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Mutant prevention concentrations (MPCs) of micafungin and anidulafungin against Candida glabrata clinical isolates

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Background: The emergence of echinocandin resistance in *Candida glabrata* is a matter of concern. The mutant prevention concentration (MPC) is a parameter previously used to optimize antibacterial treatments by minimizing the emergence of resistant mutant isolates. The echinocandin MPCs against *C. glabrata* is unknown. We assessed the MPCs of anidulafungin (AND) and micafungin (MYC) against *C. glabrata* and the corresponding mutation frequency.

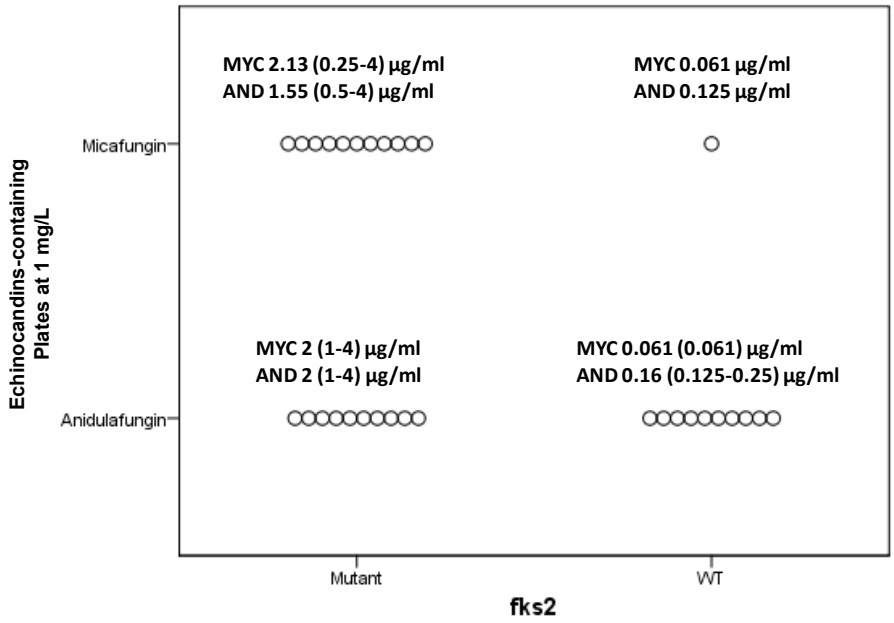
Material/methods: We studied 20 *C. glabrata* isolates from patients with candidemia admitted to Gregorio Marañón Hospital (2014 – 2015). For each isolate, AND and MYC MICs were determined using EUCAST EDef 7.2. To calculate the MPC, adjusted inocula (3-6x10^9 CFU/mL) were stroked directly onto agar plates containing MYC or AND at concentrations ranging from 0.015 mg/L (2-fold concentrations) to 2 mg/L. Plates were incubated at 35ºC and visually inspected after 1 day and 5 days of incubation; MPCs were defined as the lowest echinocandin concentration leading to a complete inhibition of fungal growth. Mutation frequency for each isolate was calculated after 5 days of incubation of the plates and was defined as the ratio between the number of *fks* mutant colonies either

on the MYC-containing plates or on the AND-containing plates [at concentrations of 1 mg/L that allowed single colonies counting] and the number of cells stroked.

Results: All isolates were initially echinocandin-susceptible. The percentage of isolates growing on plates containing AND or MYC increased when the incubation was prolonged up to 5 days, the time chosen to calculate the MPC. The MPC ranged from 0.25 to 2 mg/mL (AND), and from 0.125 to 2 mg/mL (MYC).

	Isolates (%) growing on plates with different concentrations (mg/L)							
	0.015	**0.031**	**0.062**	**0.125**	**0.25**	**0.5**	**1**	**2**
AND (Day 1/5)	100	100	100	100	75/95	30/70	10/50	0
MYC (Day 1/5)	100	100	80/100	60/85	40/80	15/55	5/35	0

Mutation frequency of MYC (5.3 - 2.2 $x10^{-8}$) was lower than that found for AND (3.9 - 1.7 $x10^{-8}$) (*P*=0.02). In 12 isolates, single colonies grew on MYC-containing plates (n=12) or AND-containing plates (n=20) at concentrations of 1 mg/L; the 32 colonies were resistant to both echinocandins but only 21/32 showed *fks2* mutations. The resistant isolates showing *fks2* wild-type sequence were more frequently found on the AND-containing plate.



Geometric mean MICs of AND and MYC against both groups of mutant isolates and wild-type isolates were significantly different. The amino acid substitutions found were delF658 (n=14), S663P (n=4), W715L (n=2), and E655A (n=1); the latter two mutations had not been previously described. In some isolates (n=4), different mutants coexisted.

Conclusions: The MPC of anidulafungin and micafungin against clinical isolates of *C. glabrata* were similar and overall ranged from 0.125 to 2 mg/L. Further studies on echinocandin *fks2* wild-type isolates showing phenotypic resistance are warranted.