

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

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BACKGROUND and OBJECTIVE

- The mutant prevention concentration (MPC) is a parameter previously used to optimize antibacterial treatments minimizing the emergence of resistant isolates.
- We assessed the MPCs and the mutant selection window (MSW) of anidulafungin and micafungin against *C. glabrata* isolates with the corresponding mutation frequency.

METHODS

20 *C. glabrata* echinocandin-susceptible isolates

3-7x10⁹ CFU/mL

Streaked onto plates with micafungin/anidulafungin (0.015 to 2 mg/L)

Incubated up to 5 days

EUCAST MICs against the colonies growing onto plates containing 1 mg/L of micafungin or anidulafungin.

Sequence of *fks1* and *fks2* genes

- MPC:** Lowest echinocandin concentration on the agar plates leading to complete inhibition of fungal growth.
- MSW:** Range of concentrations between MIC and MPC.
- Mutation frequency:** Ratio between the number of *fks* mutant colonies growing onto plates containing 1 mg/L of micafungin/anidulafungin and the number of cells streaked.

RESULTS

- The percentage of isolates growing on plates after 5 days of incubation is shown in the Table:

	Echinocandin concentrations (mg/L)							
	0.015	0.031	0.062	0.125	0.25	0.5	1	2
Anidulafungin (%)	100	100	100	100	95	70	50	0
Micafungin (%)	100	100	100	85	80	55	35	0

Table. Isolates growing on plates containing different concentration of micafungin and anidulafungin

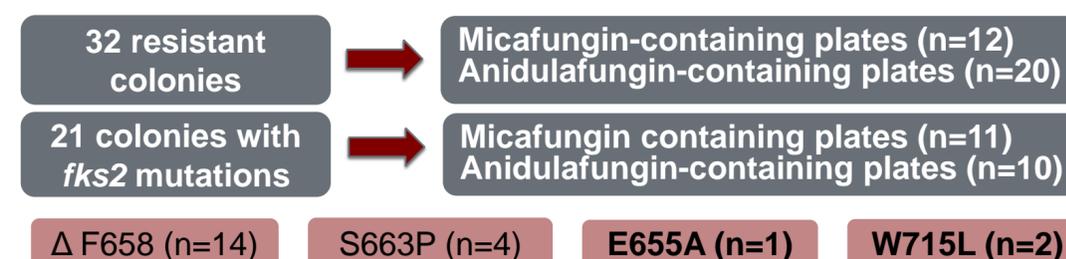
- Both echinocandins showed similar MPC ranges. The micafungin MSW was narrower than the anidulafungin MSW. Mutation frequency was lower in the presence of micafungin compared to anidulafungin ($P=0.02$) (Figure 1):

Figure 1. MPC and MSW range and mutation frequency

	MYC	AND
MPC range (GM):	0.125-2 mg/L	0.25-2 mg/L
MSW (GM):	0.015-0.73 mg/L	0.025-1.15 mg/L
M. frequency:	5.3-2.2 x10 ⁻⁸	3.9-1.7 x10 ⁻⁸

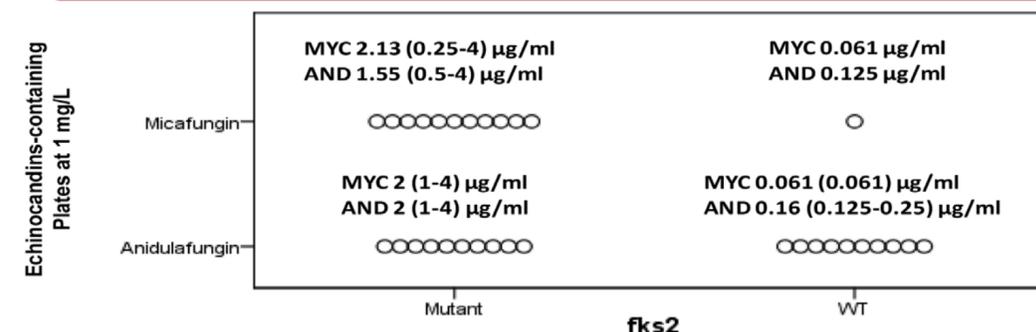
- A total of 12/20 isolates grew onto 1 mg/L micafungin/anidulafungin plates yielding 32 colonies phenotypically resistant as per EUCAST (Figure 2):

Figure 2. Colonies growing onto 1 mg/L candin-containing plates



- Mutations in bold have not been previously described
- Different mutations coexisted in four isolates
- Geometric mean MICs of anidulafungin and micafungin against mutant colonies and wild-type colonies were significantly different.
- Resistant colonies showing *fks* wild-type sequence were more frequently found on the anidulafungin-containing plate (Figure 3):

Figure 3: Colonies (n=32) growing on plates containing 1 mg/L of candins, and their corresponding *fks2* sequence and range of MICs.



CONCLUSIONS

- Our study suggests that, overall, concentrations of anidulafungin and micafungin above ≥ 2 mg/L may prevent the emergence of *C. glabrata fks2* mutant isolates.
- In contrast, concentrations below 2 mg/L may promote the development of secondary resistance to echinocandins.