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Monitoring echinocandin and azole susceptibility in a global collection of invasive fungal isolates

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Background: Continuous monitoring of antifungal susceptibility patterns and understanding resistance mechanisms against these agents seems prudent after reports of breakthrough infections, emerging resistance mechanisms, and increasing prevalence of uncommon species associated with higher resistance. We evaluated the activity of 7 antifungals against 3,557 invasive yeasts and moulds collected worldwide, and we screened resistance mechanisms among *Candida* spp. (CANS) displaying elevated echinocandin MICs and azole-resistant *Candida albicans* (CA).

Materials/methods: Fungal isolates collected during 2014-2015 in 66 hospitals in 29 countries were susceptibility tested by CLSI broth microdilution methods. CLSI interpretive criteria (clinical breakpoints and epidemiological cutoff values [ECV]) were applied. CANS isolates displaying echinocandin MIC>ECV were sequenced for *fks* hotspot (HS) mutations using PCR/sequencing. Six CA isolates were submitted to quantitative RT-PCR for Erg11, CDR1, CDR2, and MDR1 and to whole genome sequencing analysis for alterations in genes associated to azole-resistance.

Results: Susceptibility rates for the most common CANS are displayed in the table. Among 28 CANS isolates screened for *fks* HS mutations, 11 *C. glabrata* (CGLA), 3 CA (2 *fks1*HS1 S645P and 1 *fks1*HS2 R1361H) and 1 *C. krusei* (*fks1*HS1 L701M) displayed alterations. Among CGLA, 3 isolates had double substitutions with *fks1*HS1 F625S (n=3), S629P (n=3), *fks1*HS2 F659S/Y (n=4), and S663P (n=4) being the most common alterations. All azole-resistant CA belonged to novel and unrelated multilocus sequence types. Two isolates displaying fluconazole resistance and elevated MICs for other azoles displayed Erg11 alterations (G464S or D153E) associated with azole resistance. Elevated expression of MDR1/CDR1/CDR2 was observed among 2 isolates, MDR1 or CDR1/CDR2 hyper-expression alone were noted in 2 and 1 isolates, respectively. Polymorphisms on MMR1, TAC1 and UPC2 were noted, but the correlation with azole resistance is uncertain. *C. dubliniensis* (n=58) and *C. lusitaniae* (n=39) isolates displayed wild-type (WT) MICs for anidulafungin and micafungin based on ECV. The highest MIC results for fluconazole, voriconazole and posaconazole against *C.*

neoformans var. grubii (n=79) were 8, 0.12 and 0.25 mg/L, respectively. Among *Aspergillus fumigatus*, only 2 isolates displayed itraconazole MICs >4 mg/L and 1 of those isolates also displayed a voriconazole MIC at >8 mg/L. Other *Aspergillus* species were WT for mould-active azoles and caspofungin according to recently published ECVs (CLSI M59).

Conclusions: Echinocandin and azole resistance was uncommon among contemporary fungal isolates; however, genetic mechanisms encoding resistance to antifungal agents were observed among CANS isolates showing that resistance can emerge and should be monitored.

Organism (no. tested)	% susceptible using CLSI clinical breakpoints				
	Anidulafungin	Caspofungin	Micafungin	Fluconazole	Voriconazole
C. albicans (1,310)	99.9	99.8	99.8	99.5	99.8
C. glabrata (514)	95.9	96.9	97.5	NA[a]	NA
C. parapsilosis (417)	88.7	100.0	100.0	95.7	96.4
C. tropicalis (264)	100.0	100.0	100.0	96.2	97.0
C. krusei (93)	100.0	100.0	100.0	NA	100.0

[a] NA= not available.