In Vitro Interactions of Echinocandins with Triazoles Against Multidrug-Resistant *Candida auris*

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The *in vitro* interactions between echinocandins and azoles were determined against ten multidrug-resistant *Candida auris* strains by using a microdilution checkerboard technique. Our results suggest synergistic interactions between micafungin and voriconazole with FICI range values of 0.15 to 0.5, and indifferent interactions were observed when micafungin was combined with fluconazole (FICI range: 0.62-1.5). Combinations of caspofungin with fluconazole or voriconazole exhibit indifferent interactions. No antagonism was observed for any combination.

Candidiasis caused by uncommon *Candida* species has increased in recent years, particularly among immunocompromised patients (1). In the *Metschnikowiaceae* clade, *Candida auris* causes a variety of infections, ranging from superficial mucocutaneous candidiasis to severe bloodstream infections (2-3). Remarkably, in recent years, multidrug-resistant *C. auris* has emerged in Asia, Africa, Europe and America, resulting in several cases of fungemia (3-14). Although European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the diagnosis and management of candidiasis have recommended the use of azoles, polyenes, and echinocandins (15,16), toxic effects of amphotericin B restrict its clinical application. In addition, resistance to azoles and echinocandins in *Candida* species has become a severe clinical challenge (17). Fungemia due to *C. auris* is associated with a high mortality rate and treatment failure, in addition to being potentially resistant to azoles, polyenes, and/or echinocandins (18-21). Thus, accurate identification of *C. auris* and *in vitro* antifungal susceptibility testing is highly recommended (22). Due to limited available treatment choices and high rates of therapeutic failures, novel strategies are needed to improve patient outcome (23). Combinations of echinocandins and azoles seem to be an attractive treatment regimen, as both drugs have different antifungal targets and mode of action. We therefore investigated the efficacy of echinocandins plus azoles against multidrug-resistant *C. auris* clinical isolates.

A total of ten *C. auris* strains from patients with candidemia, in tertiary care hospitals in Delhi, including fluconazole-resistant isolates (n = 10) and micafungin-resistant (n = 3) (according to non-species specific *Candida* species breakpoints of > 4 µg/ml and ≥ 8 µg/ml for fluconazole- and echinocandin-resistant species, respectively [14]), were studied (Tables 1 and 2). All isolates had been identified previously by conventional and molecular methods, i.e., CHROMagar *Candida* medium (Difco, Becton Dickinson & Company, Baltimore, MD, USA),

microscopic morphology on Corn-Meal agar (CMA, Difco, laboratories, Detroit, Mich., USA) with 1 % tween 80, and sequencing of internal transcribed spacer (ITS) ribosomal DNA (rDNA) and D1/D2 regions. In addition the isolates were identified by MALDI-TOF (MALDI Biotyper OC version 3.1, Bruker Daltonics, Bremen, Germany) (18). All strains were stored in 10% glycerol broth at -80 °C at the Department of Medical Mycology, Vallabhbhai Patel Chest Institute, University of Delhi and were sub-cultured on Sabouraud dextrose agar (SDA) supplemented with 0.02% chloramphenicol at 35°C for 3 days to ensure purity and viability. All isolates were sub-cultured again on SDA before preparation of the inoculum. The interactions of caspofungin and micafungin with fluconazole or voriconazole were investigated by using a microdilution checkerboard method based on the CLSI reference technique with 96-well microtiter plates (24). Fluconazole (FLU; Pfizer, Groton, CT, USA), voriconazole (VRC; Pfizer), caspofungin (CAS; Merck) and micafungin (MFG; Astellas, Toyama, Japan), were dissolved in 100% dimethyl sulfoxide (DMSO). Drug dilutions were prepared to obtain four times the final concentration. Concentrations ranged from 8 to 0.016 µg/ml for caspofungin, from 8 to 0.016 µg/ml and 1 to 0.002 µg/ml for micafungin, from 64 to 1 µg/ml for fluconazole and from 16 to 0.25 and 1 to 0.016 µg/ml for voriconazole. The concentration range of micafungin and voriconazole depended on the MIC results of each isolates. For two-dimensional microplate preparation i.e., caspofungin plus fluconazole, caspofungin plus voriconazole, micafungin plus fluconazole and micafungin plus voriconazole, a total of 50-µL of each concentration of echinocandins (caspofungin and micafungin) were added to columns 1–11, and then 50-µL of azoles (fluconazole and voriconazole) were added to rows A–H, respectively. The wells of column 11 and the wells of row H contained 50 µL of RPMI containing 1% of the solvent. Row H and column 11 contain the echinocandins and azoles alone, respectively. Column 12 was the

drug-free wells that served as the growth control. The maximal final concentration of DMSO in the test wells was less than 1%. Trays were stored at -80 °C until the day of testing. After the microtiter trays were defrosted, 100 µL of the inoculum was added to each well. Briefly, homogeneous suspensions were measured spectrophotometrically at 530 nm wavelength to a percent transmission in the range 75–77%. The final concentration of the stock inoculum suspensions of the isolates tested ranged from 1 - 3 × 10^3 CFU/ml, as determined by quantitative colony counts on Sabouraud glucose agar (SGA, Difco). Plates were incubated at 35 °C and examined visually after 24 hr to determine MIC values for drugs alone and in combination. The MIC endpoints were determined with the aid of a reading mirror and were defined as the lowest concentration of drug that significantly reduced growth (≥50 %) compared with the growth of a drug free control. For calculations, high off-scale MICs were raised to the next $\log_2$-dilution step, while the low off-scale MICs were left unchanged (25). To assess the interaction of combinations of drugs, the fractional inhibitory concentration index (FICI) was calculated. The FICI was defined as the following equation: $FICI = FIC_A+FIC_B = (C_A/MIC_A) + (C_B/MIC_B)$, where MIC_A and MIC_B are the MICs of drugs A and B alone, and C_A and C_B are the concentrations of the drugs in combination, in all wells corresponding to an MIC. The interaction was defined as synergistic if the FICI was ≤0.5, indifferent if >0.5 – ≤4.0, and antagonistic if >4 (24).

The results for the tested drug alone and in combination against the ten *C. auris* strains are summarized in Tables 1 and 2. The MIC ranges of drugs alone against strains were 32 - ≥64 µg/ml for fluconazole, 0.5-8 µg/ml for voriconazole, 0.5-4 µg/ml for caspofungin and 0.125-8 µg/ml for micafungin (Tables1 and 2). Based on the checkerboard microdilution assay, when caspofungin was combined with fluconazole, the MIC ranges for caspofungin and fluconazole

122 decreased to 0.25 to 2 µg/ml and 8 to 64 µg/ml, respectively, the results showed that the
123 combination exhibited indifferent activity against all ten strains (FICI range: 0.56-2) and when
124 caspofungin was combined with voriconazole, the MIC ranges for caspofungin and voriconazole
125 decreased to 0.25 to 2 µg/ml and 0.063 to 4 µg/ml, respectively, demonstrated indifferent activity
126 with FICI range values of 0.62-2 against all strains (Table 1). For the combination of micafungin
127 with fluconazole, the MIC ranges of micafungin and fluconazole were reduced to 0.063 to 8
128 µg/ml and 4 to 64 µg/ml, respectively, indifference was also observed with FICI range values of
129 0.62 to 1.5 (Table 2). Synergistic effects of micafungin with voriconazole were shown against
130 ten multidrug-resistant *C. auris* (FICI range: 0.15-0.5), the MIC ranges of micafungin and
131 voriconazole were reduced to 0.008 to 2 µg/ml and 0.125 to 1 µg/ml, respectively (Table 2).
132 Overall, no antagonistic effects were observed for any combination.

133 In this study, we used the checkerboard microdilution method for analysis of drug–drug
134 interactions of echinocandins with azoles against multidrug-resistant *C. auris.* The emergence of
135 new species and antifungal resistance has raised the issue of using alternative therapeutic
136 strategies. Evidence to support treatment choices for multidrug-resistant *C. auris* disease is rare
137 at present. Except for one study (20), *in vitro* antifungal profiles are relatively scarce and based
138 on low numbers of test isolates (14, 19, 21). The *in vivo* efficacy of antifungal therapy against *C.*
139 *auris* is undetermined and also *in vitro* data from different sources are inadequate. Echinocandins
140 are the recommended treatment in patients with potent activity, excellent safety profile, and
141 favorable pharmacokinetics (26-28) but unsuccessful treatment of *C. auris* infections with
142 fluconazole, voriconazole, amphotericin B, caspofungin, and anidulafungin has been already
143 reported (6). On the other hand, micafungin is used for the prophylaxis and treatment with broad
144 spectrum of activity in both neutropenic and non-neutropenic patients (15, 29). Concordant with

other reports (30, 32), micafungin activity was shown to be as effective as caspofungin *in vitro* against *Candida glabrata* isolates with and without *fks* mutations. Micafungin was also effective *in vivo* for decreasing the fungal burden in mice infected with *C. glabrata* with *fks* mutations. It seems that lower concentrations of drugs cause fewer side-effects and improve the treatment outcomes. We have shown that interaction between micafungin with voriconazole exhibited synergistic activity against multidrug-resistant *C. auris* strains suggesting that it may be considered in patients with candidiasis. However, confirmation of *in vitro* results presented here, need *in vivo* studies with suitable animal models of *C. auris* infection. Clearly, more research is indicated to explore clinical management. In conclusion, combination of micafungin and voriconazole exhibited synergistic activity against multidrug-resistant *C. auris* suggesting an alternative approach to overcome antifungal drug resistance. However, using this combination therapy *in vivo* needs further study in addition to determination of the underlying mechanism of this synergistic action.

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Conflict of interest

J.F.M. received grants from Astellas, Merck, and Basilea. He has been a consultant to Basilea and Merck and received speaker fees from Merck, Pfizer, Gilead, and United Medical. During the past 5 years, E.D has received research grants from MSD and Gilead; travel grants from Gilead, MSD, Pfizer, and Astellas, and speaker's fee from Gilead, MSD, and Astellas. All other authors no potential conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Legends:

Table 1. *In vitro* interactions of caspofungin with fluconazole and voriconazole against *Candida auris*

Table 2. *In vitro* interactions of micafungin with fluconazole and voriconazole against *Candida auris*

Table 1. *In vitro* interactions of caspofungin with fluconazole and voriconazole against *Candida auris*

Strains nr	CAS+FLU				CAS+VRC			
	MIC (µg/ml)				MIC (µg/ml)			
	CAS	FLU	CAS/FLU	FICI/INT	CAS	VRC	CAS/VRC	FICI/INT
VPCI 482/P/13*	2	≥64	1/32	0.75/IND	2	2	1/0.5	0.75/IND
VPCI 1132/P/13*	2	32	1/8	0.75/IND	2	0.5	1/0.063	0.62/IND
VPCI 1133/P/13*	4	≥64	2/64	1/IND	4	1	2/0.25	0.75/IND
VPCI 265/P/14*	4	32	2/32	1.5/IND	4	8	2/0.25	0.75/IND
VPCI 1510/P/14*	0.5	32	0.5/32	2/IND	0.5	4	0.5/4	2/IND
VPCI 1514/P/14*	1	≥64	0.5/32	0.75/IND	1	0.5	1/0.25	1.5/IND
VPCI 266/P/14*	2	≥64	1/32	0.75/IND	2	0.5	1/0.25	1/IND
VPCI 267/P/14*	2	32	1/8	0.75/IND	2	0.5	2/0.063	0.62/IND
VPCI 487/P/14*	1	≥64	0.5/8	0.56/IND	1	1	0.5/0.125	0.62/IND
VPCI 518/P/14*	0.5	≥64	0.25/8	0.56/IND	0.5	1	0.25/0.25	0.75/IND

Abbreviations: CAS; caspofungin, FLU; fluconazole, VRC; voriconazole, FICI; Fractional Inhibitory Concentration Index, IND; Indifference, SYN; synergy; MIC; minimal inhibitory concentration, INT; interpretation, * fluconazole-resistant isolates (n = 10).

Table 2. *In vitro* interactions of micafungin with fluconazole and voriconazole against *Candida auris*

Strains nr	MFG+FLU				MFG+VRC			
	MIC (µg/ml)				MIC (µg/ml)			
	MFG	FLU	MFG/FLU	FICI/INT	MFG	VRC	MFG/VRC	FICI/INT
VPCI 482/P/13*	0.25	≥64	0.25/64	1.5/ IND	0.25	2	0.016/0.5	0.31/SYN
VPCI 1132/P/13*	0.5	32	0.25/4	0.62/ IND	0.5	0.5	0.016/0.125	0.28/SYN
VPCI 1133/P/13*, **	8	≥64	4/32	0.75/ IND	8	1	2/0.25	0.5/SYN
VPCI 265/P/14*	0.5	32	0.5/8	1.25/ IND	0.5	8	0.063/1	0.25/SYN
VPCI 1510/P/14*	0.125	32	0.063/8	0.75/ IND	0.125	4	0.016/0.25	0.19/SYN
VPCI 1514/P/14*, **	8	≥64	8/16	1.12/ IND	8	0.5	1/0.125	0.37/SYN
VPCI 266/P/14*	0.25	≥64	0.25/32	1.25/ IND	0.25	0.5	0.008/0.125	0.28/SYN
VPCI 267/P/14*, **	8	32	8/8	1.25/ IND	8	0.5	1/0.125	0.37/SYN
VPCI 487/P/14*	4	≥64	4/32	1.25/ IND	4	1	0.5/0.125	0.25/SYN
VPCI 518/P/14*	0.5	≥64	0.25/64	1/ IND	0.5	1	0.016/0.125	0.15/SYN

Abbreviations: MFG; micafungin, FLU; fluconazole, VRC; voriconazole, FICI; Fractional Inhibitory Concentration Index, IND; Indifference, SYN; synergy, MIC; minimal inhibitory concentration, INT; interpretation, * fluconazole-resistant isolates (*n* = 10), ** micafungin-resistant (n =3).