

In Vitro Antimicrobial Activity of Taurolidine against Isolates Associated with Catheter-Related Bloodstream Infections

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BACKGROUND

- Taurolidine is a novel antimicrobial with broad spectrum antibacterial/antifungal activity and two mechanisms of action that does not lend itself to clinically relevant microbial resistance at concentrations contained within a central venous catheter.
- Taurolidine exerts its activity through damage to microbial cell walls and inhibiting adherence of microorganisms to biological surfaces.
- Taurolidine is a component of a recently FDA-approved catheter lock solution (DefenCath®, taurolidine 13,500 µg/mL and heparin 1000 Units/mL) indicated for reducing the incidence of CRBSI in adult patients receiving chronic hemodialysis through a central venous catheter (HD-CVC).
- Although individual isolates from the clinical program were not available for testing, this study evaluated the in vitro antimicrobial activity of taurolidine against a set of recent clinical isolates representative of those recovered from the LOCK-IT-100 trial and/or commonly associated with CRBSI.

METHODS

LOCK-IT-100 Study Design and Outcomes

- LOCK-IT-100 was a phase 3, randomized, double-blind, active-control, multicenter study aimed to evaluate the efficacy and safety of DefenCath® (taurolidine 13,500mg/L and heparin 1000 units/mL) as a catheter lock solution for the reduction of CRBSI in adult patients receiving chronic hemodialysis.
- Patients randomized 1:1 receive a quantity sufficient to fill each catheter lumen of either taurolidine/heparin or heparin 1000 units/mL following each dialysis session.
- The primary end point was the time to CRBSI as determined by a blinded clinical adjudication committee defined as one positive blood culture (other than for coagulase-negative staphylococci, which required a confirmatory culture) from either a peripheral site, the catheter hub, or the dialysis blood line, signs and symptoms of infection, and no other apparent source of bloodstream infection.
- Among the 327 patients in the taurolidine/heparin arm and the 326 in the heparin arm, there were 9 and 32 cases of CRBSI, respectively; these equated to a 71% reduction in risk of CRBSI for taurolidine/heparin (Figure 1)
- Table 1 depicts the pathogens recovered from both treatment arms in LOCK-IT-100
- As the actual isolates from LOCK-IT-100 were unavailable, this study includes representative contemporary pathogens.

Taurolidine In Vitro Studies

- 442 bacterial and 50 yeast isolates were selected from the SENTRY Antimicrobial Surveillance Program
- All isolates were collected from the bloodstream of U.S. patients between 2018–2023.
- Challenge isolates were included such as MRSA, MRCoNS, MDR Enterobacterales, MDR Pseudomonas aeruginosa, and MDR Acinetobacter baumannii-calcoaceticus sc.
- Testing followed CLSI broth microdilution guidelines using JMI Laboratories produced susceptibility test panels.
- CAMHB was used for testing bacterial isolates which was supplemented with 2.5–5% LHB for testing Streptococci or 5% OADC when testing MAC isolates.
- RPMI 1640 broth buffered with MOPS and 0.2% (w/v) glucose was used for testing fungal isolates.
- Taurolidine MIC values reported were read at 100% growth inhibition.

ABBREVIATIONS

CAMHB, Caton-adjusted Mueller-Hinton broth
CLSI, Clinical and Laboratory Standards Institute
CRBSI, catheter-related bloodstream infections
LHB, lysed horse blood
MAC, Mycobacterium avium complex
MDR, multidrug-resistant
MOPS, morpholinepropanesulfonic acid
MRCoNS, methicillin-resistant coagulase-negative Staphylococcus
MRSA, methicillin-resistant Staphylococcus aureus
ND, not determined
OADC, oleic acid-albumin-decathionate
RPMI, Roswell Park Memorial Institute
sc, species complex
VRE, vancomycin-resistant Enterococcus

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DISCLOSURES

This study was funded by CorMedix Inc. Element Iowa City (JMI Laboratories) received compensation for services related to the preparation of this poster.

RESULTS

Table 1. Pathogens recovered from CRBSI during LOCK-IT-100 trial

Organism	Taurolidine/ Heparin		Heparin	
	n	%	n	%
Total	9		34 ^a	
Gram-Positive	8	88.9%	20	58.8%
<i>S. aureus</i>	7	77.8%	8	23.5%
MSSA	3	33.3%	3	8.8%
MRSA	4	44.4%	5	14.7%
<i>S. epidermidis</i>	1	11.1%	4	11.8%
<i>S. lugdunensis</i>			1	2.9%
<i>S. sanguinis</i>			2	5.9%
<i>S. bovis</i>			1	2.9%
Viridans streptococci			1	2.9%
<i>E. faecalis</i>			3	8.8%
Gram-Negative	1	11.1%	14	41.2%
<i>C. koseri</i>			2	5.9%
<i>E. aerogenes</i>			1	2.9%
<i>E. cloacae</i>			4	11.8%
<i>K. pneumoniae</i>	1	11.1%	2	5.9%
<i>S. maltophilia</i>			1	2.9%
<i>S. marcescens</i>			3	8.8%
<i>P. aeruginosa</i>			1	2.9%

^a Polymicrobial: *P. aeruginosa* and *S. epidermidis*; *S. epidermidis* and Viridans streptococcus

- Taurolidine exhibited broad antimicrobial activity against all isolates tested, with 95.5% of all MIC values ≤1,024 µg/mL (Tables 2).
- All taurolidine MIC values were ≤ 1,024 µg/mL against Gram-positive bacteria:
 - S. aureus* (MIC_{50/90}: 512/512µg/mL)
 - Coagulase-negative Staphylococcus (MIC_{50/90}: 512/512 µg/mL)
 - Enterococcus species (MIC_{50/90}: 512/512 µg/mL)
 - Viridans group streptococci (MIC_{50/90}: 512/512 µg/mL)
 - Non-tuberculosis Mycobacteria (MIC_{50/90}: 1,024/2,048 µg/mL)
 - Activity was maintained regardless of methicillin susceptibility for Staphylococcal isolates or vancomycin resistance among Enterococcal species.
- All taurolidine MIC values were ≤2,048 µg/mL against Gram-negative bacteria:
 - Enterobacterales (MIC_{50/90}: 512/512 µg/mL)
 - P. aeruginosa* (MIC_{50/90}: 1,024/1,024 µg/mL)
 - S. maltophilia* (MIC_{50/90}: 256/512 µg/mL)
 - A. baumannii-calcoaceticus* sc (MIC_{50/90}: 512/512 µg/mL)
 - Burkholderia cepacia* (MIC_{50/90}: 256/2,048 µg/mL)
 - Activity was maintained in multidrug-resistant Enterobacterales, *P. aeruginosa*, and *A. baumannii-calcoaceticus* sc isolates.
- All taurolidine MIC values were ≤1,024 µg/mL among *Candida glabrata* (MIC_{50/90}: 512/512 µg/mL) and *Candida parapsilosis* (MIC_{50/90}: 256/512 µg/mL) isolates
- MIC_{50/90} values of 4,096/4,096 µg/mL were observed for *C. albicans*

Figure 1. Comparison CRBSI cases between taurolidine/heparin and control arms of LOCK-IT-100 Trial

	Taurolidine/ heparin (n=327)	Control (n=326)
No. of cases (CBRSI/1000 CD)	9 (0.13)	32 (0.46)
Total catheter-days follow-up	67,593	68,890
Hazard ratio (95% CI)*	0.29 (0.14, 0.62) p = 0.001	
Log-rank Test	p = 0.006	

*Cox Proportional Hazards Model

CD: Catheter Days; CI: Confidence Interval

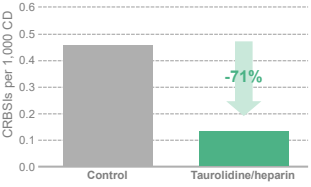


Table 2. Distributions of taurolidine MIC values against various species/groups

Organism (No. isolates)	No. of isolates inhibited at a taurolidine MIC (µg/mL) of:								Taurolidine	
	≤32	64	128	256	512	1,024	2,048	4,096	MIC ₉₀	MIC ₉₉
<i>S. aureus</i> (76)				1	75				512	512
MSSA (37)					37				512	512
MRSA (39)				1	38				512	512
CoNS (52) ^a				10	38	4			512	512
<i>S. epidermidis</i> (36)					32	4			512	1,024
MSCoNS (21)				7	14				512	512
MRCoNS (31)				3	24	4			512	1,024
Enterococcus species (48)				6	40	2			512	512
<i>E. faecalis</i> (38)				1	35	2			512	512
<i>E. faecium</i> (10)				5	5				256	512
VRE (6) ^b				3	3				256	ND
Viridans group streptococci (18) ^c		1	2	5	10				512	512
Nontuberculous Mycobacteria (21)					7	7	7		1,024	2,048
<i>M. avium</i> complex (11) ^d						4	7		2,048	2,048
<i>M. abscessus</i> (10)					7	3			512	1,024
Enterobacterales (137)			1	22	106	8			512	512
<i>E. coli</i> (44)				1	43				512	512
<i>K. pneumoniae</i> (43)				2	38	3			512	512
<i>P. mirabilis</i> (10)				10					256	256
<i>E. cloacae</i> sc (10)					6	4			512	1,024
Citrobacter species (10)				9	1				256	256
<i>S. marcescens</i> (20)					18	1			512	512
MDR Enterobacterales (20) ^e			1	17	2				512	512
<i>P. aeruginosa</i> (45)				20	23	2			1,024	1,024
MDR <i>P. aeruginosa</i> (10)					8	2			512	1,024
<i>S. maltophilia</i> (15)				12	2	1			256	512
<i>A. baumannii-calcoaceticus</i> sc (15)				2	13				512	512
MDR <i>A. baumannii</i> sc (15)				1	5				512	ND
<i>B. cepacia</i> sc (15)				10	1	2	2		256	2,048
<i>C. albicans</i> (17)							5	12	4,096	4,096
<i>C. glabrata</i> (17)				3	13	1			512	512
<i>C. parapsilosis</i> (16)		3		9	4				256	512

^a Staphylococcus capitis (2), *S. epidermidis* (36), *S. haemolyticus* (2), *S. lugdunensis* (10), and *S. saprophyticus* (2).

^b Enterococcus faecium (6).

^c Streptococcus anginosus group (2), *S. bovis* group (5), *S. gallolyticus* (2), *S. mitis* group (2), *S. salivarius* group (2), and *S. sanguinis* (5).

^d Mycobacterium avium (5) and Mycobacterium intracellulare (5).

^e Enterobacter cloacae species complex (2), Escherichia coli (5), and Klebsiella pneumoniae (8).

SUMMARY

- Taurolidine activity was very similar among a large collection of Gram-positive, Gram-negative, and yeast organisms.
- MIC₉₀ values for all species/groups were ≤1,024 µg/mL, except for MAC and *B. cepacia* sc (MIC₉₀: 2,048 µg/mL) and *C. albicans* (MIC₉₀: 4,096 µg/mL) where slightly higher MIC₉₀ values were observed.
- The activity of taurolidine was unaffected by resistance to antibiotics (i.e., methicillin, vancomycin, or multi-drug resistance) among Gram-positive or Gram-negative organisms.
- Based on these data, catheter lock solutions containing the broad-spectrum antimicrobial taurolidine at 13,500 µg/mL have the potential to reduce the risk of CRBSI caused by a variety of species, including those observed in the recent LOCK-IT-100 clinical trial and other common bloodstream pathogens.