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Update on the Activity of Ceftobiprole against Gram-positive Clinical Bacterial Isolates Causing Skin and Skin-structure Infections in the United States (2016–2020).

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Introduction

- Ceftobiprole is an advanced cephalosporin intervenous antibiotic with activity against difficult to treat Gram-positive bacteria, including *Staphylococcus aureus* (including methicillin-resistant [MRSA]), *Streptococcus pneumoniae* (including penicillin non-susceptible), and *Enterococcus faecalis* as well as non-ESBL producing Enterobacterales.
- This agent was recently (April 2024) approved by the United States (US) Food and Drug Administration (FDA) for treatment of adult *S. aureus* bacteremia, including right-sided infective endocarditis, acute bacterial skin and skin structure infections (ABSSSI) in adults, and adult and pediatric community-acquired bacterial pneumonia (CABP).
- Ceftobiprole is approved for treatment of community- and hospital-acquired pneumonia in Europe and other regions.
- This study assessed the *in vitro* activity of ceftobiprole and comparator agents against contemporary clinical isolates causing SSSIs in patients in the US.

Materials and Methods

Bacterial Isolates

- Clinical isolates evaluated in this study were those causing SSSI included in the SENTRY Antimicrobial Surveillance Program for 2016–2020.
- A total of 12,202 clinical isolates recovered from patients seen in 33 US medical centers were included and bacterial identification was confirmed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 guidelines using frozen-form broth microdilution panels manufactured by Element Iowa City (JMI Laboratories, North Liberty, IA, USA).
- MIC interpretations used CLSI, FDA, and EUCAST breakpoint criteria, where applicable.
- The recently approved FDA ceftobiprole susceptibility breakpoints include ≤2/4/≥8 mg/L (susceptible/intermediate/resistant) for *S. aureus* and ≤0.5/-/- mg/L for *Streptococcus pyogenes*.

Results

- A total of 8,120 Gram-positive isolates (Figure 1) from medical centers in all 9 US Census Bureau Divisions were recovered from SSSI and included in this study.
  - Gram-positive isolates were recovered primarily from internal medicine (*n*=1,739, 21.4%), ambulatory/outpatient (*n*=1,094, 13.5%), emergency (*n*=1,091, 13.4%), surgery (*n*=944, 11.6%), pediatric (*n*=632, 7.8%), and dermatology (*n*=385, 4.7%) medical services.
- Ceftobiprole was active against *S. aureus* with MIC_{50} of 0.5 and MIC_{90} of 1 mg/L. A total of 99.8% of *S. aureus* were characterized as susceptible according to the EUCAST and FDA criteria (Table 1).
  - Against MRSA (*n*=2,729) and MSSA (*n*=3,677) isolates, ceftobiprole maintained activity with 99.5% MRSA and 100% MSSA inhibited at the FDA/EUCAST susceptible breakpoint of ≤2 mg/L.
  - Levofloxacin ($MIC_{50/90}$, 0.25/>4 mg/L; 68.7% susceptible), and erythromycin ($MIC_{50/90}$, >8/>8 mg/L; 44.0% susceptible) displayed limited activity against *S. aureus* (Table 1).
- Against MRSA and clindamycin, erythromycin, or tetracycline-resistant MRSA—ceftobiprole maintained activity (97.8–99.5% susceptible per FDA; Table 2 and Figure 2)
- Ceftobiprole displayed activity against other Gram-positive species groups, including BHS ($MIC_{50/90}$, 0.015/0.03 mg/L), Viridans group streptococci ($MIC_{50/90}$, 0.06/0.12 mg/L) and *E. faecalis* ($MIC_{50/90}$ 0.5/2 mg/L).
- Ceftobiprole also displayed activity against vancomycin-resistant *E. faecalis* ($MIC_{50/90}$, 2/2 mg/L) and *S. pyogenes* isolates ($MIC_{50/90}$, 0.008/0.015 mg/L; 100% susceptible per FDA).

Conclusions

- Ceftobiprole showed potent *in vitro* activity against clinical Gram-positive bacterial isolates from major SSSI pathogen groups causing these infections in US hospitals, including antimicrobial-resistant subsets.
- With the recent FDA approvals for various serious bacterial infections, ceftobiprole becomes an additional option to treat SSSI in the US.

Acknowledgments

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Figure 1: Distribution of all organisms and organism groups tested

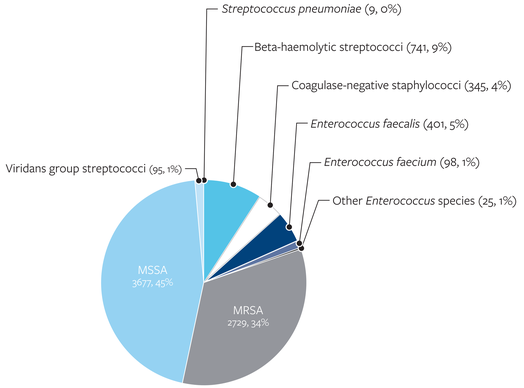
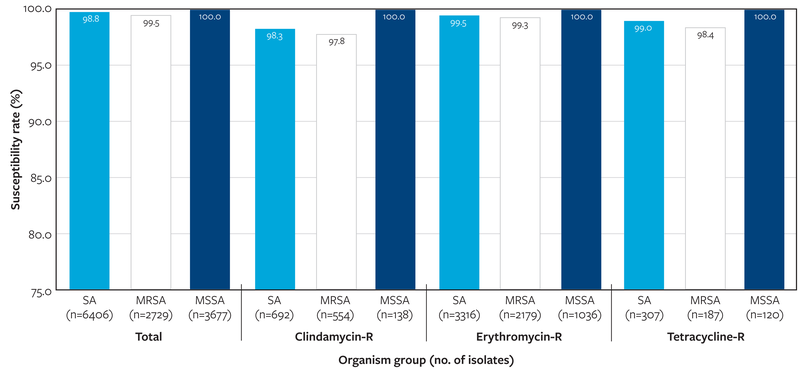


Figure 2: Ceftobiprole activity against antimicrobial-resistant *Staphylococcus aureus* subsets



Abbreviations: SA, *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; R, resistant.
CLSI (2024) breakpoints were applied to categorize comparator agents. Ceftobiprole FDA breakpoints were used.

Table 1. Cumulative distributions of ceftobiprole and comparator agent MIC values for *Staphylococcus aureus* isolates

Organism/Organism Group Antimicrobial Agent	Number and cumulative % of isolates at MIC (mg/L):															n	MIC_{50}	MIC_{90}	% S[A]
	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>				
Staphylococcus aureus																			
Ceftobiprole					1	1	21	1009	2780	2037	542	15				6406	0.5	1	99.8[B]
					0.1	0.1	0.4	16.1	59.5	91.3	99.8	100							
Clindamycin								5698	6	3	7				692	6406	≤0.25	>2	89.0
								88.9	89.0	89.1	89.2				100				
Erythromycin						39	1153	1542	86	25	106	138	89		3226	6404	>8	>8	44.0
						0.6	18.6	42.7	44.0	44.4	46.1	48.2	49.6		100				
Levofloxacin					0	50	1192	2863	214	79	40	899			1066	6403	0.25	>4	68.7
					0.0	0.8	19.4	64.1	67.5	68.7	69.3	83.4			100				
Oxacillin								1339	1843	453	42				2729	6406	>2	>2	16.9
								20.9	49.7	56.7	57.4				100				
Trimethoprim-sulfamethoxazole									6175	66	21	11			133	6406	≤0.5	≤0.5	97.7
									96.4	97.4	97.8	97.9			100				
Vancomycin							1	18	2540	3811	36					6406	1	1	100
							0.1	0.3	39.9	99.4	100								

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; MIC, minimal inhibitory concentration; S, susceptible
[A] % susceptible per CLSI (2024) breakpoint criteria, if available
[B] % susceptible per FDA (2024) breakpoint criteria

Table 2. Activity of ceftobiprole against main organisms and resistant subsets

Organism/Group (No. tested)	MIC_{50}	MIC_{90}	Range	EUCAST[A]		US FDA[A]		
				%S	%R	%S	%I	%R
S. aureus (6,407)	0.5	1	≤0.03 to 4	99.8	0.2	99.8	0.2	0.0
Ceftriaxone-resistant MRSA (2,730)	1	2	0.25 to 4	99.5	0.5	99.5	0.5	0.0
Clindamycin-resistant MRSA (555)	1	2	0.25 to 4	97.8	2.2	97.8	2.2	0.0
Tetracycline-resistant MRSA (187)	1	2	0.25 to 4	98.4	1.6	98.4	1.6	0.0
MSSA (3,677)	0.5	0.5	≤0.03 to 1	100	0.0	100	0.0	0.0
E. faecalis (401)	0.5	2	≤0.03 to >4					
Vancomycin-resistant *E. faecalis* (13)	2	2	0.12 to 4					
S. pyogenes (430)	0.008	0.015	0.002 to 0.06			100		

Abbreviations: EUCAST European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration; I, intermediate; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MIC, minimal inhibitory concentration; R, resistant; S, susceptible; US, United States
[A] Criteria as published by EUCAST (2024), and US FDA (2024).

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