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Candida Bloodstream Infection: Comparison of Species Distribution and Resistance to Micafungin and Azole Antifungal Agents in Intensive Care Unit and Non-ICU Settings

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SENTRY ANTIMICROBIAL SURVEILLANCE

Abstract

Background: 30-50% of *Candida* bloodstream infections (CBI) occur in the intensive care unit (ICU). However, most data on species distribution and antifungal resistance (R) in ICUs are limited to single medical centers, and do not compare species distribution and micafungin (MCF) or azole R profile to those from non-ICU environments.

Methods: We analyzed CLSI MIC data from the SENTRY Antimicrobial Surveillance Program (2008-2009) to compare the antifungal-R profiles and species of CBI isolates obtained from patients in ICU vs non-ICU locations in 79 medical centers. MIC results were obtained for MCF, fluconazole (FLC), posaconazole (PSC) and voriconazole (VRC) after 24-hours incubation. Recently revised CLSI breakpoints for R were employed: MCF MICs >0.5 µg/ml were R for *C. albicans* (Ca), *C. tropicalis* (Ct) and *C. krusei* (Ck); MICs >4 µg/ml were R for *C. parapsilosis* (Cp); [for MCF] MICs >0.12 µg/ml were R for *C. glabrata* (Cg); FLC MICs >4 µg/ml were R for Ca, Cp and Ct; MICs >32 µg/ml were R for Cg; and PSC and VRC MICs >2 µg/ml were considered R for all species.

Results: 1,752 *Candida* spp. were obtained from ICU (779) and non-ICU (973). 96% of the isolates in both settings were identified as Ca, Cg, Cp, Ct and Ck. The highest proportions of CBI due to Ca (50.4 vs. 47.4%) and Ct (10.5 vs 9.6%) were detected in the ICU and the highest proportions of Cg (18.1 vs 12.5%) and Cp (18.9 vs 15.1%) were seen in the non-ICU settings. There were no MCF-R strains of Cp, Ct or Ck in either setting; however MICs >0.5 µg/ml were found in 0.3% of Ca isolates, 0.7% of Cg from the ICU and in 1.2% of non-ICU isolates of Cg. Among Cg isolates from the ICU, 7.4% were R to PSC and 5.0% were R to VRC, where only 0.6 and 1.1% of non-ICU Cg isolates were R to PSC and VRC, respectively. Ct isolates from the ICU were more R to FLC (6.1 vs 2.2%) and VRC (4.9 vs 1.1%) than non-ICU CBI isolates.

Conclusions: Differences in both species distribution and antifungal R were detected between ICU and non-ICU hospital settings. ICU isolates of Cg and Ct were clearly more R to the azoles when compared to non-ICU isolates. MCF R was very uncommon in both treatment environments.

Introduction

Invasive candidiasis cases occur in approximately 30 and 50% of inpatients hospitalized in the intensive care unit (ICU) setting. Despite the monitoring by several antifungal surveillance programs throughout the world, very few explicitly describe the species distribution and antifungal resistance profiles for invasive candidiasis in ICUs, and those that do are often limited to single center studies. Similarly, only a few studies have compared species occurrence and resistance profiles of isolates from ICUs versus those from non-ICU environments. Whereas, it is well-known that multidrug-resistant (MDR) bacteria are more common in the ICU settings than elsewhere in the hospital, like data is limited for invasive candidiasis. Given the fact that crude mortality rates for invasive candidiasis in the ICU are among the highest of any nosocomial infection, a more detailed understanding of isolates of *Candida* spp. from ICU patients appears warranted.

In the present study, we evaluated species distribution according to ICU versus non-ICU location, and the associated resistance profiles for the contemporary echinocandin and azole antifungal agents using the SENTRY Program database for 2008-2009, including geographic variation in ICU candidemia. Additionally, we applied the recently revised Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoints.

Methods

Organisms and study sites: Between January 2008 and December 2009, a total of 2,085 bloodstream infections (BSI) isolates of *Candida* spp. from 79 medical centers throughout the world were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for identification and antifungal susceptibility testing with fluconazole, posaconazole, voriconazole, anidulafungin, caspofungin and micafungin. The isolates represented consecutive incident isolates from 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. Among those 2,085 episodes of BSI, patient location (ICU versus non-ICU) was provided for 1,752 (84%).

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

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

Results

- Among the 1,752 episodes of candidemia, 779 (44.5%) occurred in the ICU setting and 973 (55.5%) occurred in patients cared for in other hospital locations (Table 1). The frequency of ICU-associated BSIs due to *Candida* spp. was higher in Latin America (56.5%) compared to that in Europe (44.4%) and North America (39.6%). In Latin America and North America, the frequency of candidemia in the ICU decreased between 2008 and 2009 (Table 1).
- Minor differences in species frequency were observed comparing isolates from the ICU versus non-ICU. *C. albicans* and *C. tropicalis* were more common among ICU infections, while *C. glabrata* and *C. parapsilosis* were more common among non-ICU BSI (Table 2).
- Resistance to the echinocandins was uncommon among the five major species of *Candida* causing BSI in both ICU and non-ICU settings. No echinocandin resistance was detected among ICU and non-ICU isolates of *C. parapsilosis* and *C. tropicalis* (Table 3).
- One *C. albicans* from an ICU patient demonstrated resistance to all three echinocandins (MIC values ranging from 1 to 4 µg/ml), whereas one isolate of this species from a non-ICU patient was resistant to caspofungin (MIC, 1 µg/ml) but appeared susceptible to both anidulafungin (MIC, 0.12 µg/ml) and micafungin (MIC, 0.06 µg/ml). A single isolate of *C. krusei* from each group was resistant to caspofungin (MIC, 1 µg/ml for both isolates).
- Overall, fluconazole resistance was detected in 5.0% of ICU isolates and 4.4% of non-ICU isolates. Additionally, 38% of fluconazole resistance detected in ICU isolates was found in species other than *C. glabrata* and *C. krusei.* Resistance to fluconazole was observed in 6.8% of ICU isolates and 4.3% of non-ICU isolates of *C. parapsilosis*, whereas cross-resistance among the three triazoles was detected in *C. tropicalis* isolates from both ICU and non-ICU locations (Table 3).
- *C. glabrata* was the only species in which resistance to both azoles and echinocandins was observed and this MDR phenotype was found in ICU and non-ICU populations (Table 3).

Table 1. Geographic and temporal variation in the frequency of *Candida* bloodstream infections (BSI) occurring in the intensive care unit (ICU) versus non-ICU hospital locations: SENTRY Antimicrobial Surveillance Program, 2008-2009.

			No. (%) of BSI according to origin and year	
Location	Year	Total no. BSI	ICU	non-ICU
Europe	2008	350	155 (44.3)	195 (55.7)
	2009	292	130 (44.5)	162 (55.5)
	2008-2009	642	285 (44.4)	357 (55.6)
Latin America	2008	202	131 (64.9)	71 (35.1)
	2009	122	52 (42.6)	70 (57.4)
	2008-2009	324	183 (56.5)	141 (43.5)
North America	2008	442	180 (40.7)	262 (59.3)
	2009	344	131 (38.1)	213 (61.9)
	2008-2009	786	311 (39.6)	475 (60.4)
Total	2008	994	466 (46.9)	528 (53.1)
	2009	758	313 (41.3)	445 (58.7)
	2008-2009	1,752	779 (44.5)	973 (55.5)

Table 2. Species distribution of *Candida* BSI isolates from ICU and non-ICU locations.

	% of total (no. tested) for each species according to origin	
Species	ICU (779)	non-ICU (973)
C. albicans	50.4	47.4
C. glabrata	17.5	18.1
C. parapsilosis	15.1	18.9
C. tropicalis	10.5	9.6
C. krusei	2.1	2.0
Misc.[a]	4.4	4.0

a. Miscellaneous species including *C. lusitaniae* (31 isolates), *C. dubliniensis* (16 isolates), *C. guilliermondii* (eight isolates), *C. kefyr* (six isolates), three each of *C. famata* and *C. lipolytica*, and two each of *C. rugosa, C. sake* and *C. pelliculosa*.

Table 3. Frequency of antifungal resistance among ICU and non-ICU BSI isolates of *Candida* spp.: SENTRY Antimicrobial Surveillance Program, 2008-2009.

		% of isolates resistant (R) to each antifungal[b]			
		ICU		non-ICU	
Species	Antifungal agent	No.[b]	%R	No.[b]	%R
C. albicans	Anidulafungin	393	0.3	461	0.0
	Caspofungin	393	0.3	461	0.2
	Micafungin	393	0.3	461	0.0
	Fluconazole	393	0.0	461	0.0
	Posaconazole	393	0.0	461	0.0
	Voriconazole	393	0.0	461	0.0
C. glabrata	Anidulafungin	136	2.2	176	2.3
	Caspofungin	136	2.2	176	3.4
	Micafungin	136	2.2	176	1.7
	Fluconazole	136	5.9	176	6.3
	Posaconazole	136	4.4	176	4.1
	Voriconazole	136	5.9	176	2.3
C. parapsilosis	Anidulafungin	118	0.0	184	0.0
	Caspofungin	118	0.0	184	0.0
	Micafungin	118	0.0	184	0.0
	Fluconazole	118	6.8	184	4.3
	Posaconazole	118	0.0	184	0.0
	Voriconazole	118	0.0	184	0.0
C. tropicalis	Anidulafungin	82	0.0	93	0.0
	Caspofungin	82	0.0	93	0.0
	Micafungin	82	0.0	93	0.0
	Fluconazole	82	4.9	93	2.2
	Posaconazole	82	1.2	93	1.1
	Voriconazole	82	4.9	93	1.1
C. krusei[c]	Anidulafungin	16	0.0	20	0.0
	Caspofungin	16	6.3	20	5.0
	Micafungin	16	0.0	20	0.0
	Posaconazole	16	0.0	20	0.0
	Voriconazole	16	0.0	20	0.0

a. Resistance (R) defined as a MIC > 0.5 µg/ml for anidulafungin, caspfungin and micafungin versus *C. albicans, C. tropicalis*, and *C. krusei* and as a MIC >4 µg/ml for *C. parapsilosis*; R defined as a MIC >0.5 µg/ml for anidulafungin and caspofungin and as a MIC of >0.12 µg/ml for micafungin versus *C. glabrata*; R defined as a MIC >4 µg/ml for fluconazole versus *C. albicans, C. tropicalis*, and *C. parapsilosis* and as a MIC >32 µg/ml versus *C. glabrata*; R defined as a MIC >2 µg/ml for posaconazole and voriconazole versus all species.
b. No. = total number of isolates tested.
c. Fluconazole was not active against this species.

Conclusions

- ICU-related candidemia may be more prominent in some geographic regions than others. However, a trend towards a decrease in ICU-associated candidemia was apparent in this study.
- Species distribution and antifungal resistance profiles were very similar for ICU isolates and those from other hospital locations.
- The only species found for which resistance to both azoles and echinocandins was *C. glabrata,* and this MDR profile was noted to a similar extent among ICU and non-ICU-associated isolates.
- Our findings indicate that invasive candidiasis can no longer be considered to be an ICU-related infection and efforts to design preventative and diagnostic strategies must necessarily be broadened to consider other at-risk hospitalized populations. Such a shift in the epidemiology of invasive candidiasis will make these efforts more difficult and argues for continued antifungal agent resistance surveillance as an aid in optimizing these strategies.

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