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Antifungal drug susceptibility and resistance

A 7-year review of Candida isolates and anti-fungal susceptibility from clinical specimens in Alberta, Canada

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Objectives: The aim of the present study was to compare the species distribution and *in vitro* antifungal susceptibility profiles of *Candida* isolates from clinical specimens received over a 7-year period.

Methods: Clinical isolates of *Candida* species recovered from all microbiology specimens submitted to the Provincial Laboratory for Public Health (Microbiology) in Alberta, Canada between January 1, 2007 and November 29, 2013 were tested against amphotericin B (AMB), 5-flucytosine (5FC), itraconazole (ITRA), fluconazole (FLUC), voriconazole (VORI), posaconazole (POSA), caspofungin (CASP), and micafungin (MICA) using the broth microdilution method outlined in the CLSI M27-S4 document. Growth endpoints were measured at 24 hours of incubation and MIC values determined as per CLSI methodology. MIC90 and the mode for the MIC distribution of each antifungal agent were determined. These values were compared to the revised interpretive clinical breakpoints (CBPs; CLSI 2013) and/or published epidemiological cut-off values (ECOFFs).

Results: During the time course of this study, 2225 isolates of yeast were identified as *Candida spp.* The four most common species isolated were *C. albicans* complex (45%), *C. glabrata*(32%)*, C. parapsilosis* (7.6%)*,* and *C. tropicalis* (5.8%). MIC distribution results for these four species are displayed in Table 1. There were no temporal trends of increasing MIC noted for any antifungal:species pair tested. Resistance to FLUC for *C. albicans*, *C. glabrata*, and *C. parapsilosis* was less than 6% but was 15% for *C. tropicalis*; using ECOFFs for itraconazole and posaconazole for these species, ~50% of non-wildtype MIC values were one dilution above the ECOFF. Resistance to micafungin was detected in *C. glabrata* (4%). However, 97% of *C. glabrata* tested resistant to caspofungin with a mode of 0.5 mg/L. Non-susceptible caspofungin MICs for *C. albicans* also concentrated 1 to 2 dilutions above the CBP. Amphotericin B continues to remain an agent with low MICs for all species evaluated.

Conclusions: Seven-year surveillance demonstrates MIC distributions with no evidence of change over time of common *Candida* species to available antifungals. Application of the new CLSI CBPs for caspofungin against *C. glabrata*, and *C. albicans* to a lessor extent, bisects the normal population distribution despite very little resistance to micafungin. This is consistent with recently published data and requires further evaluation. Similarly, non-wildtype MICs for posaconazole and itraconazole are more likely attributed to challenges with standardized visual

endpoint determination but molecular studies will be required to verify these findings.

Table 1. MIC and MEC Distributions of the most common species of *Candida* isolated.

Species	Agent (*n*)	Mode (mg/L)	MIC90 (mg/L)	CBP (ECOFF)	≤CBP/ ECOFF
C. albicans	AMB (977)	0.5	1.0	(2)	100
	5FC (977)	0.125	>64	(0.5)	68.6
	ITRA (977)	0.06	0.25	(0.125)	86.5
	FLUC (977)	0.25	1	2	94.0
	VORI (977)	0.015	0.125	0.12	95.1
	POSA (633)	0.03	0.06	(0.06)	88.9
	CASP (977)	0.25	0.5	0.25	85.7
	MICA (519)	0.015	0.015	0.25	100
C. glabrata	AMB (722)	1.0	1.0	(2)	100
	5FC (722)	0.06	0.125	(0.5)	98.1
	ITRA (722)	0.5	1.0	(0.125)	94.2
	FLUC (722)	8.0	32	≤32	93.8
	VORI (722)	0.25	1.0	(0.5)	97.4
	POSA (492)	0.5	1.0	(2)	97.25
	CASP (722)	0.5	1.0	≤0.12	2.6
	MICA (419)	0.015	0.03	≤0.06	96.9
C. parapsilosis	AMB (170)	1.0	1.0	(2)	100
	5FC (170)	0.125	0.25	(0.5)	96.5
	ITRA (170)	0.06	0.25	(0.125)	80.6
	FLUC (170)	0.5	1.0	2	95.3
	VORI (170)	0.015	0.06	0.12	95.9
	POSA (116)	0.03	0.125	(0.06)	82.8
	CASP (170)	1.0	1.0	2	99.4
	MICA (103)	0.5	1.0	2	100
C. tropicalis	AMB (129)	1.0	2.0	(2)	100
	5FC (129)	0.125	0.5	(0.5)	98.5
	ITRA (129)	0.06	0.5	(0.125)	62.0
	FLUC (129)	0.25	4.0	2	84.5
	VORI (129)	0.06	0.5	0.12	71.3
	POSA (82)	0.06	0.25	(0.06)	74.4
	CASP (129)	0.25	0.5	2	100
	MICA (69)	0.015	0.06	2	100