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Ceftobiprole Activity against Gram-Positive Pathogens Causing Bone and Joint Infections in the United States from 2016 through 2019

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Introduction

- Bone and joint infections (BJIs) cause serious morbidity and mortality and present significant treatment challenges (Colston and Atkins [2018]).
- Ceftobiprole medocaril is a parenteral, advanced-generation cephalosporin prodrug that is approved in many European and non-European countries for the treatment of adults with community- and hospital-acquired pneumonia, excluding ventilator-associated pneumonia.
- Ceftobiprole was designed to inhibit penicillin-binding protein 2A (encoded by *mecA*), which confers methicillin (oxacillin) resistance in *Staphylococcus aureus*.
- Ceftobiprole exhibits potent *in vitro* antimicrobial activity against many important Gram-positive pathogens like *S. aureus* (including methicillin-resistant [MRSA] isolates) and *Streptococcus pneumoniae*.
- Ceftobiprole also exhibits antimicrobial activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates that is similar to other cephalosporins like cefepime.
- Ceftobiprole is not approved in the United States (USA) but has a qualified infectious disease product designation for the potential treatment of acute bacterial skin and skin structure infections (ABSSSIs), *S. aureus* bacteremia, and community-acquired pneumonia.
- Ceftobiprole is being evaluated in two phase 3 clinical trials for patients with:
  - ABSSSIs (completed in 2019)
  - *S. aureus* bacteremia, including infective endocarditis (expected completion in 2022).
- In this study, the *in vitro* activity of ceftobiprole and comparators was evaluated against recent Gram-positive clinical isolates collected from BJIs in the USA.

Materials and Methods

Bacterial Isolates

- 306 Gram-positive pathogens were collected from patients with BJIs at 27 US medical centers between 2016 and 2019.
- Bacterial species were identified by the submitting laboratories and confirmed by JMI Laboratories using standard microbiology methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).
- The major Gram-positive BJI species and pathogen groups, which included *S. aureus*, coagulase-negative staphylococci (CoNS), *Enterococcus faecalis*, and β-hemolytic streptococci (BHS), are shown in Figure 1.

Susceptibility Testing

- Susceptibility to ceftobiprole and comparator agents was tested using current Clinical and Laboratory Standards Institute (CLSI) methods (M07, 2018; M100, 2020).
- CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were applied according to current guidelines.
  - For *S. aureus*, the EUCAST susceptibility breakpoint for ceftobiprole is 2 mg/L.
  - The susceptibilities of pathogen groups without specific published interpretive criteria for ceftobiprole were evaluated using the EUCAST pharmacokinetic-pharmacodynamic (PK-PD) non-species-related breakpoint of 4 mg/L (EUCAST, 2020); further studies are required to evaluate the full clinical utility of ceftobiprole against such organisms.
  - US Food and Drug Administration criteria were used as an alternative breakpoint source for tigecycline.
- JMI Laboratories followed current CLSI quality assurance practices when performing the susceptibility tests.
  - MIC values were validated by concurrently testing CLSI-recommended (M100, 2020) ATCC quality control (QC) reference strains.
  - QC ranges for tested reference strains were those criteria approved or published by CLSI (M100, 2020).
  - The inoculum density during susceptibility testing was monitored by bacterial colony counts.

Results

- The major Gram-positive species and pathogen groups from BJIs included *S. aureus* (67%), β-hemolytic streptococci (BHS; 14%), coagulase-negative staphylococci (CoNS; 9%), and *E. faecalis* (7%) (Figure 1).
- Ceftobiprole was highly active against the full BJI *S. aureus* isolate set ($MIC_{50/90}$ values, 0.5/1 mg/L; 100.0% susceptible by EUCAST criteria) (Table 1).
  - Ceftobiprole activity was nearly identical to the corresponding activity reported for all US 2016 *S. aureus* isolates from multiple infection sources ($MIC_{50/90}$ values, 0.5/2 mg/L; 99.7% susceptible by EUCAST criteria; Pfaller et al. [2018]).
  - Against the methicillin-resistant *S. aureus* subset (MRSA; 35.1% of all *S. aureus*), the $MIC_{50/90}$ values increased by only 2-fold (Table 1 and Table 3; $MIC_{50/90}$ values, 1/2 mg/L; 100% susceptible).
  - All MRSA isolates were also susceptible to daptomycin, linezolid, tigecycline, and vancomycin (Table 3). Corresponding MIC data for methicillin-susceptible *S. aureus* isolates are displayed in Table 2.
  - 97.2% of the MRSA isolates were susceptible to ceftaroline (Table 3).
- Ceftobiprole also exhibited potent activity against other Gram-positive cocci, including (Table 1):
  - BHS ($MIC_{50/90}$ values, 0.015/0.03 mg/L; 100% inhibited at ≤4 mg/L, which is the EUCAST PK-PD non-species-related breakpoint).
  - CoNS ($MIC_{50/90}$ values, 1/4 mg/L; 100% inhibited at ≤4 mg/L).
  - *E. faecalis* ($MIC_{50/90}$ values, 0.5/2 mg/L; 100.0% inhibited at ≤4 mg/L).
    - Ceftaroline ($MIC_{50/90}$, 2/8 mg/L) was 4-fold less potent than ceftobiprole ($MIC_{50/90}$, 0.5/2 mg/L) against the *E. faecalis* subset (data not shown).

Conclusions

- Ceftobiprole was highly active against clinical BJI isolates from the major Gram-positive pathogen groups collected at US medical centers during 2016–2019.
  - *S. aureus* comprised the majority (67%) of the Gram-positive BJI pathogens.
    - The *S. aureus* BJI isolate set, including MRSA, was 100.0% susceptible to ceftobiprole.
    - Ceftobiprole activity against the BJI isolate set was nearly identical to previously reported activity against combined US isolates obtained from various infection types (Pfaller et al. [2018]).
  - The remaining Gram-positive isolate sets (BHS, *E. faecalis*, and CoNS) also were 100% susceptible to ceftobiprole using the EUCAST PK-PD non-species-related breakpoint.
- The potent antibacterial activity of ceftobiprole, including against MRSA, supports its further evaluation for the potential treatment of BJIs caused by Gram-positive pathogens.

Table 1 Cumulative distributions of MIC values for ceftobiprole against the main Gram-positive species and groups from bone and joint infections

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													MIC_{50}	MIC_{90}
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	> [a]		
Staphylococcus aureus (205)					0 0.0	1 0.5	0 0.5	35 17.6	100 66.3	54 92.7	15 100.0			0.5	1
Methicillin-susceptible (133)					0 0.0	1 0.8	0 0.8	35 27.1	96 99.2	1 100.0				0.5	0.5
Methicillin-resistant (72)								0 0.0	4 5.6	53 79.2	15 100.0			1	2
Coagulase-negative staphylococci (29) [b]						0 0.0	3 10.3	1 13.8	8 41.4	14 89.7	0 89.7	3 100.0		1	4
Methicillin-susceptible (6)						0 0.0	1 16.7	1 33.3	2 66.7	2 100.0				0.5	
Methicillin-resistant (23)						0 0.0	2 8.7	0 8.7	6 34.8	12 87.0	0 87.0	3 100.0		1	4
Enterococcus faecalis (21)						0 0.0	1 4.8	4 23.8	10 71.4	2 81.0	2 90.5	2 100.0		0.5	2
β-hemolytic streptococci (42)	0 0.0	2 4.8	8 23.8	11 50.0	20 97.6	1 100.0								0.015	0.03
Streptococcus agalactiae (24)			0 0.0	3 12.5	20 95.8	1 100.0								0.03	0.03
Streptococcus dysgalactiae (7)	0 0.0	1 14.3	0 14.3	6 100.0										0.015	
Streptococcus pyogenes (11)	0 0.0	1 9.1	8 81.8	2 100.0										0.008	0.015

[a] Greater than the highest concentration tested.
[b] Species included *Staphylococcus epidermidis* (17), *Staphylococcus haemolyticus* (4), *Staphylococcus hominis* (2), *Staphylococcus lugdunensis* (4), and *Staphylococcus simulans* (2).

Table 2 Activity of ceftobiprole and comparator agents when tested against 133 methicillin-susceptible *Staphylococcus aureus* isolates from bone and joint infections

Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Ceftobiprole	0.5	0.5	0.06 to 1				100.0		0.0
Ceftaroline	0.25	0.25	≤0.06 to 0.5	100.0 [b]	0.0	0.0	100.0 [c] 100.0 [d]	0.0	0.0 0.0
Ceftriaxone	4	8	≤0.25 to 8	100.0		0.0			
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	96.2	0.0	3.8	95.5	0.8	3.8
Daptomycin	0.25	0.5	≤0.12 to 0.5	100.0			100.0		0.0
Erythromycin	0.25	>8	≤0.06 to >8	71.4	9.8	18.8	72.2	3.8	24.1
Gentamicin	≤1	≤1	≤1 to >8	99.2	0.0	0.8	99.2 [e]		0.8
Levofloxacin	0.25	0.5	0.06 to >4	93.2	0.0	6.8	[f]	93.2	6.8
Linezolid	1	2	≤0.12 to 2	100.0		0.0	100.0		0.0
Oxacillin	0.5	1	≤0.25 to 2	100.0		0.0	100.0		0.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.5	0.8	3.8	94.7	0.8	4.5
Tigecycline	0.12	0.12	0.03 to 0.25	100.0 [g]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to 2	100.0		0.0	100.0	0.0	0.0
Vancomycin	1	1	0.5 to 2	100.0	0.0	0.0	100.0		0.0

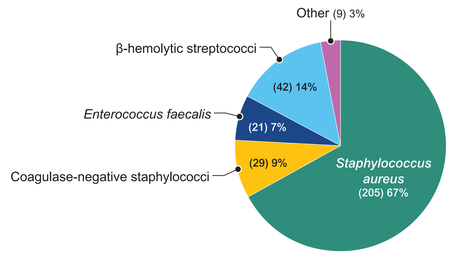
[a] Criteria as published by CLSI (2020) and EUCAST (2020).
[b] Intermediate interpreted as susceptible-dose dependent.
[c] Using other than pneumonia breakpoints.
[d] Using pneumonia breakpoints.
[e] For systemic infections, aminoglycosides must be used in combination with other active therapy.
[f] An arbitrary susceptible breakpoint of ≤0.001 mg/L has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure (EUCAST 2020).
[g] FDA breakpoints published 2017-DEC-13.

Table 3 Activity of ceftobiprole and comparator agents when tested against 72 methicillin-resistant *Staphylococcus aureus* isolates from bone and joint infections

Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Ceftobiprole	1	2	0.5 to 2				100.0		0.0
Ceftaroline	0.5	1	0.25 to 2	97.2 [b]	2.8	0.0	97.2 [c] 97.2 [d]	2.8	0.0 2.8
Ceftriaxone	>8	>8	>8 to >8	0.0		100.0			
Clindamycin	≤0.25	>2	≤0.25 to >2	73.6	0.0	26.4	73.6	0.0	26.4
Daptomycin	0.25	0.5	≤0.12 to 0.5	100.0			100.0		0.0
Erythromycin	>8	>8	0.12 to >8	13.9	0.0	86.1	13.9	0.0	86.1
Gentamicin	≤1	≤1	≤1 to >8	97.2	0.0	2.8	97.2 [e]		2.8
Levofloxacin	4	>4	0.06 to >4	27.8	2.8	69.4	[f]	27.8	72.2
Linezolid	1	2	0.5 to 4	100.0		0.0	100.0		0.0
Oxacillin	>2	>2	>2 to >2	0.0		100.0	0.0		100.0
Tetracycline	≤0.5	8	≤0.5 to >8	88.9	4.2	6.9	88.9	0.0	11.1
Tigecycline	0.06	0.12	0.03 to 0.25	100.0 [g]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	91.7		8.3	91.7	0.0	8.3
Vancomycin	1	1	0.5 to 2	100.0	0.0	0.0	100.0		0.0

[a] Criteria as published by CLSI (2020) and EUCAST (2020).
[b] Intermediate interpreted as susceptible-dose dependent.
[c] Using other than pneumonia breakpoints.
[d] Using pneumonia breakpoints.
[e] For systemic infections, aminoglycosides must be used in combination with other active therapy.
[f] An arbitrary susceptible breakpoint of ≤0.001 mg/L has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure (EUCAST 2020).
[g] FDA breakpoints published 2017-DEC-13.

Figure 1 Gram-positive species and groups (number of isolates) isolated from bone and joint infections



The "other" group included *Enterococcus avium* (1), *Enterococcus faecium* (2), *Streptococcus mitis/oralis* (3), and *Streptococcus pneumoniae* (3).

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