

Candida Bloodstream Infection: Comparison of Species Distribution and Antifungal Resistance Patterns in Community Onset and Nosocomial Candida Bloodstream Infection Isolates

RN JONES, HS SADER, MA PFALLER - JMI Laboratories, North Liberty, IA, USA

ABSTRACT

Background: Community onset (CO) candida bloodstream infection (CBI), defined as a positive blood culture taken at or within two days of hospital admission, has substantial morbidity and mortality. However, limited data exists concerning species distribution and antifungal resistance (R) profiles for isolates from CO- vs nosocomial (NOS)-CBI.

Methods: We compared antifungal-R profiles and species distribution of *Candida* isolates from patients with CO and NOS CBI in 79 hospitals from the SENTRY Program (2008-2009). MICs were obtained for anidulafungin (ANF), caspofungin (CSF), micafungin (MCF), fluconazole (FLC), posaconazole (PSC), and voriconazole (VRC). Recently revised CLSI breakpoints for R were employed: ANF, CSF, and MCF MICs >0.5 mg/L were R for *C. albicans* (Ca), *C. glabrata* (Cg), *C. tropicalis* (Ct) and *C. krusei* (Ck); MICs >4 mg/L were R for *C. parapsilosis* (Cp); FLC MICs >4 mg/L were R for Ca, Cp and Ct; MICs >32 mg/L were R for Cg; and PSC and VRC MICs >2 mg/L were R for all species.

Results: 1,354 *Candida* were obtained from CO (494; 36.5%) and NOS (860; 63.5%) CBIs. 96% of both CBI types were Ca, Cg, Cp, Ct and Ck. Ca was more common CO CBIs (51.0%) than in NOS CBIs (46.9%); whereas Ca and Ck, respectively, were greater in CO CBIs (15.4 and 0.8%). Cg and Ct, respectively were comparable in both CO (18.4 and 10.5%) and NOS (18.1 and 10.6%) groups. R to ANF, MCF and CSF was uncommon in CO CBI; however MICs >0.5 mg/L were noted in 0.3-0.5% of NOS Ca isolates and 1.3-5.1% of NOS isolates of Cg. Among CO isolates of Cg, 5.5% were R to PSC and 2.2% were R to VRC, whereas only 0.6% of Cg NOS isolates were R to new azoles. NOS Ct isolates were more R to FLC (3.3 vs 0.0%) and VRC (2.2 and 0.0%) than CO isolates.

Conclusions: More than 30% of CBI episodes monitored were CO. NOS isolates of Ca and Cg had greater echinocandin-R, whereas higher azole-R was noted among CO isolates of Cg. CO CBIs are not uncommon, but as yet are not associated with elevated R rates.

The isolates were identified by standard methods and stored as water suspensions until processed 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 susceptibility to the echinocandins and triazoles using Clinical and Laboratory Standards Institute (CLSI) broth microdilution 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 ($\geq 50\%$ inhibition) of growth below the control level. We used the recently revised CLSI clinical breakpoints (CBP) to identify strains of *Candida* resistant to the echinocandins and fluconazole: anidulafungin, caspofungin and micafungin MICs at >0.5 mg/L were considered resistant for *C. albicans*, *C. tropicalis*, and *C. krusei* and MIC values at >4 mg/L were considered resistant for *C. parapsilosis*; anidulafungin and caspofungin MIC values at >0.5 mg/L and micafungin MICs >0.12 mg/L were declared resistant for *C. glabrata*; fluconazole MIC values of >4 mg/L were categorized as resistant for *C. albicans*, *C. parapsilosis*, and *C. tropicalis* and MICs at >32 mg/L were considered resistant for *C. glabrata*. All isolates of *C. krusei* were considered as resistant to fluconazole. The CLSI resistance breakpoint for voriconazole (MIC, >2 mg/L) was also an indicator of resistance for posaconazole tested against all species. Quality control was performed by testing CLSI-recommended strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019.

RESULTS

• 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. Among the episodes of candidemia, 494 (36.5%) were CO and 860 (63.5%) were nosocomial (Table 1). The frequency of CO candidemia was considerably higher in North America (50.8%) compared to that observed in Europe (22.4%) and Latin America (28.0%).

• Variation in the frequency of CO candidemia was considerable (Table 1). Interestingly, the proportion of CO candidemia in locations such as Taiwan (3%), Brazil (9%) and Spain (11%) were considerably lower than in the USA.

• Comparing the frequency of isolation of different species by CO and nosocomial BSI, we found only minor differences. *C. albicans* was more common among CO infections, while *C. parapsilosis* and *C. krusei* were more common among nosocomial candidemias.

• No resistance to anidulafungin, caspofungin, micafungin, posaconazole or voriconazole was detected among CO isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis* or *C. krusei* (Table 2). Resistance to fluconazole was observed in isolates of *C. parapsilosis* and a small number of *C. glabrata* isolates displayed resistance to anidulafungin, caspofungin and all three triazoles.

• None of the nosocomial isolates of *C. parapsilosis* or *C. tropicalis* were resistant to the echinocandins; however 5.8% of the nosocomial *C. parapsilosis* and 3.3% of the nosocomial *C. tropicalis* were resistant to fluconazole. One nosocomial *C. albicans* isolate (Germany) was resistant to all three echinocandins, whereas no resistance to the azoles was detected.

• 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 (Table 2).

• Resistance was infrequent among nosocomial isolates of *C. krusei* where only two isolates resistant to caspofungin were detected (Table 2).

• 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 2).

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

Region	Total no. 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)

Table 2. Frequency of antifungal resistance among community onset and nosocomial bloodstream infection isolates of *Candida* spp.: SENTRY Antimicrobial Surveillance Program (2008-2009).

Species	Antifungal agent	% of isolates resistant (R) to each antifungal ^a			
		Community-onset		Nosocomial	
		No. ^b	%R	No. ^b	%R
<i>C. albicans</i>	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
<i>C. glabrata</i>	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
<i>C. parapsilosis</i>	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
<i>C. tropicalis</i>	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
<i>C. krusei</i>	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 an MIC >0.5 mg/L for anidulafungin, caspofungin and micafungin versus *C. albicans*, *C. tropicalis* and *C. krusei* and as a MIC >4 mg/L for *C. parapsilosis*; resistance defined as a MIC of >0.5 mg/L for anidulafungin and caspofungin and as a MIC of >0.12 mg/L for micafungin versus *C. glabrata*; resistance defined as a MIC >4 mg/L for fluconazole versus *C. albicans*, *C. tropicalis*, and *C. parapsilosis* and as a MIC >32 mg/L for posaconazole and voriconazole versus all species.

b. No., total number of isolates tested.

CONCLUSIONS

• CO candidemias were not rare and appear to be increasing worldwide due to changes in healthcare practices. Whereas the species distribution was similar between CO and nosocomial BSI, resistance to the azoles and echinocandins was quite uncommon.

• Our observations support the potential emergence of MDR phenotypes among nosocomial isolates of *C. glabrata* with cross resistance in azole and echinocandin classes.

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INTRODUCTION

Invasive candidiasis (IC; candidemia and other deep-seated infections including disseminated candidiasis, endocarditis, meningitis, and hepatosplenic infection) is now widely recognized as an important public health problem with considerable morbidity, mortality and associated healthcare costs. Although much of the literature concerning IC has focused on nosocomial bloodstream infections (BSI), especially those occurring in the intensive care unit (ICU), an increasing incidence of IC overall, 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 (USA), suggest that the burden of IC may be shifting from the ICU to other healthcare settings.

Community onset (CO) candidemia represented a distinct clinical entity with substantial morbidity and mortality. Compared with 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 healthcare facility or nursing home. Thus candidemia has spread beyond the confines of acute care hospitals and failure to consider CO candidemia in at-risk subjects may have adverse consequences.

In the present study, we evaluated geographic 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, Iowa, USA) 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 at or within two days of hospital admission; whereas nosocomial BSI was defined as an infection not present on admission and having onset more than two days beyond hospital admission. Although some authors divide CO BSI into healthcare associated (HCA) infections (healthcare-associated risk factors including recent hospitalization, nursing home, indwelling medical device, chemotherapy, dialysis) and community-acquired (CA) infections (no HCA risk factors), most studies of CO candidemia do not and the SENTRY Antimicrobial Surveillance 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 (CO versus nosocomial) was provided for 1,354 (65%) patient episodes.