Echinocandin MICs against Candida species at hospitals that routinely perform susceptibility testing of bloodstream isolates

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A collaboration among investigators from nine centers in the United States, Australia and New Zealand

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Background

- Reference broth microdilution methods of testing Candida strains for susceptibility to echinocandins are limited by inter-laboratory variability in caspofungin minimum inhibitory concentrations (MICs)
- Revised Clinical Laboratory Standards Institute (CLSI) breakpoint MICs for echinocandin non-susceptibility may not be valid for commercial assays employed in hospital microbiology laboratories

Goals

- To report on echinocandin susceptibility testing methods, echinocandin MICs, and susceptibility patterns for Candida bloodstream isolates (BSI), as determined by hospital microbiology laboratories that perform routine testing

Methods

- We performed a retrospective, mutlicenter study of nine hospitals in the United States, Australia and New Zealand that routinely tested Candida for echinocandin susceptibility from 2005-2013
  - University of Pittsburgh, Johns Hopkins, Henry Ford Hospital, New York Presbyterian, University of Florida, University of Utah, Cleveland Clinic, Auckland City Hospital, Westmead Hospital
- *C. glabrata* strains with discrepant echinocandin suscpetibility profiles (caspofungin-R or I/others-S) were sequenced for *FKS* mutations

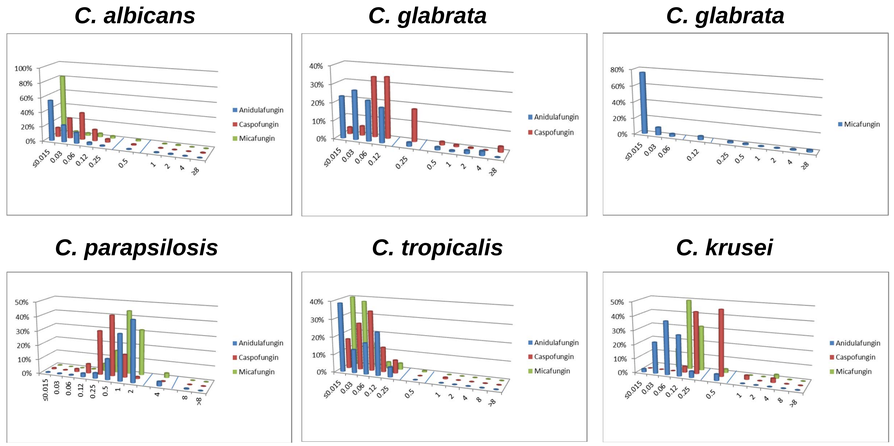
Results

- We first surveyed 15 large tertiary care hospitals in the U.S., and determined that 53% (8/15) routinely performed echinocandin susceptibility testing of Candida BSI
- At the nine centers in this study, 2,897 BSI were tested
  - Anidulafungin (1,467), Caspofungin (2,355), Micafungin (2,004)
  - 8/9 centers used YeastOne; 1/9 used CLSI broth microdiluation
  - *C. albicans* (1,067), *C. glabrata* (911), *C. parapsilosis* (476), *C. tropicalis* (185), *C. krusei* (104)
  - *C. lusitaniae* (57), *C. dubliniensis* (36), *C. guilliermondii* (36), *C. kefyr* (17), others (8)
    - MIC distributions shown in Table 1
- There were no significant trends in emergence of resistance over time

Table 1. Echinocandin MICs against Candida spp.

Species	Agent	n	MIC ≤ 0.06	MIC 0.125	MIC 0.25	MIC 0.5	MIC 1	MIC 2	MIC 4	MIC ≥ 8
C. albicans	ANF	555	93.7%	3.2%	1.1%	0.5%	0.5%	0.7%	0.2%	0%
	CSF	906	77.9%	15.6%	4.3%	1.2%	0.3%	0.1%	0.0%	0.6%
	MCF	704	88.8%	4.8%	3.0%	2.0%	0.4%	0.9%	0.0%	0.1%
C. glabrata	ANF	480	72.7%	19.2%	2.1%	1.5%	0.6%	1.7%	2.3%	0%
	CSF	754	42.3%	34.0%	17.8%	1.7%	0.9%	0.4%	0.0%	2.9%
	MCF	634	88.3%	4.3%	2.1%	1.3%	0.3%	0.3%	1.1%	2.4%
C. parapsilosis	ANF	241	1.2%	2.5%	3.7%	14.5%	32.4%	42.3%	2.9%	0.4%
	CSF	396	3.0%	6.6%	30.8%	42.2%	15.9%	1.3%	0.3%	0.0%
	MCF	329	0.3%	0.3%	5.2%	15.5%	44.1%	31.6%	3.0%	0.0%
C. tropicalis	ANF	90	70.0%	24.4%	5.6%	0.0%	0.0%	0.0%	0.0%	0.0%
	CSF	135	77.8%	14.1%	7.4%	0.0%	0.7%	0.0%	0.0%	0.0%
	MCF	140	92.1%	3.6%	3.6%	0.7%	0.0%	0.0%	0.0%	0.0%
C. krusei	ANF	45	62.2%	28.9%	4.4%	4.4%	0.0%	0.0%	0.0%	0.0%
	CSF	71	0.0%	4.2%	43.7%	46.5%	2.8%	0.0%	2.8%	0.0%
	MCF	79	13.9%	49.4%	31.6%	2.5%	0.0%	0.0%	2.5%	0.0%
C. lusitaniae[1]	ANF	31	12.9%	51.6%	22.6%	12.9%	0.0%	0.0%	0.0%	0.0%
	CSF	44	15.9%	15.9%	34.1%	27.3%	4.5%	0.0%	0.0%	2.3%
	MCF	44	50.0%	38.6%	2.3%	9.1%	0.0%	0.0%	0.0%	0.0%
C. dubliniensis[2]	ANF	16	50.0%	37.5%	0.0%	0.0%	0.0%	0.0%	0.0%	12.5%
	CSF	26	61.5%	30.8%	0.0%	0.0%	0.0%	0.0%	0.0%	7.7%
	MCF	26	88.5%	3.8%	0.0%	0.0%	0.0%	0.0%	0.0%	7.7%

Figure 1. Echinocandin MICs against five most common Candida spp.



- Modal MICs and susceptibility patterns were essentially unchanged if data were only taken from centers that used YeastOne

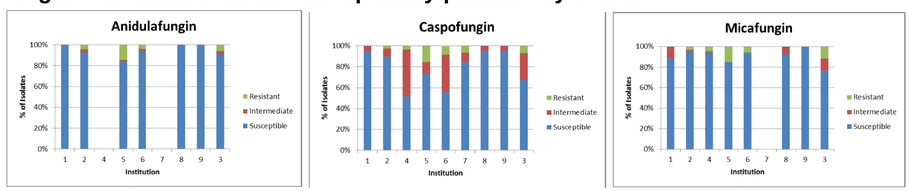
Table 2. Echinocandin MIC distribution by center

Anidulafungin									
	Center								
MIC	1	2	4	5	6	7	8	9	3
C. albicans									
≤0.008	1	8	0	0	1	NT	6	0	0
0.015	2	44	0	42	17	NT	10	28	150
0.03	5	22	1	29	29	NT	7	18	18
0.06	0	13	0	23	12	NT	4	15	15
0.125	0	3	0	3	2	NT	2	6	2
0.25	0	0	0	2	1	NT	1	0	2
0.5	1	0	0	0	2	NT	0	0	1
1	0	0	0	0	0	NT	0	1	2
2	0	0	0	0	1	NT	0	0	3
≥4	0	0	0	0	0	NT	0	0	1
C. glabrata									
≤0.008	2	1	0	0	0	NT	1	0	0
0.015	2	29	0	14	7	NT	4	24	28
0.03	5	50	0	33	22	NT	6	14	0
0.06	0	9	0	14	11	NT	2	4	67
0.125	0	1	0	4	8	NT	0	0	79
0.25	0	3	0	1	1	NT	0	0	5
0.5	0	1	0	0	1	NT	0	0	5
1	0	2	0	1	0	NT	0	0	0
2	0	1	0	5	1	NT	0	0	1
≥4	0	0	0	5	0	NT	0	0	6
C. parapsilosis									
≤0.008	0	0	0	0	0	NT	0	0	0
0.015	0	0	0	0	0	NT	0	0	1
0.03	0	0	0	0	1	NT	0	0	0
0.06	0	0	0	0	0	NT	0	0	1
0.125	0	0	0	4	0	NT	1	0	1
0.25	0	2	0	5	1	NT	0	0	1
0.5	0	6	0	11	8	NT	3	2	5
1	1	17	0	18	11	NT	8	4	19
2	1	9	0	21	11	NT	4	3	53
≥4	0	0	0	0	0	NT	0	0	8
C. tropicalis									
≤0.008	0	0	0	0	0	NT	0	0	0
0.015	0	0	0	3	3	NT	0	2	27
0.03	0	4	0	2	4	NT	0	2	0
0.06	0	2	0	0	7	NT	0	2	5

Caspofungin									
	Center								
MIC	1	2	4	5	6	7	8	9	3
C. albicans									
≤0.015	9	5	3	1	5	0	3	4	85
0.03	56	48	2	41	29	21	19	28	10
0.06	75	39	1	34	37	51	18	26	56
0.125	32	4	0	20	22	20	9	8	26
0.25	10	1	4	2	5	5	0	1	11
0.5	1	0	0	0	6	1	0	0	3
1	0	0	0	0	1	0	0	0	2
2	0	0	0	0	0	0	0	0	1
≥4	0	0	0	0	1	1	2	0	1
C. glabrata									
≤0.015	0	0	0	0	0	1	1	0	26
0.03	3	11	2	2	5	2	2	11	1
0.06	27	46	11	26	24	25	14	20	59
0.125	28	39	2	29	36	65	4	9	44
0.25	3	8	13	8	41	10	1	2	48
0.5	0	1	0	2	3	3	0	0	4
1	0	0	0	2	4	0	0	0	1
2	0	2	0	0	0	0	0	0	1
≥4	0	0	1	8	2	4	0	0	7
C. parapsilosis									
≤0.015	0	0	0	0	0	0	0	0	3
0.03	0	0	0	0	0	0	0	0	1
0.06	2	1	0	0	1	0	1	0	3
0.125	4	0	0	8	1	5	2	0	6
0.25	19	12	1	29	10	19	5	5	22
0.5	38	21	2	15	28	13	12	4	34
1	9	5	0	5	14	1	5	0	24
2	0	0	0	1	0	0	0	0	4
≥4	0	0	0	0	0	0	0	0	1
C. tropicalis									
≤0.015	0	0	1	0	8	0	0	2	12
0.03	3	9	4	4	6	5	5	5	0
0.06	6	6	2	4	5	5	3	1	14
0.125	3	3	0	1	4	1	0	1	6
0.25	0	3	0	0	5	1	0	1	0
0.5	0	0	0	0	0	0	0	0	0
1	1	0	0	0	0	0	0	0	0

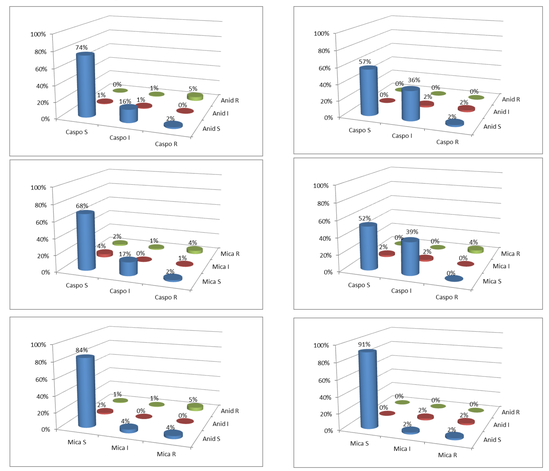
Micafungin									
	Center								
MIC	1	2	4	5	6	7	8	9	3
C. albicans									
≤0.008	8	42	73	70	48	NT	23	36	0
0.015	0	40	65	24	9	NT	5	23	106
0.03	0	1	17	3	3	NT	0	4	1
0.06	0	0	3	1	1	NT	2	1	16
0.125	0	1	1	0	1	NT	0	0	31
0.25	0	0	0	1	0	NT	0	0	20
0.5	0	0	0	0	1	NT	0	0	13
1	0	0	0	0	0	NT	0	0	3
2	0	0	0	0	2	NT	0	1	3
≥4	0	0	0	0	0	NT	0	0	1
C. glabrata									
≤0.008	1	8	31	13	19	NT	7	19	0
0.015	7	64	79	49	27	NT	6	18	133
0.03	0	15	32	7	2	NT	0	2	1
0.06	0	4	1	0	1	NT	0	1	13
0.125	1	1	2	0	0	NT	1	0	22
0.25	0	1	1	1	0	NT	0	0	10
0.5	0	0	1	1	1	NT	0	0	5
1	0	0	0	2	0	NT	0	0	0
2	0	1	0	0	0	NT	0	0	1
≥4	0	0	1	5	8	2	NT	0	6
C. parapsilosis									
≤0.008	0	0	0	0	0	0	NT	0	0
0.015	0	0	0	0	0	0	NT	0	1
0.03	0	0	0	0	0	0	NT	0	0
0.06	0	0	0	0	0	0	NT	0	0
0.125	0	0	0	0	0	0	NT	0	1
0.25	0	0	0	0	0	0	NT	0	0
0.5	0	0	0	0	0	0	NT	0	0
1	0	0	0	0	0	0	NT	0	0
2	0	0	0	0	0	0	NT	0	0
≥4	0	0	0	0	0	0	NT	0	0
C. tropicalis									
≤0.008	0	0	0	0	4	NT	0	0	0
0.015	0	2	12	2	9	NT	0	4	23
0.03	0	12	25	5	5	NT	1	5	0
0.06	0	5	10	2	1	NT	0	1	1

Figure 2. Echinocandin susceptibility patterns by center



- *C. glabrata* resistance rates for each agent were comparable across centers
- *C. glabrata* intermediate rates varied more for caspofungin (5% to 45%) than anidulafungin (0% to 3.1%) or micafungin (0% to 11.5%)
- Intercenter variability in MICs was lessened if only YeastOne data were considered
  - Modal caspofungin MICs were within 2 dilutions against *C. glabrata* and a single dilution against other spp.
  - Modal anidulafungin and micafungin MICs were within a single dilution against each of the 5 most common Candida spp.

Figure 3. Categorical agreement in susceptibility patterns



- Using CLSI breakpoints, 18% and 19% of *C. glabrata* were anidulafungin-susceptible/caspofungin-non-susceptible and micafungin-susceptible/caspofungin-non-susceptible, respectively
- Likewise, 38% and 39% of *C. krusei* were anidulafungin-susceptible/caspofungin-non-susceptible and micafungin-susceptible/caspofungin-non-susceptible, respectively
- Only 6.7% (2/30) of *C. glabrata* strains with discrepant susceptibility patterns (caspofungin-non-susceptibile/other agents-susceptible) had *FKS* mutations

Conclusions

- YeastOne assays employed in hospitals may reduce the inter-laboratory variability in caspofungin MICs against Candida spp. that are observed between reference laboratories using CLSI or EUCAST broth microdilution methods
- Echinocandin resistance was most common for *C. glabrata* and *C. krusei*, but rates were stable over the study period
- Hospitals may overstate caspofungin-non-susceptibility rates among *C. glabrata* and *C. krusei* by using CLSI breakpoints to interpret YeastOne MICs
- The classification of *C. glabrata* strains as caspofungin-non-susceptible and aniudlafungin/micafungin susceptible is likely a breakpoint artifact, as few strains carry *FKS* mutations.