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Candida glabrata can acquire in-vitro resistance to echinocandins after exposure to low micafungin concentrations

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Background: Echinocandin resistance in *Candida glabrata* isolates seems to be emerging in some geographic areas, particularly in patients receiving long term treatments with echinocandins. We studied whether *C. glabrata* can potentially acquire *in vitro* resistance to echinocandins after exposing clinical isolates to low micafungin concentrations.

Material/methods: We studied 5 isolates from patients with *C. glabrata* candidemia admitted to Ramón y Cajal Hospital, Madrid, Spain. Anidulafungin and micafungin MICs were determined using the EUCAST EDef 7.2 procedure. MICs were studied before the exposure to micafungin ($MIC_{initial}$) and during the exposure conditions as follows: isolates were stroke on 0.031 mg/L micafungin-containing plates and were incubated for 24 hours at 35ºC; isolates were further stroke on the same kind of plates up to nine propagation steps. The MICs of the echinocandins and the presence of *fks1* and *fks2* mutations were studied in isolates recovered from the suspensions prepared at each propagation step ($MIC_{subsequent}$) including the last one (MIC_{final}). Genotyping proved the absence of contaminations.

Results: All isolates were initially echinocandin-susceptible (micafungin/anidulafungin $MIC_{initial}$ = 0.015 mg/L) but they became phenotypically echinocandin-resistant after growing between two and four days.

Isolates	Propagation day when the isolate become phenotypically resistant	EUCAST MIC (mg/L) Micafungin/Anidulafungin		Amino acid substitution *Fks2* HS1
		$MIC_{subsequent}$	MIC_{final}	
1	2nd	2/2	2/2	S663P
2	4th	2/2	2/2	W715L
3	3rd	1/2	4/4	S663P
4	3rd	2/1	2/1	delF658
5	2nd	2/1	4/2	S663P

Mutations in the HS1 of the *fks2* gene were found in all isolates showing phenotypic resistance with the S663P being the most frequent one; other substitutions located outside the HS1 (deletion at F658 and a substitution newly described at W715L) were also found. Substitutions found in the suspensions used for the calculation of both $MIC_{subsequent}$ and MIC_{final} were identical.

Conclusions: *C. glabrata* isolates can become resistant to echinocandins when exposed in agar plates containing low concentrations of micafungin. Future studies should explain why this species is able to develop echinocandin resistance although only few resistant-isolates cause invasive disease.