

Azole and echinocandin antifungal susceptibility profiles of bloodstream *Candida* isolates tested at the Mycology Reference Laboratory, Public Health Institution of Turkey

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Objectives: *Candida* bloodstream infections are responsible for significant morbidity and mortality. Accurate data on species identification and antifungal susceptibility is critical to support appropriate treatment guidelines. The Clinical and Laboratory Standards Institute (CLSI) recently revised the azole and echinocandin clinical breakpoints (CBPs) against *Candida* species and these new breakpoints are both drug and species specific. In the absence of specific CPBs, establishing wild-type (WT) MIC distributions and epidemiological cutoff values (ECVs) provides sensitive means for detecting emerging resistance. In this study we aimed to determine the rates of WT isolates and isolates with acquired resistance among bloodstream *Candida* isolates by using the new CLSI CBPs.

Methods: In this study, results of the antifungal susceptibility testing of *Candida* bloodstream isolates (n=118) that were sent to Public Health Institution of Turkey, Mycology Reference Laboratory between March-September 2014 from tertiary care teaching and university hospitals in Turkey (n=4) were evaluated. Identification of the species was performed by conventional methods. Susceptibility testing was performed for anidulafungin, caspofungin, fluconazole and voriconazole with the broth microdilution method according to CLSI M27-A3, and interpreted according to CLSI M27-S4, as susceptible (S), susceptible-dose dependent (S-DD), resistant (R) and ECVs criteria, as appropriate.

Results: The identification of the 118 bloodstream isolates revealed 106 isolates from 5 common (*Candida albicans*, n=39; *Candida glabrata*, n=25; *Candida krusei*, n=18; *Candida parapsilosis*, n=13; *Candida tropicalis*, n=11) and 12 isolates from three rare (*Candida kefyr*, n=9; *Candida pelliculosa*, n=2; *Candida lusitanae*, n=1) *Candida* species. Among the common species anidulafungin resistance was not observed, however 10 isolates (9.4%) were found intermediate. Caspofungin resistance was observed in three isolates (2.8%) (*C. glabrata*, n=2; *C. krusei*, n=1) and 17 isolates (16.0%) were found intermediate. Fluconazole resistance was detected in four (3.8%) isolates: *C. glabrata*, n=1; *C. parapsilosis*, n=2; *C. tropicalis*, n=1, however 24 of *C. glabrata* (24/25), 3 of *C. parapsilosis* (3/13) and 3 of *C. tropicalis* (3/11) isolates were found S-DD to fluconazole. Voriconazole resistance was not detected among *C. albicans*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* but three isolates (2.8%) (*C. parapsilosis*, n=2; *C. tropicalis* n=1) were found SDD to voriconazole. Due to the lack of species specific CBPs for the less common species (n=12), evaluation for this group was done according to the ECVs; the *C. lusitanae* isolate was found non-WT for fluconazole and voriconazole, and five *C. kefyr* (5/9) were found non-WT for caspofungin (Table 1).

Conclusion: Overall, a total of four *Candida* isolates were determined as resistant for fluconazole and three for caspofungin. This resistance rate in *Candida* isolates is higher than what was recently reported. This can be linked to the characteristics of our reference laboratory which often receives isolates from patients exposed to antifungals and who are failing therapy.

Table 1. Antifungal susceptibility and wild type distributions of bloodstream *Candida* isolates (n=118) determined by CLSI broth microdilution method after 24-hour incubation.

Organism	Antifungal agent	ECV		CBP			
		WT	Non-WT	S	S-DD	I	R
<i>Candida albicans</i> (n=39)	Anidulafungin	25	14	38	NA	1	-
	Caspofungin	25	14	30	NA	9	-
	Fluconazole	35	4	39	-	NA	-
	Voriconazole	38	1	39	-	NA	-
<i>Candida glabrata</i> (n=25)	Anidulafungin	25	-	20	NA	5	-
	Caspofungin	20	5	20	NA	3	2
	Fluconazole	24	1	NA	24	NA	1
	Voriconazole	25	-	NA	NA	NA	NA
<i>Candida krusei</i> (n=18)	Anidulafungin	17	1	17	NA	1	-
	Caspofungin	16	2	16	NA	1	1
	Fluconazole	18	-	NA	NA	NA	NA
	Voriconazole	18	-	18	-	NA	-
<i>Candida parapsilosis</i> (n=13)	Anidulafungin	13	-	10	NA	3	-
	Caspofungin	8	5	9	NA	4	-
	Fluconazole	8	5	8	3	NA	2
	Voriconazole	11	2	11	2	NA	-
<i>Candida tropicalis</i> (n=11)	Anidulafungin	11	-	11	NA	-	-
	Caspofungin	11	-	11	NA	-	-
	Fluconazole	10	1	7	3	NA	1
	Voriconazole	10	1	10	1	NA	-
<i>Candida kefyr</i> (n=9)	Anidulafungin	9	-	NA	NA	NA	NA
	Caspofungin	4	5	NA	NA	NA	NA
	Fluconazole	9	-	NA	NA	NA	NA
	Voriconazole	9	-	NA	NA	NA	NA
<i>Candida pelliculosa</i> (n=2)	Anidulafungin	2	-	NA	NA	NA	NA
	Caspofungin	2	-	NA	NA	NA	NA
	Fluconazole	2	-	NA	NA	NA	NA
	Voriconazole	2	-	NA	NA	NA	NA
<i>Candida lusitanae</i> (n=1)	Anidulafungin	1	-	NA	NA	NA	NA
	Caspofungin	1	-	NA	NA	NA	NA
	Fluconazole	-	1	NA	NA	NA	NA
	Voriconazole	-	1	NA	NA	NA	NA

Abbreviations: ECV, epidemiological cutoff value; CBP, clinical breakpoint; WT, wild type; non-WT, non-wild type; S, susceptible; S-DD, susceptible-dose dependent; I, intermediate; R, resistant; NA, not applicable.