suggest that increases in *C. glabrata* incidences might be related to fluconazole usage, although other host and health care factors could also have an effect on this trend (37, 47, 48).

Population-based surveillance identifies all cases of the disease being studied regardless of the health care setting in which it occurs and allows a population-representative description of the epidemiology and predisposing conditions associated with this disease to be made. Our data show several associations between patients with candidemia and various risk factors. First,is the presence of CVCs; nearly 80% of patients diagnosed with candidemia had a catheter in place at the time of diagnosis. Second is the recognition that candidemia is no longer associated exclusively with the ICU, as only 36% of patients in this study were in an ICU at the time of diagnosis. In addition, this study follows the trend recognized earlier (16) in that 28% of all candidemia cases and 38% of *C. parapsilosis* BSI were acquired outside the hospital. Although these infections did not meet the definition for nosocomial acquisition, these patients still shared health care-related risk factors, since most had indwelling vascular catheters at the time of diagnosis and had a history of recent hospitalizations. Furthermore, the relationship among *C. parapsilosis* fungemia, intravascular catheters, and parenteral nutrition is well appreciated (45). These findings reflect the changes in health care delivery in the United States, such as the management at home of patients with indwelling catheters and various chronic diseases. Third, the distributions of various *Candida* species by age group and underlying condition were very similar, with some minor exceptions. Other recently published reports noted that some species, such as *C. glabrata*, may be more common among older persons (8) or among patients with hematologic malignancies (3). These differences may have been observed because of the nature of the centers where the studies were conducted. These included major cancer or other referral centers, a fact which makes these observations more relevant to patient groups at these centers rather than to the population as a whole or to the majority of hospital settings.

We confirmed the continuing predominance of *C. albicans* and *C. parapsilosis* in the neonatal population that Kao et al. (16) and Pfaller et al. (29) previously reported. The high incidence of candidemia among infants, as well as the significant difference by race in this age group, was noted in the study of Kao et al. (16) and is known to be an important public health problem in this population (17, 35, 42). In addition to low gestational age and birth weight, the striking association of candidemia with race is reemphasized in this study. Although this association may be related to the higher incidence of prematurity among black infants (14), our findings further emphasize the need to identify preventable risk factors and the need to implement preventive measures, such as azole prophylaxis, for this high-risk group (17).

The high candidemia-associated mortality observed in this study (36%) is another reminder of the public health importance of this condition. Similar crude mortality rates were recently reported from other surveillance studies (12, 39). Other groups have also studied risk factors for candidemia associated with mortality (12, 13, 21, 39, 42). These usually include factors related to the severity of disease in the host, such as older age, ICU admission, higher acute physiology and chronic health evaluation scores, and underlying conditions, such as neutropenia. In this study, mortality was similar among patients regardless of the species causing candidemia, with the exception of *C. parapsilosis*, which had significantly lower case-fatality rates. In order to determine factors associated with mortality in our study, we are currently conducting additional analyses with an extended database of detailed clinical information and are taking into consideration the antifungal susceptibility profiles, treatment regimens, and other clinical factors that may affect patient outcome.

In this article, we have described the current epidemiology of candidemia at selected sites in the United States, highlighting the significant morbidity and mortality that continue to be associated with this infection, both within and outside the hospital setting. *Candida* BSI now result in significant costs to the health care system, averaging millions of dollars per year (31). Our findings emphasize the need to conduct further studies that will identify preventable risk factors and define subgroups of high-risk individuals who could potentially benefit from targeted prevention efforts, such as azole chemoprophylaxis (38). The low incidence of fluconazole resistance among bloodstream isolates of *C. albicans* is reassuring. However, as *Candida* species other than *C. albicans* become more common causes of candidemia, further studies will be needed to understand more clearly the interaction between these organisms and host conditions as well as environmental factors in different health care settings. In addition, studies will be needed to understand better the correlation of azole resistance with clinical outcome. Periodic surveillance, either population based or sentinel, is warranted to continue monitoring trends in the incidence of various *Candida* species causing bloodstream infections as well as the incidence of azole drug resistance.

ACKNOWLEDGMENTS

We are grateful to the many individuals in the hospitals and laboratories in the surveillance areas for help in identifying cases and obtaining isolates for evaluation at the CDC. We thank Mario Hairston, Nathelia LeSane, Ren-Kai Li, Gabriel Ponce de Leon, W. Ruth Pruitt, and Gwendolyn Smith for assistance.

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