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Ceftobiprole Activity against Drug-Resistant *Staphylococcus aureus* Clinical Isolates Collected in the United States from 2016 through 2020

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Introduction

- Multidrug-resistant (MDR) and methicillin-resistant *Staphylococcus aureus* (MRSA) present significant treatment challenges and can cause serious morbidity and mortality.
- Ceftobiprole medocaril is a parenteral prodrug of the advanced cephalosporin ceftobiprole and 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 has a strong affinity for penicillin-binding proteins (PBPs), including PBP 2A, which mediates resistance to β-lactams in MRSA.
- Ceftobiprole exhibits potent *in vitro* antimicrobial activity against many important Gram-positive pathogens like *S. aureus*, including MRSA.
- Ceftobiprole also exhibits antimicrobial activity against *Enterobacterales* and *Pseudomonas aeruginosa* isolates that is similar to other advanced cephalosporins like cefepime.
- Ceftobiprole was designated by the Food and Drug Administration as a qualified infectious disease product (QIDP) 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 to support a New Drug Application in the United States for the treatment of adult patients with:
  - ABSSSIs [completed in 2019; Overcash et al. (2020)]
  - *S. aureus* bacteremia, including infective endocarditis [expected enrollment completion in 2021; Hamed et al. (2020)].
- In this study, the activity of ceftobiprole and comparators was evaluated against recent MRSA and MDR *S. aureus* clinical isolates collected in the United States.

Materials and Methods

Bacterial Isolates

- 13,868 *S. aureus* isolates were collected from patients with various infection types at 34 US medical centers from 2016–2020 (Table 1).
  - Isolates were obtained from all 9 US Census Bureau Divisions.
- Isolates were categorized as MDR if they were nonsusceptible (CLSI criteria) to ≥3 of the following antimicrobials: clindamycin, daptomycin, erythromycin, gentamicin, levofloxacin, linezolid, tetracycline, tigecycline, trimethoprim-sulfamethoxazole, or vancomycin. Isolates displaying oxacillin MIC values ≥4 mg/L were categorized as MRSA.
  - While Magiorakos et al. (2012) defined any MRSA isolate as MDR, resistance to oxacillin was omitted from the MDR definition in this study to allow for analysis of the MDR MRSA isolate subset.

Susceptibility Testing

- Susceptibility to ceftobiprole and comparator agents was tested using current Clinical and Laboratory Standards Institute (CLSI) methods (M07, 2018; M100, 2021).
- CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2021) interpretive criteria were applied according to current guidelines.
  - For *S. aureus*, the EUCAST susceptibility breakpoint for ceftobiprole is 2 mg/L.
  - US Food and Drug Administration criteria were used as an alternative breakpoint source for tigecycline (FDA, 2021).
- JMI Laboratories followed current CLSI quality assurance practices when performing the susceptibility tests.
  - MIC values were validated by concurrently testing CLSI-recommended (M100, 2021) ATCC quality control (QC) reference strains.
  - QC ranges for tested reference strains were those criteria approved or published by CLSI (M100, 2021).
  - The inoculum density during susceptibility testing was monitored by bacterial colony counts.

Results

- As observed in Pfaller et al. (2018), ceftobiprole was highly active against the full set of *S. aureus* isolates ($MIC_{50/90}$ values, 0.5/2 mg/L; 99.7% susceptible [S]) and against the MRSA subset ($MIC_{50/90}$ values, 1/2 mg/L; 99.2% S) (Table 2).
  - 42.6% of the isolates were MRSA (Table 1).
  - Ceftobiprole was more active than ceftaroline against MRSA (99.2% S versus 94.0% S, respectively) (Table 4).
- Ceftobiprole was also highly active against isolates nonsusceptible to clindamycin, daptomycin, erythromycin, gentamicin, levofloxacin, linezolid, tetracycline, tigecycline, or trimethoprim-sulfamethoxazole (97.7%–100.0% S; Figure 1).
  - No vancomycin-nonsusceptible isolates were detected.
  - Ceftobiprole activity ($MIC_{50/90}$ values, 0.5/2 mg/L) was identical for the *S. aureus* isolate subsets with vancomycin MIC values of ≤1 mg/L and >1 mg/L (Table 2).
  - Ceftobiprole maintained activity against 88.0% of the ceftaroline-nonsusceptible isolates, but ceftaroline was only active against 6.5% of the ceftobiprole-nonsusceptible isolates (Table 4).
- Importantly, ceftobiprole maintained activity against the MDR MRSA subset of isolates ($MIC_{50/90}$ values, 2/2 mg/L; 97.7% S; Table 3).
  - Ceftobiprole was more active (97.7% S) than ceftaroline (83.0% S) against the subset of MDR MRSA isolates (Table 3).
  - The MDR MRSA isolate subset was also >90% S to daptomycin, linezolid, tigecycline, and vancomycin (Table 3).

Conclusions

- Ceftobiprole was highly active *in vitro* against MRSA, MDR, and MDR MRSA isolates collected at US medical centers during 2016–2020.
- Ceftobiprole was more active than ceftaroline against the MDR MRSA isolate subset.
- The potent antibacterial activity of ceftobiprole, including against MDR MRSA, supports the further development of ceftobiprole to treat *S. aureus* infections in the United States.

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Table 1. Prevalence of various subsets of *Staphylococcus aureus* clinical isolates by year

Staphylococcus aureus isolate subset	No. of isolates					
	All years	2016	2017	2018	2019	2020
Staphylococcus aureus (all)	13,868	2,930	2,855	2,777	2,626	2,680
MSSA	7,962	1,670	1,620	1,609	1,536	1,527
MRSA	5,906	1,260	1,235	1,168	1,090	1,153
Ceftobiprole-nonsusceptible (>2 mg/L)	46	9	9	14	4	10
Ceftaroline-nonsusceptible (>1 mg/L)	357	45	83	70	52	107
Clindamycin-nonsusceptible (>0.5 mg/L)	1,933	431	397	379	376	350
Daptomycin-nonsusceptible (>1 mg/L)	4	1	0	0	1	2
Erythromycin-nonsusceptible (>0.5 mg/L)	7,851	1,660	1,635	1,567	1,444	1,545
Gentamicin-nonsusceptible (>4 mg/L)	299	67	55	58	52	67
Levofloxacin-nonsusceptible (>1 mg/L)	4,715	1,094	1,013	893	859	856
Linezolid-resistant (>4 mg/L) [a]	1	0	0	1	0	0
Tetracycline-nonsusceptible (>4 mg/L)	758	109	170	161	146	172
Tigecycline-nonsusceptible (>0.5 mg/L)	4	0	1	1	2	0
Trimethoprim-sulfamethoxazole-resistant (>2 mg/L) [a]	317	62	46	48	76	85
Vancomycin (≤1 mg/L)	13,779	2,916	2,827	2,763	2,613	2,660
Vancomycin (>1 mg/L)	89	14	28	14	13	20
MDR	2,013	444	400	375	400	394
MDR MRSA	1,750	389	347	326	336	352
MDR MSSA	263	55	53	49	64	42

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*
[a] There is no CLSI intermediate criterion.

Table 2. Cumulative distributions of MIC values for ceftobiprole against the various *Staphylococcus aureus* isolate subsets

Subset (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:									MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	> [a]		
Staphylococcus aureus (all; 13,868)	1 <0.1	6 0.1	60 0.5	2,234 16.6	5,969 59.6	3,994 88.4	1,558 99.7	46 100.0		0.5	2
MSSA (7,962)	1 <0.1	6 0.1	58 0.8	2,216 28.6	5,661 99.7	20 100.0				0.5	0.5
MRSA (5,906)		0 0.0	2 <0.1	18 0.3	308 5.6	3,974 72.8	1,558 99.2	46 100.0		1	2
Ceftobiprole-nonsusceptible (>2 mg/L) (46)							0 0.0	46 100.0		4	4
Ceftaroline-nonsusceptible (>1 mg/L) (357)					0 0.0	4 1.1	310 88.0	43 100.0		2	4
Clindamycin-nonsusceptible (>0.5 mg/L) (1,933)		0 0.0	6 0.3	117 6.4	277 20.7	648 54.2	844 97.9	41 100.0		1	2
Daptomycin-nonsusceptible (>1 mg/L) (4)				0 0.0	2 50.0	1 75.0	1 100.0			0.5	
Erythromycin-nonsusceptible (>0.5 mg/L) (7,851)	0 0.0	2 <0.1	19 0.3	624 8.2	2,318 37.7	3,359 80.5	1,483 99.4	46 100.0		1	2
Gentamicin-nonsusceptible (>4 mg/L) (299)			0 0.0	23 7.7	96 39.8	84 67.9	89 97.7	7 100.0		1	2
Levofloxacin-nonsusceptible (>1 mg/L) (4,715)	0 0.0	1 <0.1	10 0.2	208 4.6	745 20.4	2,355 70.4	1,350 99.0	46 100.0		1	2
Linezolid-resistant (>4 mg/L) (1)						0 0.0	1 100.0				
Tetracycline-nonsusceptible (>4 mg/L) (758)	0 0.0	1 0.1	5 0.8	70 10.0	299 49.5	243 81.5	135 99.3	5 100.0		1	2
Tigecycline-nonsusceptible (>0.5 mg/L) (4)			0 0.0	2 50.0	0 50.0	0 50.0	2 100.0			0.25	
Trimethoprim-sulfamethoxazole-resistant (>2 mg/L) (317)			0 0.0	7 2.2	61 21.5	190 81.4	59 100.0			1	2
Vancomycin (≤1 mg/L) (13,779)	1 <0.1	6 0.1	60 0.5	2,218 16.6	5,940 59.7	3,974 88.5	1,535 99.7	45 100.0		0.5	2
Vancomycin (>1 mg/L) (89)			0 0.0	16 18.0	29 50.6	20 73.0	23 98.9	1 100.0		0.5	2
MDR (2,013)		0 0.0	4 0.2	93 4.8	244 16.9	720 52.7	911 98.0	41 100.0		1	2
MDR MRSA (1,750)		0 0.0	1 0.1	6 0.4	72 4.5	719 45.6	911 97.7	41 100.0		2	2
MDR MSSA (263)		0 0.0	3 1.1	87 34.2	172 99.6	1 100.0				0.5	0.5

EUCAST, European Committee on Antimicrobial Susceptibility Testing; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*
[a] Greater than the highest concentration tested.

Table 3. Activity of ceftobiprole and comparator agents when tested against 1,750 MDR MRSA isolates

Antimicrobial agent	No. of isolates	mg/L			CLSI[a]			EUCAST[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Ceftobiprole	1,750	2	2	0.12 to 4				97.7		2.3
Ceftaroline	1,750	1	2	0.12 to 4	83.0	17.0 [b]	0.0	83.0 [c] 83.0 [d]	17.0	0.1 17.0
Ceftriaxone	1,750	>8	>8	2 to >8	0.0		100.0			
Clindamycin	1,750	>2	>2	≤0.25 to >2	14.8	0.9	84.3	14.7	0.1	85.2
Daptomycin	1,750	0.25	0.5	≤0.12 to 2	99.9			99.9		0.1
Erythromycin	1,750	>8	>8	0.12 to >8	0.5	0.9	98.7	0.5	0.2	99.3
Gentamicin	1,750	≤1	8	≤1 to >8	89.9	0.2	9.9	89.7 [e]		10.3
Levofloxacin	1,750	>4	>4	0.06 to >4	1.6	0.7	97.7	[f]	1.6	98.4
Linezolid	1,750	1	2	0.25 to >8	99.9		0.1	99.9		0.1
Oxacillin	1,750	>2	>2	>2 to >2	0.0		100.0	0.0		100.0
Tetracycline	1,748	≤0.5	>8	≤0.5 to >8	82.2	0.6	17.3	77.0	4.7	18.3
Tigecycline	1,749	0.12	0.25	≤0.015 to 2	99.8 [g]			99.8		0.2
Trimethoprim-sulfamethoxazole	1,750	≤0.5	>4	≤0.5 to >4	86.5		13.5	86.5	0.9	12.6
Vancomycin	1,750	1	1	0.25 to 2	100.0	0.0	0.0	100.0		0.0

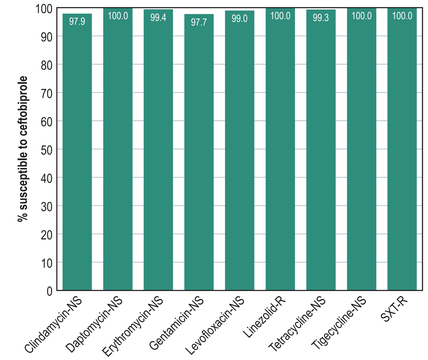
CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; I, intermediate; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; R, resistant; S, susceptible
[a] Criteria as published by CLSI (2021) and EUCAST (2021).
[b] Intermediate is 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 and/or >50 mm 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.
[g] US FDA breakpoints were applied.

Table 4. Activity of ceftobiprole and ceftaroline when tested against various *Staphylococcus aureus* isolate subsets

Group	Number	% Susceptible [a]	
		Ceftobiprole	Ceftaroline
All	13,868	99.7	97.4
MDR	2,013	98.0	85.2
MRSA	5,906	99.2	94.0
MDR MRSA	1,750	97.7	83.0
Ceftobiprole-NS	46	0.0	6.5
Ceftaroline-NS	357	88.0	0.0

MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; NS, nonsusceptible
[a] Clinical and Laboratory Standards Institute (CLSI) interpretive criteria were applied for all antimicrobials except ceftobiprole and ceftaroline, for which European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were used.

Figure 1. Activity of ceftobiprole against *Staphylococcus aureus* isolates nonsusceptible to various antimicrobials



NS, nonsusceptible; R, resistant; SXT, trimethoprim-sulfamethoxazole
See Table 1 for numbers of isolates per subset.

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