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Candida Bloodstream Infections: Comparison of Species Distributions and Antifungal Resistance Patterns in Community-Onset and Nosocomial Isolates in the SENTRY Antimicrobial Surveillance Program, 2008-2009▽

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Community-onset (CO) candidemia, defined as a positive blood culture taken at or within 2 days of hospital admission, represents a distinct clinical entity associated with substantial morbidity and mortality. Reference MIC results from the SENTRY Antimicrobial Surveillance Program (2008-2009) were analyzed to compare the antifungal resistance patterns and species distributions from patients with CO and nosocomial bloodstream infections (BSI) in 79 medical centers. Among 1,354 episodes of BSI, 494 (36.5%) were classified as CO and 860 (63.5%) as nosocomial in origin. More than 95% of the isolates from both BSI types were contributed by *Candida albicans* (48.4%), *C. glabrata* (18.2%), *C. parapsilosis* (17.1%), *C. tropicalis* (10.6%), and *C. krusei* (2.0%). *C. albicans* was more common in CO BSI (51.0%) than nosocomial BSI (46.9%), whereas *C. parapsilosis* and *C. krusei* were more common in nosocomial BSIs (18.1 and 2.7%, respectively) than in CO BSIs (15.4 and 0.8%, respectively). *C. glabrata* and *C. tropicalis* were comparable in both CO (18.4 and 10.5%, respectively) and nosocomial (18.1 and 10.6%, respectively) episodes. Resistance to azoles (fluconazole, posaconazole, and voriconazole) and echinocandins (anidulafungin, caspofungin, and micafungin) was uncommon (<5%) in CO BSI using recently established Clinical and Laboratory Standards Institute breakpoint criteria. Resistance to echinocandins (anidulafungin [3.8%], caspofungin [5.1%], and micafungin [3.2%]) and azoles (fluconazole [7.7%], posaconazole [5.1%], and voriconazole [6.4%]) was most prevalent among nosocomial BSI isolates of *C. glabrata*. CO candidemia is not uncommon and appears to be increasing worldwide due to changing health care practices. Although resistance to the azoles and echinocandins remains uncommon among CO isolates, we demonstrate the emergence of nosocomial occurrences of *C. glabrata* expressing resistance to both monitored classes of antifungal agents.

Invasive candidiasis (IC; candidemia and other deep-seated infections, including disseminated candidiasis, endocarditis, meningitis, and hepatosplenic infection) now is widely recognized as an important public health problem, with considerable morbidity, mortality, and associated health care costs (1, 6, 11, 14, 17, 19, 23, 36, 44). Although much of the literature concerning IC has focused on nosocomial (NOS) bloodstream infections (BSI), especially those occurring in the intensive care unit (ICU) (3, 12, 13, 25, 27, 49), an increasing incidence of IC overall (35, 50), combined with data from the National Nosocomial Infection System survey, which found a decline in the frequency of candidemia among ICU patients in the United States (47), suggest that the burden of IC is shifting from the ICU to other health care settings. Hajjeh et al. (17) have shown that in 1998 through 2000, only 36% of *Candida* BSIs occurred in the ICU, whereas 28% were community onset (CO), an increase of almost 10% above that reported in 1992 and 1994 (19). Subsequently, Sofair et al. (45) determined that 31% of 1,143 cases of candidemia were CO infections (occurring ≤2 days after hospital admission). These observations led participants in a recent health care-associated (HCA) infection summit to conclude that clinicians should be aware of the potential for *Candida* to be a cause of BSI in patients presenting to the emergency department (20).

Recently, Shorr et al. (42) found that CO candidemia represented a distinct clinical entity with substantial morbidity and mortality. Compared to other types (bacterial) of CO BSIs, patients with CO candidemia were more severely ill and likely to have been recently discharged from an acute-care hospital or admitted from another health care facility or nursing home (42). Thus, candidemia has spread beyond the confines of acute-care hospitals, and the failure to consider CO candidemia in at-risk subjects may have adverse consequences (42).

There now are several candidemia surveys that have provided estimates of the frequency of CO compared to that of nosocomial cases in different geographic locations (1, 6, 10, 11, 17, 19, 22, 26, 32, 38, 41, 45, 48); however, very few have examined the distribution of species in these two settings, and none provide data concerning the resistance profiles of CO versus nosocomial isolates to the available systemically active antifungal agents.

The SENTRY Antimicrobial Surveillance Program (antifungal objective), active since 1997, has reported previously that 25% of candidemia episodes (1,184) from an international survey in 1997-1999 were nonnosocomial or CO (38). In the present study, we update this landmark information using the SENTRY program database from 2008-2009, including geo-

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TABLE 1. Geographic variation in community-onset versus nosocomial *Candida* BSI: SENTRY Antimicrobial Surveillance Program (2008-2009)

Region	Total no. of BSI	No. (%) of BSI according to origin	
		Community onset	Nosocomial
Europe	477	107 (22.4)	370 (77.6)
Latin America	257	72 (28.0)	185 (72.0)
North America	620	315 (50.8)	305 (49.2)
Total	1,354	494 (36.5)	860 (63.5)

graphic variation in CO candidemia, species distribution indexed by CO and nosocomial status, and the associated resistance patterns for the contemporary echinocandin and azole antifungal agents.

MATERIALS AND METHODS

Organisms and study sites. Between January 2008 and December 2009, a total of 2,085 BSI isolates of *Candida* spp. from 79 medical centers throughout the world were submitted to JMI Laboratories (North Liberty, IA) for identification and reference antifungal susceptibility testing with fluconazole, posaconazole, voriconazole, anidulafungin, caspofungin, and micafungin. The isolates represented consecutive incident cases of patients with candidemia treated at hospitals in the Asia-Pacific (16 centers; 51 isolates), European (25 centers; 750 isolates), Latin American (10 centers; 348 isolates), and North American (28 centers; 936 isolates) regions. CO BSI was defined as an infection detected (positive blood culture) at or within 2 days of hospital admission, whereas nosocomial BSI was defined as an infection not present on admission and having onset more than 2 days after hospital admission. Although some authors divide CO BSI into health care-associated (HCA) infections (health care-associated risk factors include recent hospitalization, nursing home, indwelling medical device, chemotherapy, and dialysis) and community-acquired (CA) infections (no HCA risk factors) (6, 18, 24), most studies of CO candidemia do not (17, 42, 45), and the SENTRY Program database does not allow for that level of discrimination. Among the more than 2,000 episodes of BSI in the present study, the time of candidemia onset was provided for 1,354 (65%) patient episodes.

The isolates were identified by standard methods and stored as water suspensions until processed in the study. Before being tested, each isolate was passaged on Sabouraud dextrose agar (Remel, Lenexa, Kansas) and CHROMagar (Becton Dickinson, Sparks, Maryland) to ensure purity and viability.

A total of 12 NOS isolates of *C. glabrata* for which caspofungin MIC values were ≥0.5 μg/ml were further characterized for the presence or absence of mutations in the hot spot (HS) regions of *fks1* and *fks2* as described previously (4, 28, 37).

Antifungal susceptibility testing. All *Candida* spp. isolates were tested for susceptibility to the echinocandins and triazoles using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods (7). MIC results for anidulafungin, caspofungin, micafungin, and fluconazole were read following 24 h of incubation, whereas MIC results for posaconazole and voriconazole were read after a 48-h incubation. In all instances the MICs were determined visually as the lowest concentration of drug that caused a significant diminution (≥50% inhibition) of growth below the control level (7). We used the recently revised CLSI clinical breakpoints (CBP) to identify strains of *Candida* that are resistant to the echinocandins and fluconazole (33, 34, 37): anidulafungin, caspofungin, and micafungin MICs at >0.5 μg/ml were considered resistant for *C. albicans*, *C. tropicalis*, and *C. krusei*, and MICs at >4 μg/ml were considered resistant for *C. parapsilosis*; anidulafungin and caspofungin MICs at >0.5 μg/ml and micafungin MICs of >0.12 μg/ml were declared resistant for *C. glabrata*; fluconazole MICs of >4 μg/ml were categorized as resistant for *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, and MICs at >32 μg/ml were considered resistant for *C. glabrata*. All isolates of *C. krusei* were considered resistant to fluconazole. The CLSI resistance breakpoint for voriconazole (MIC, >2 μg/ml) also was an indicator of resistance for posaconazole tested against all species (8, 39). Quality control was performed by testing CLSI-recommended strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (8).

TABLE 2. Distribution of *Candida* bloodstream infections: health care setting for community-onset versus nosocomial BSI[a]

Location (reference or source)	Time period	Total no. of BSI	% of total BSI[b]		
			CO	CA/HCA	Nosocomial
Australia (41)	1999–2008	1,137	12	NA/NA	88
Australia (6)	2001–2004	1,095	19	7/12	81
Brazil (32)	1995–2003	210	9	2/7	91
Spain (1)	2002–2003	345	11	NA/NA	89
Taiwan (22)	1995–2005	2,073	3	<1/2	97
Canada (26)	1992–1996	202	17	NA/NA	83
United States (48)	1992–1993	843	16	NA/NA	84
United States (19)	1992–1993	767	20	NA/NA	80
United States (45)	1998–2000	1,143	31	8/23	69
United States (10)	1999–2000	929	10	NA/NA	90
United States (11)	1998–2001	254	4	NA/NA	96
Global (38)	1997–1999	1,184	25	NA/NA	75
Global (present study)	2008–2009	1,354	36	NA/NA	64

[a] NA, data not available.
[b] CO infection (positive blood culture ≤48 h after hospital admission) includes CA (no health care-associated risk factors) and HCA (health care-associated risk factors, including recent hospitalization, nursing home, indwelling medical device, chemotherapy, and dialysis); nosocomial, BSI not present in admission and occurring >48 h after admission

RESULTS AND DISCUSSION

Frequency of CO candidemia in three geographic regions. Among the 1,354 episodes of candidemia, 494 (36.5%) were CO and 860 (63.5%) were nosocomial (Table 1). The frequency of CO candidemias was considerably higher in North America (50.8%) than that observed in Europe (22.4%) and Latin America (28.0%). In each region, however, the frequency of CO candidemia increased from 2008 to 2009 (data not shown).

These data may be compared to that of 12 different surveys spanning the last 17 years and covering several different geographic settings (Table 2). Whereas some of these studies identified CA and HCA BSIs, most used the definition for CO defined for the present study, without the differentiation of CA and HCA. Those who identified CA, HCA, and nosocomial BSIs found that patients presenting with HCA BSI were similar to those with nosocomial infections, whereas those with CA infections included patients with intravenous drug use, gastrointestinal disorders, and diabetes (6). Although the SENTRY program does not collect clinical or risk factor data, we assume that the vast majority of the CO BSI patients in this survey have HCA risk factors.

Although the variation in the frequency of CO candidemia was considerable (Table 2), most of these studies reported that greater than 10% of *Candida* BSI may be categorized as CO, with the highest proportions being detected in the United States. Within the United States, it is notable that the CO candidemia frequency has increased from 16 to 20% in 1992-1993 (19, 48), to 31% in 1998-2000 (45), and to 50.8% in the present study. Whereas the latter figure seems high, the trend in the United States is unmistakable and supports the concerns voiced by Kollef et al. (20) and Shorr et al. (42).

As cost containment pressures continue to mount and hospital discharges to secondary-care facilities (including home care) are expedited, clearly the boundaries between nosocomial and CO infection may no longer be valid (9, 10, 18, 24, 42, 43). In the United States, increasing numbers of patients are being managed in the community with risk-increasing proce-

TABLE 3. Studies showing pathogen distribution between patients with CO versus NOS *Candida* bloodstream infections

Species	% of total (no. tested) for each species according to reference and isolate origin											
	Present study		Almirante et al. (1)		Sofair et al. (45)		Kao et al. (19)		Chen et al. (6)		Playford et al. (41)	
	CO (494)	NOS (860)	CO (37)	NOS (308)	CO (356)	NOS (787)	CO (155)	NOS (612)	CO (170)	NOS (749)	CO (135)	NOS (1,002)
C. albicans	51	47	62	50	37	49	45	54	40	50	30	47
C. glabrata	18	18	11	8	25	24	16	11	NA[a]	NA	10	14
C. parapsilosis	15	18	16	23	16	12	26	20	31	17	42	25
C. tropicalis	11	11	5	10	15	11	7	11	NA	NA	3	5
C. krusei	1	3	0	4	5	1	6	4	NA	NA	2	3

[a] NA, data not available.

dures such as chemotherapy, dialysis, parenteral nutrition, parenteral antimicrobial agents, and indwelling catheters (9, 20, 42, 45). Given these considerations, it is interesting that the proportion of CO candidemia in non-U.S. locations, such as Taiwan (3%), Brazil (9%), and Spain (11%), are considerably lower than that in the United States (Table 2), possibly due to a difference in outpatient central venous catheter use and the increasing practice in the United States of the management of various chronic diseases at home rather than in the hospital (1, 17, 45).

Species distribution between CO and nosocomial BSI. The 1,354 *Candida* BSI isolates included 655 (48.4%) *C. albicans*, 247 (18.2%) *C. glabrata*, 232 (17.1%) *C. parapsilosis*, 143 (10.6%) *C. tropicalis*, 27 (2.0%) *C. krusei*, and 50 (3.7%) miscellaneous species, including *C. dubliniensis* (16 isolates), *C. guilliermondii* (eight isolates), *C. kefyr* (six isolates), *C. famata* (three isolates), *C. lipolytica* (three isolates), *C. rugosa* (two isolates), *C. sake* (two isolates), *C. pelliculosa* (two isolates), and one isolate each of *C. lambica*, *C. utilis*, *C. haemulonii*, *C. norvegensis*, and *C. inconspicua*.

In analyzing the frequency of the isolation of different species by CO and nosocomial BSI, we found only minor differences (Table 3). *C. albicans* was more common among CO infections, while *C. parapsilosis* and *C. krusei* were more common among nosocomial candidemias. Most of the other surveys where pathogen distribution was reported showed that *C. albicans* was more common in nosocomial BSI and that *C. parapsilosis* was more common in CO infections (Table 3). Although it has been speculated that the prominence of *C. parapsilosis* as a cause of candidemia in CO infections is due to the exogenous introduction of this skin commensal into the bloodstream via long-term vascular catheters, there is little objective evidence to support this hypothesis (6, 45).

Differences in antifungal agent susceptibilities among isolates from CO and nosocomial BSIs. As shown in Table 4, no resistance to anidulafungin, caspofungin, micafungin, posaconazole, or voriconazole was detected among CO isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis*, or *C. krusei.* In fact, the only resistance to fluconazole detected in these four species was observed in isolates of *C. parapsilosis.* Among CO isolates of *C. glabrata*, resistance to anidulafungin, caspofungin, and all three triazoles was found in a small number of isolates.

Among the nosocomial isolates of *C. albicans*, one isolate (from a patient in Germany) was resistant to all three echinocandins, whereas no resistance to the azoles was detected. None of the nosocomial isolates of *C. parapsilosis* or *C. tropicalis* were resistant to the echinocandins; however, 5.8% of the

TABLE 4. Frequency of antifungal resistance among community-onset and nosocomial bloodstream infection isolates of *Candida* spp.: SENTRY Antimicrobial Surveillance Program (2008-2009)

Species and antifungal agent	% of isolates resistant (R) to each antifungal[a]			
	Community-onset		Nosocomial	
	No.[b]	%R	No.[b]	%R
C. albicans				
Anidulafungin	252	0.0	403	0.25
Caspofungin	252	0.0	403	0.5
Micafungin	252	0.0	403	0.25
Fluconazole	252	0.0	403	0.0
Posaconazole	252	0.0	403	0.0
Voriconazole	252	0.0	403	0.0
C. glabrata				
Anidulafungin	91	1.1	156	3.8
Caspofungin	91	2.2	156	5.1
Micafungin	91	0.0	156	3.2
Fluconazole	91	3.3	156	7.7
Posaconazole	91	3.3	156	5.1
Voriconazole	91	3.3	156	6.4
C. parapsilosis				
Anidulafungin	76	0.0	156	0.0
Caspofungin	76	0.0	156	0.0
Micafungin	76	0.0	156	0.0
Fluconazole	76	6.6	156	5.8
Posaconazole	76	0.0	156	0.0
Voriconazole	76	0.0	156	0.0
C. tropicalis				
Anidulafungin	52	0.0	91	0.0
Caspofungin	52	0.0	91	0.0
Micafungin	52	0.0	91	0.0
Fluconazole	52	0.0	91	3.3
Posaconazole	52	0.0	91	0.0
Voriconazole	52	0.0	91	2.2
C. krusei				
Anidulafungin	4	0.0	23	0.0
Caspofungin	4	0.0	23	8.7
Micafungin	4	0.0.	23	0.0
Posaconazole	4	0.0	23	0.0
Voriconazole	4	0.0	23	0.0

[a] Resistance defined as a MIC of >0.5 μg/ml for anidulafungin, caspofungin, and micafungin against *C. albicans*, *C. tropicalis,* and *C. krusei* and as a MIC of >4 μg/ml for *C. parapsilosis*; resistance defined as a MIC of >0.5 μg/ml for anidulafungin and caspofungin and as a MIC of >0.12 μg/ml for micafungin against *C. glabrata*; resistance defined as a MIC >4 μg/ml for fluconazole against *C. albicans, C. tropicalis,* and *C. parapsilosis,* and as a MIC of >32 μg/ml for posaconazole and voriconazole against all species.

[b] Total number of isolates tested.

TABLE 5. MIC distributions of three echinocandins against nosocomial *Candida glabrata* strains tested for the presence of *fks* mutations: SENTRY Antimicrobial Surveillance Program (2008-2009)

MIC (μg/ml)	Anidulafungin			Caspofungin			Micafungin		
	No. of isolates[a]	No. tested[b]	No. of mutations[c]	No. of isolates[a]	No. tested[b]	No. of mutations[c]	No. of isolates[a]	No. tested[b]	No. of mutations[c]
≤0.03	3						107		
0.06	69						40	4	0
0.12	68	3	0	29			4	3	1
0.25	9	2	0	89			2	2	2
0.5	1	1	1	30	5	0	1	1	1
1	4	4	3	6	5	4			
2	1	1	1				1	1	1
4	1	1	1						
≥8				2	2	2	1	1	1

[a] Total number of *C. glabrata* isolates tested against each echinocandin using the CLSI M27-A3 method (7).
[b] Number of isolates tested for the presence of *fks1* and *fks2* mutations.
[c] Number of isolates with *fks1* or *fks2* mutations.

nosocomial *C. parapsilosis* and 3.3% of the nosocomial *C. tropicalis* strains were resistant to fluconazole. The finding of resistance to fluconazole but not to the echinocandins among CO and nosocomial isolates of *C. parapsilosis* should be noted in light of the recommendation of the Infectious Diseases Society of America that infection with this species should be treated with either an azole or amphotericin B (lipid formulation) rather than an echinocandin (30). This recommendation may inadvertently result in increased drug pressure on *C. parapsilosis*, with a subsequent increase in azole resistance. Thus, fluconazole resistance among *C. parapsilosis* isolates must be recognized as a possibility, and this species should be monitored closely in the future. Cross-resistance between fluconazole and voriconazole was noted in 2.2% of *C. tropicalis* isolates of nosocomial origin. Overall, fluconazole resistance was observed in 2.6% of CO isolates but 5.8% of nosocomial isolates. Along these lines, it should be noted that *C. parapsilosis* and *C. tropicalis* accounted for 29% of all fluconazole resistance in this survey. Resistance was infrequent among nosocomial isolates of *C. krusei*, where only two isolates resistant to caspofungin were detected.

Resistance to both azoles and echinocandins was most prominent in *C. glabrata* isolates, with the highest resistance rates to anidulafungin (3.8%), caspofungin (5.1%), micafungin (3.2%), fluconazole (7.7%), posaconazole (5.1%), and voriconazole (6.4%) found in the isolates of nosocomial origin (Table 4). A total of 12 nosocomial isolates of *C. glabrata* (caspofungin MIC, ≥0.5 μg/ml) were selected to be tested for the presence of *fks* mutations; five were classified as intermediate (MIC, 0.5 μg/ml), and several were classified as resistant (MIC, ≥1 μg/ml) to caspofungin. None of the isolates for which the caspofungin MIC was 0.5 μg/ml contained an *fks* mutation, while six of the seven resistant isolates were shown to have a mutation in either *fks1* or *fks2* (Table 5). Of the six isolates shown to have *fks* mutations, five were categorized as resistant and one as intermediate to anidulafungin and micafungin (Table 5), confirming the utility of the resistant CBP.

Other investigators have noted the propensity of *C. glabrata* to mutate to a multidrug-resistant (MDR) phenotype *in vivo* in a single patient (5, 21) and have suggested that the expression of resistance to echinocandins and other classes of antifungal agents in *C. glabrata* is facilitated by the haploid nature of the genome (5, 40). Our observations support the potential emergence of an MDR phenotype among nosocomial isolates of *C. glabrata* with cross-resistance in azole and echinocandin classes. The fear of azole resistance and the generally excellent wild-type susceptibility of most species of *Candida* to the echinocandins has driven the use of echinocandins for the treatment of IC (30). The increase of MDR *C. glabrata* strains has become a serious concern expressed by several investigators (5, 40, 46), and it argues for continued close resistance surveillance and the increased application of standardized antifungal susceptibility testing.

The increasing recognition of CO candidemia raises the issue of whether an antifungal therapy should be added to the first-line empirical antimicrobial regimen for patients presenting with sepsis (9, 20, 42, 45). It is now evident that a delay in initiating antifungal therapy in the critically ill patient is associated with compromised outcomes (an increase in mortality of 8% for each hour in which appropriate therapy is delayed), excessive costs of hospitalization, and potentially devastating complications such as endocarditis, endophthalmitis, osteomyelitis, and disseminated candidiasis (2, 15, 16, 23, 29, 31, 42). Shorr et al. (42) demonstrated that the risk-adjusted mortality rate (28.3%), length of stay in hospital (13.7 days), and attributable cost ($30,219 per episode) was greater for CO candidemia patients than that for patients with CO bacteremia. Ideally the decision to initiate antifungal therapy should be guided by rapid diagnostic markers and/or risk stratification schema to maximize benefits and reduce the risk of drug toxicity and resistance development (9, 20). In the absence of such diagnostic aids, it seems reasonable to consider treating high-risk patients with clinical evidence of sepsis with an antifungal agent with systemic activity against *Candida* spp. This would be especially true if the patient was known to be colonized with a yeast (9, 20, 42). The lack of resistance to both the echinocandins and azoles among CO candidemia isolates shown in the present study suggests that at least for now, such decisions may be made without fear of resistance.

There are several notable findings in this survey of contemporary CO and nosocomial *Candida* BSI isolates. First, it is evident that CO candidemias are not rare and appear to be increasing worldwide due to changes in health care practices. Second, whereas the species distribution is similar between CO

and nosocomial BSI, resistance to the azoles and echinocandins is quite uncommon among CO isolates. Third, the frequency of azole resistance among CO and nosocomial isolates of *C. parapsilosis* is important and bears watching. Fourth, the finding of both azole and echinocandin resistance in nosocomial isolates of *C. glabrata* is very disturbing and indicates that this species will continue to pose a major therapeutic problem even in the current echinocandin era. These findings argue for increased awareness of CO candidemia as a distinct clinical entity that appears to be becoming more common throughout the world. An increased level of suspicion and the prompt application of appropriate systemically active antifungal therapy, coupled with timely and accurate identification and antifungal susceptibility testing, will be necessary to optimize the management of this important infectious process.

Being a descriptive and sentinel-based survey, there are certain limitations inherent in the SENTRY surveillance program that must be acknowledged. The lack of clinical data, severity of illness measures, risk factors, and antifungal drug exposure limits the clinical utility of this study. Despite a long-standing protocol for testing and reporting consecutive isolates from individual infectious episodes and the collection of a necessarily limited amount of demographic information, there are no controls for participant compliance with the isolate submission and completion of the demographic data forms from one year to the next. Despite these limitations, the overall size of the data set presented herein does provide useful descriptive information. Such information will continue to be useful as a basis for future studies regarding the prevalence of CO candidemia and antifungal susceptibility of associated species as agents of invasive candidiasis throughout the world.

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