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Antimicrobial Activity of Ceftobiprole When Tested against Gram-Positive Cocci Causing Serious Infections (2016–2017): Endocarditis, Diabetic Foot, and Bone/Joint Infections

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Introduction

- Ceftobiprole is a parenteral advanced-generation cephalosporin that is active against Gram-positive and Gram-negative bacteria
- Ceftobiprole exhibits excellent *in vitro* activity against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) and penicillin-resistant *Streptococcus pneumoniae*
- Against *Enterobacteriaceae* and *Pseudomonas aeruginosa,* ceftobiprole displays potent *in vitro* activity that is similar to other advanced-generation cephalosporins like cefepime
- This agent is administered as the prodrug ceftobiprole medocaril, which is rapidly hydrolyzed *in vivo* to the active form of ceftobiprole
- Ceftobiprole is approved in around 20 European and non-European countries for the treatment of adults with community- and hospital-acquired pneumonia (excluding ventilator-associated pneumonia)
- While not approved in the United States (US), ceftobiprole medocaril has qualified infectious disease product (QIDP) status, and BARDA is supporting Phase 3 studies in acute bacterial skin and skin structure infections and *S. aureus* bacteremia
- This study evaluated the activity of ceftobiprole and comparator agents against recent (2016–2017) Gram-positive isolates causing serious infections (including endocarditis, diabetic foot infections, and bone/joint infections) associated with significant morbity and mortality

Materials and Methods

Bacterial isolates

- In 2016–2017, a total of 209 clinical isolates, comprising 155 *S. aureus* (39.4% methicillin-resistant), 25 coagulase-negative staphylococci (CoNS; 76.0% methicillin-resistant), and 29 *Enterococcus faecalis* isolates, were collected from patients in US medical centers
  - Isolates were from bone/joint (130 isolates; 62.2%), diabetic foot (52 isolates; 24.9%), and endocarditis infections (27 isolates; 12.9%) (Figure 1)
  - A total of 58 (27.8%) patients had an associated bloodstream infection
  - Species identification was confirmed by matrix-assisted laser desorption ionization-time of flight mass spectrometry, when necessary, using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions

Susceptibility testing

- Ceftobiprole, comparator antibiotics, and quality control organisms were tested according to Clinical and Laboratory Standards Institute guidelines (CLSI, 2018a) using broth microdilution panels
- CLSI (2018b) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2018) interpretive criteria were applied
- MIC values for organisms without a species-specific ceftobiprole breakpoint were interpreted with the EUCAST ceftobiprole pharmacokinetic-pharmacodynamic (PK-PD) non-species related breakpoint (susceptible, ≤4 mg/L) (EUCAST, 2018)

Results

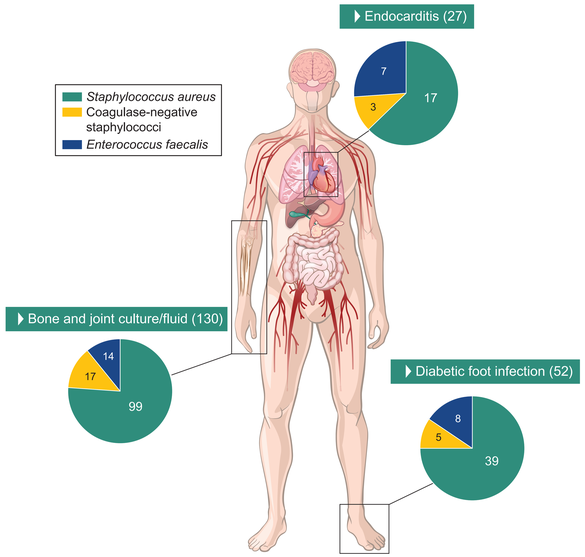
- The ceftobiprole $MIC_{50/90}$ values against *S. aureus* were 0.5/2 mg/L (99.4% susceptible; Tables 1 and 2)
  - 39.4% of *S. aureus* isolates were MRSA
  - The $MIC_{50/90}$ values for MRSA and MSSA were 1/2 mg/L and 0.5/0.5 mg/L, respectively (Table 1)
  - Ceftobiprole and ceftaroline were the most potent cephalosporins tested against the 94 MSSA isolates and were 8- to 32-fold more potent than ceftriaxone (data not shown)
  - 95.1% of MRSA isolates were susceptible to ceftaroline, while 98.4% were susceptible to ceftobiprole
    - Erythromycin resistance (93.4%) and levofloxacin resistance (73.8%) were high (data not shown)
- The $MIC_{50/90}$ values for ceftobiprole against 25 CoNS isolates were 1/4 mg/L, and all MIC values were ≤4 mg/L (Tables 1 and 2)
  - The ceftobiprole $MIC_{50/90}$ values for MR-CoNS and MS-CoNS were 1/4 and 0.12/- mg/L, respectively (Table 1)
  - Ceftaroline ($MIC_{50/90}$, 0.25/2 mg/L) and ceftobiprole ($MIC_{50/90}$, 1/4 mg/L) were the most potent β-lactam agents tested against CoNS (Table 2)
- Ceftobiprole exhibited potent activity against *E. faecalis* ($MIC_{50/90}$, 0.5/2 mg/L; n=29) (Tables 1 and 2)

Table 1 Antimicrobial activity of ceftobiprole tested against the main organisms and organism groups

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)								MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4		
Staphylococcus aureus (155)			0 0.0	35 22.6	62 62.6	42 89.7	15 99.4	1 100.0	0.5	2
MRSA (61)			0 0.0	1 1.6	2 4.9	42 73.8	15 98.4	1 100.0	1	2
MSSA (94)			0 0.0	34 36.2	60 100.0				0.5	0.5
Coagulase-negative staphylococci (CoNS) (25)[a]		0 0.0	4 16.0	1 20.0	6 44.0	10 84.0	1 88.0	3 100.0	1	4
MR-CoNS (19)				0 0.0	5 26.3	10 78.9	1 84.2	3 100.0	1	4
MS-CoNS (6)			0 0.0	4 66.7	1 83.3	1 100.0			0.12	—
Enterococcus faecalis (29)	0 0.0	1 3.4	4 17.2	6 37.9	13 82.8	2 89.7	1 93.1	2 100.0	0.5	2

[a] Organisms include: *Staphylococcus cohnii* (1), *S. epidermidis* (14), *S. haemolyticus* (4), *S. hominis* (2), *S. lugdunensis* (1), *S. pseudintermedius* (1), *S. schleiferi* (1), *S. simulans* (1)
Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; MS-CoNS, methicillin-susceptible coagulase-negative staphylococci

Figure 1 Main organisms and organism groups stratified by infection source



Conclusions

- Ceftobiprole exhibited potent activity against contemporary clinically relevant Gram-positive isolates causing serious infections, including endocarditis, diabetic foot infections, and bone/joint infections, among hospitalized patients in US medical centers
- Importantly, 99.4% of the *S. aureus* isolates (39.4% MRSA) were susceptible to ceftobiprole (EUCAST, 2018)
- These *in vitro* susceptibility data indicate that ceftobiprole may be an attractive option for treating serious infections caused by Gram-positive pathogens including MRSA

Table 2 Activity of ceftobiprole and comparator antimicrobial agents against Gram-positive cocci

Organism group/antimicrobial agent	Antimicrobial activity (mg/L)			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R
***Staphylococcus aureus* (155)**									
Ceftobiprole	0.5	2	0.25 to 4				99.4		0.6
Ceftaroline	0.25	1	0.12 to 2	98.1	1.9	0.0	98.1	1.9	0.0 [b]
Ceftriaxone	4	>8	1 to >8	60.6		39.4			
Clindamycin	≤0.25	>2	≤0.25 to >2	84.5	0.0	15.5	84.5	0.0	15.5
Daptomycin	0.25	0.5	≤0.12 to 1	100.0			100.0		0.0
Erythromycin	4	>8	≤0.06 to >8	45.2	8.4	46.4	45.8	3.9	50.3
Levofloxacin	0.25	>4	0.06 to >4	66.5	0.6	32.9	66.5		33.5
Linezolid	1	1	0.25 to 4	100.0		0.0	100.0		0.0
Oxacillin	1	>2	≤0.25 to >2	60.6		39.4	60.6		39.4
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	93.5	0.6	5.8	91.6	1.9	6.5
Tigecycline	0.06	0.12	0.03 to 0.5	100.0 [c]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	98.7		1.3	98.7	0.0	1.3
Vancomycin	0.5	1	0.25 to 1	100.0	0.0	0.0	100.0		0.0
Coagulase-negative staphylococci (25)[d]									
Ceftobiprole	1	4	0.12 to 4				100.0 [e]		0.0
Ceftaroline	0.25	2	≤0.06 to 2						
Ceftriaxone	>8	>8	0.5 to >8	24.0		76.0			
Clindamycin	≤0.25	>2	≤0.25 to >2	60.0	4.0	36.0	60.0	0.0	40.0
Daptomycin	0.25	0.5	≤0.12 to 0.5	100.0			100.0		0.0
Erythromycin	>8	>8	≤0.06 to >8	20.0	0.0	80.0	20.0	0.0	80.0
Levofloxacin	4	>4	0.06 to >4	40.0	8.0	52.0	40.0		60.0
Linezolid	0.5	1	0.25 to 2	100.0		0.0	100.0		0.0
Oxacillin	>2	>2	≤0.25 to >2	24.0		76.0	24.0		76.0
Tetracycline	≤0.5	2	≤0.5 to >8	92.0	0.0	8.0	88.0	4.0	8.0
Tigecycline	0.12	0.12	0.03 to 0.12				100.0		0.0
Trimethoprim-sulfamethoxazole	2	>4	≤0.5 to >4	56.0		44.0	56.0	12.0	32.0
Vancomycin	1	2	0.5 to 2	100.0	0.0	0.0	100.0		0.0
***Enterococcus faecalis* (29)**									
Ceftobiprole	0.5	2	0.06 to 4				100.0 [e]		0.0
Ampicillin	1	1	≤0.5 to 2	100.0		0.0	100.0	0.0	0.0
Ceftaroline	2	8	0.12 to >8						
Daptomycin	0.5	1	≤0.25 to 1	100.0					
Levofloxacin	1	>4	0.25 to >4	82.8	0.0	17.2	82.8		17.2
Linezolid	1	2	0.5 to 2	100.0	0.0	0.0	100.0		0.0
Teicoplanin	≤0.5	≤0.5	≤0.5 to >16	96.6	0.0	3.4	96.6		3.4
Tigecycline	0.06	0.12	≤0.015 to 0.12	100.0 [f]			100.0	0.0	0.0
Vancomycin	1	2	0.5 to >16	96.6	0.0	3.4	96.6		3.4

[a] Criteria as published by CLSI 2018b and EUCAST 2018
[b] Using other than pneumonia breakpoints
[c] FDA breakpoints published December 2017
[d] Organisms include: *Staphylococcus cohnii* (1), *S. epidermidis* (14), *S. haemolyticus* (4), *S. hominis* (2), *S. lugdunensis* (1), *S. pseudintermedius* (1), *S. schleiferi* (1), *S. simulans* (1)
[e] Using the PK-PD (non-species related) breakpoint based on the standard dose (EUCAST, 2018)
[f] FDA breakpoints published December 2017 applied to all *E. faecalis* but approved for vancomycin-susceptible isolates only

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