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In Vitro Activity of Taurolidine against Clinical *Candida auris* Isolates; Relevance to Catheter-related Bloodstream Infections

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BACKGROUND

- *Candida auris* is a highly concerning, emerging global health threat characterized by extensive drug resistance, invasive infections, and high morbidity and mortality.[1,2]
- Persistent colonization of *C. auris* on skin and abiotic surfaces have led to multiple outbreaks and poses a risk for invasive disease, including bloodstream infections.[3-5]
- Mortality rates following *C. auris* bloodstream infections have been reported to be 42-47% and frequently associated with central venous catheters.[3,6]
- Given the propensity of central lines as a source for bloodstream infections, guidelines have suggested the use of catheter lock solutions as a preventive method in certain patients.[7]
- Taurolidine is a broad-spectrum antimicrobial contained in the first FDA approved catheter lock solution at a concentration of 13,500 mg/L combined with 1,000 Units/mL of heparin.[8,9]
- While the activity of taurolidine has been described for a number of Candida species, no data for *C. auris* are available.
- The purpose of this study was to assess the in vitro activity of taurolidine against *C. auris*.

METHODS

- The in vitro activity of taurolidine was evaluated against 106 isolates obtained from USA, Europe, and Africa; the majority (82%) were recovered from blood cultures.
- Minimum inhibitory concentrations (MIC) for taurolidine and comparators were determined by broth microdilution according to CLSI guidelines with MICs being read after 24 hours.
- The tentative resistant CDC breakpoints were applied for fluconazole (R ≥32 mg/L), amphotericin B (R ≥2 mg/L), and caspofungin (R ≥2 mg/L). No breakpoints are available for taurolidine.

RESULTS

- Taurolidine exhibited antimicrobial activity against all tested *C. auris* isolates with MIC values of ≤1,024 mg/L, whether read at 50% or 100% inhibition.
- The $MIC_{50/90}$ values were similar when using 50% inhibition ($MIC_{50/90}$, 256/512 mg/L) or 100% reading criterion ($MIC_{50/90}$, 512/512 mg/L; Table 1).
- Taurolidine activity was similar for all *C. auris* subsets tested regardless of source.
- 57.5% of *C. auris* isolates (n=61; MIC ≥2 mg/L) were resistant to amphotericin B, 3.7% (n=3; MIC ≥2 mg/L) were resistant to caspofungin, and 86.8% (n=92; MIC ≥32 mg/L) were resistant to fluconazole (Table 1).
- Taurolidine activity was unaffected by resistance to amphotericin B, caspofungin, or fluconazole as similar MIC50/90 values were observed for all three resistant subsets (Table 2).

Table 1. Cumulative distributions of MIC values for taurolidine and comparators tested against *Candida auris*

Antimicrobial agent (No. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of: 0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	> [a]	MIC_{50}	MIC_{90}
Taurolidine 50% inhibition (106)										0 0.0	1 0.9	12 12.3	58 67.0	35 100.0			256	512
Taurolidine 100% inhibition (106)												0 0.0	14 13.2	89 97.2	3 100.0		512	512
Amphotericin B (106)			0 0.0	13 12.3	32 42.5	59 [b] 98.1	0 98.1									2 100.0	2	2
Caspofungin (81)	15 18.5	35 61.7	20 86.4	7 95.1	1 96.3	0 96.3	0 96.3	0 96.3								3 100.0	0.12	0.5
Fluconazole (106)					0 0.0	1 0.9	9 9.4	3 12.3	1 13.2	4 17.0	17 33.0					71 100.0	>64	>64

[a] Greater than the highest concentration tested.
[b] Shaded values represent resistant isolates according to CDC tentative MIC breakpoints published at https://www.cdc.gov/fungal/*candida*-auris/c-auris-antifungal.html.

Table 2. Cumulative distributions of MIC values for taurolidine tested against comparator-resistant *Candida auris* subsets

Resistant [a]subset (No. of isolates) Antimicrobial agent	No. and cumulative % of isolates inhibited at MIC (mg/L) of: 16	32	64	128	256	512	1,024	> [b]	MIC_{50}	MIC_{90}
Amphotericin B-resistant isolates (61)										
Taurolidine 50% inhibition			0 0.0	1 1.6	37 62.3	23 100.0			256	512
Taurolidine 100% inhibition				0 0.0	1 1.6	57 95.1	3 100.0		512	512
Caspofungin-resistant isolates (3)										
Taurolidine 50% inhibition				0 0.0	2 66.7	1 100.0			256	-
Taurolidine 100% inhibition					0 0.0	3 100.0			512	-
Fluconazole-resistant isolates (92)										
Taurolidine 50% inhibition		0 0.0	1 1.1	11 13.0	48 65.2	32 100.0			256	512
Taurolidine 100% inhibition				0 0.0	12 13.0	77 96.7	3 100.0		512	512

[a] CDC tentative MIC breakpoints published at https://www.cdc.gov/fungal/*candida*-auris/c-auris-antifungal.html.
[b] Greater than the highest concentration tested.

SUMMARY

- Taurolidine exhibited antimicrobial activity against all tested *C. auris* isolates with MIC values of ≤1,024 mg/L.
- The MIC distribution was narrow with MIC_{50} and MIC_{90} values 512 mg/L, over 20-fold lower than lock solution concentrations of ≥13,500 mg/L.
- The activity of taurolidine was unaffected by drug resistance to amphotericin B, caspofungin, or fluconazole..
- The data generated herein support the broad-spectrum activity of taurolidine against *C. auris*, with MIC values well below concentrations utilized in commercially available catheter lock solutions.
- Given the recent observation of *C. auris* outbreaks and the association with central venous catheters, these data provide the theoretical basis for anticipating prevention of *C. auris* catheter-related bloodstream infection using taurolidine-based catheter lock solutions.
- Future studies could evaluate these in vitro findings in animal and/or clinical studies.

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