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Establishment of EUCAST Micafungin ECOFFs for the most common *Candida* species using multicentre minimum inhibitory concentration (MIC) values.

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Objective

Micafungin is a broad spectrum antifungal agent for which EUCAST breakpoints (BP) have not yet been established. Until such are available EUCAST has recommended anidulafungin testing as a marker for the echinocandin class of agents. However, recent data have suggested a differential activity of the three echinocandins as some *C. glabrata* isolates retained full *in vitro* and *in vivo* susceptibility to micafungin though not to caspofungin and anidulafungin.
Hence individual micafungin BPs have become urgently needed. The first step in the breakpoint setting process is to establish species specific epidemiological cut off values (ECOFFs) based on MIC ranges from several sites. We evaluated the EUCAST MICs for 4,241 clinical Candida isolates from 7 different data sets and propose species specific ECOFFs.

Materials & Methods

C. albicans (1669), *C. glabrata* (692), *C. krusei* (483), *C. parapsilosis* (743), *C. tropicalis* (732) and *C. guilliermondii* (22) were included.

502 were tested in Denmark, 507 in Spain, 500 in Austria, 500 in the UK and following the EUCAST EDEF7.2 method.

The MFG concentration range was 0.004-2 mg/L (three centres) or 0.03-16 mg/L (one centre).

Additionally, the micafungin EUCAST MICs for 2,332 isolates from 3 datasets were provided by Astellas. The micafungin concentration range tested in these data sets were 0.015-8, 0.002-4 and 0.008-4 mg/L, respectively.

Micafungin EUCAST MIC distributions

Micafungin MICs from the seven datasets were in agreement with one exception (one centre presented a bimodal *C. albicans* distribution with one peak at 0.004 mg/L and a second peak at 0.03 mg/L). This data set was excluded for further analysis.

The following ECOFFs were selected: *C. albicans*: 0.016 mg/L, *C. glabrata*: 0.03 mg/L, *C. krusei*: 0.25 mg/L, *C. parapsilosis*: 2 mg/L and C. tropicalis: 0.06 mg/L. The number of *C. guilliermondii* isolates was too low to select an ECOFF.

For 15 isolates with elevated MICs *FKS* sequence data were available and all harboured hot spot mutations (given in parenthesis). Including the *FKS* mutants, the proportion of isolates above the ECOFFs was 1.7-4%.

Species (no.)	0.004	0.008	0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	ECOFF	No. (%) above the ECOFF
***C. albicans* (1569)**	290	273	241	4	5							0.016	49 (3.1%)
	ND	ND	ND	107									
	ND	ND	520	35	2	1			2				
	ND	87	2										
***C. glabrata* (692)**	90	182	100	33	3	5 (1/1)				2		0.03	12 (1.7%)
	ND	ND	ND	100									
	ND	ND	173	2				1	1				
***C. krusei* (483)**	1		4	26	185	215	37	9	2 (2/2)	4		0.25	15 (3.1%)
***C. parapsilosis* (743)**			3	1		1	35	113	332	244	14	2	14 (1.9%)
***C. tropicalis* (732)**	48	51	247	200	59	14	2 (2/2)	1 (1/1)	6 (4/4)	4 (4/4)		0.06	29 (4.0%)
	ND	ND	ND	98		1				1 (1/1)			
***C. guilliermondii* (22)**						1	5	7	8	1		ND	

ND: Not done

Numbers in parenthesis indicate number of isolates with *fks* hotspot mutations / number of isolates for which the *FKS* region was sequenced

Conclusion

- Micafungin showed potent and uniform *in vitro* activity against WT isolates of *C. albicans, C. glabrata* and *C. tropicalis*. With ECOFFs of 0.015; 0.03 and 0.06 mg/L, respectively
- The MICs against *C. krusei* were slightly higher (ECOFF of 0.25 mg/L).The implication of this (if any) remains to be elucidated.
- These ECOFFs have been utilised for the clinical breakpoint selection process.
- Current EUCAST BPs are available at www.eucast.org

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