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Ceftobiprole Activity against Pathogens Causing Bacterial Skin and Skin Structure Infections in the United States from 2016 through 2018

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Introduction

- Ceftobiprole medocaril is an advanced parenteral cephalosporin prodrug that is approved in 17 European countries, Argentina, Canada, Jordan, Peru, and Saudi Arabia for the treatment of adults with community (CAP)- and hospital-acquired pneumonia (excluding ventilator-associated pneumonia)
- Ceftobiprole was specifically 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*
- Additionally, ceftobiprole exhibits antimicrobial activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates that is similar to other advanced cephalosporins like cefepime
- Ceftobiprole is not approved in the United States (USA) but has qualified infectious disease product status for the potential treatment of acute bacterial skin and skin structure infections (ABSSSIs), *S. aureus* bacteremia, and CAP
- Ceftobiprole is being evaluated in 2 phase 3 clinical trials for patients with
  - ABSSSIs (expected completion in 2019)
  - *S. aureus* bacteremia, including infective endocarditis (expected completion in 2021)
- In this study, the *in vitro* activity of ceftobiprole and comparators was evaluated against recent clinical isolates collected in the USA from patients with skin and skin structure infections (SSSIs)

Materials and Methods

Bacterial isolates

- A total of 7,354 clinical isolates were collected from patients with SSSIs at 32 US medical centers from 2016 through 2018
- 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 extended-spectrum β-lactamase (ESBL) phenotype was defined for *Escherichia coli*, *Klebsiella pneumoniae, Klebsiella oxytoca,* and *Proteus mirabilis* as an MIC value ≥2 mg/L for ceftriaxone, ceftazidime, and/or aztreonam (CLSI, 2019)
- The major SSSI species and pathogen groups included *S. aureus* (53%), *Enterobacteriaceae* (23%), *P. aeruginosa* (7%), β-hemolytic streptococci (BHS; 6%), *Enterococcus* spp. (4%), and coagulase-negative staphylococci (CoNS; 2%) (Figure 1)

Susceptibility testing

- Susceptibility to ceftobiprole and comparator agents was tested using current Clinical and Laboratory Standards Institute (CLSI) methods
- CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were applied according to current guidelines
  - 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, 2019) ATCC quality control (QC) reference strains
  - QC ranges for tested reference strains were those approved or published by CLSI (M100, 2019)
  - The inoculum density during susceptibility testing was monitored by bacterial colony counts
- The susceptibilities of pathogen groups without specific published interpretive criteria for ceftobiprole were evaluated using the EUCAST non-species-specific breakpoint of 4 mg/L (EUCAST, 2019); further studies are required to evaluate the full clinical utility of ceftobiprole against such organisms

Results

- Ceftobiprole was highly active against *S. aureus* from SSSIs (MIC$_{50/90}$, 0.5/1 mg/L; 99.7% susceptible at the EUCAST breakpoint of 2 mg/L) (Table 1)
  - Ceftobiprole activity against *S. aureus* was virtually identical when the data were stratified by year (Figure 2)
  - Against the MRSA subset (41.9% of all *S. aureus*), the MIC$_{50/90}$ values increased by only 2-fold (99.4% susceptible) (Table 2)
  - All MRSA isolates were susceptible to daptomycin, tigecycline, and vancomycin (Table 2)
  - 97.1% of the MRSA isolates were susceptible to ceftaroline (Table 2)
- Ceftobiprole also exhibited potent activity against the other major groups of Gram-positive cocci associated with SSSIs, including
  - BHS (MIC$_{50/90}$, 0.015/0.03 mg/L; 100% inhibited at ≤0.12 mg/L [4 mg/L is the EUCAST pharmacokinetic/pharmacodynamic non-species-related breakpoint]) (Table 1)
  - *Enterococcus faecalis* (MIC$_{50/90}$, 0.5/2 mg/L; 99.6% inhibited at ≤4 mg/L) (Table 1)
    - Ceftaroline (MIC$_{50/90}$, 2/8 mg/L) was 4-fold less potent than ceftobiprole (Table 2)
  - CoNS (MIC$_{50/90}$, 0.5/1 mg/L; 100% inhibited at ≤4 mg/L) (Table 1)
    - Ceftobiprole was only 2-fold less potent against the methicillin-resistant CoNS subset (MIC$_{50/90}$, 1/2 mg/L; data not shown)
- The overall susceptibility of all *Enterobacteriaceae* SSSI isolates to ceftobiprole was 84.8% (Table 3)
  - *Enterobacteriaceae* susceptibility to ceftobiprole was similar to other expanded-spectrum cephalosporins like cefepime (89.7%) and ceftazidime (85.0%) (Table 3)
  - The majority of *E. coli* and *K. pneumoniae* isolates exhibited a non-ESBL phenotype (coincidentally 77.6% for both species)
  - Ceftobiprole exhibited potent activity against *E. coli* (MIC$_{50/90}$, 0.03/0.06 mg/L; 99.7% susceptible) and *K. pneumoniae* (MIC$_{50/90}$, 0.03/0.06 mg/L; 99.3% susceptible) isolates that exhibited a non-ESBL phenotype (Table 3)
  - Ceftobiprole also exhibited potent activity against *P. mirabilis*, *Serratia marcescens*, and *Enterobacter cloacae* species complex isolates from SSSIs (Table 1)
- A total of 74.4% of *P. aeruginosa* isolates were inhibited by ceftobiprole at ≤4 mg/L (Table 1)
  - 85.9% were susceptible to cefepime and 84.3% were susceptible to ceftazidime (Table 3)
- As expected, ceftobiprole was largely inactive against *Enterococcus faecium* (MIC$_{50/90}$, >4/>4 mg/L; data not shown) and *E. coli* and *K. pneumoniae* isolates that exhibited an ESBL phenotype (Table 1)

Figure 1 Species and groups (number of US isolates) that were isolated from skin and skin structure infections

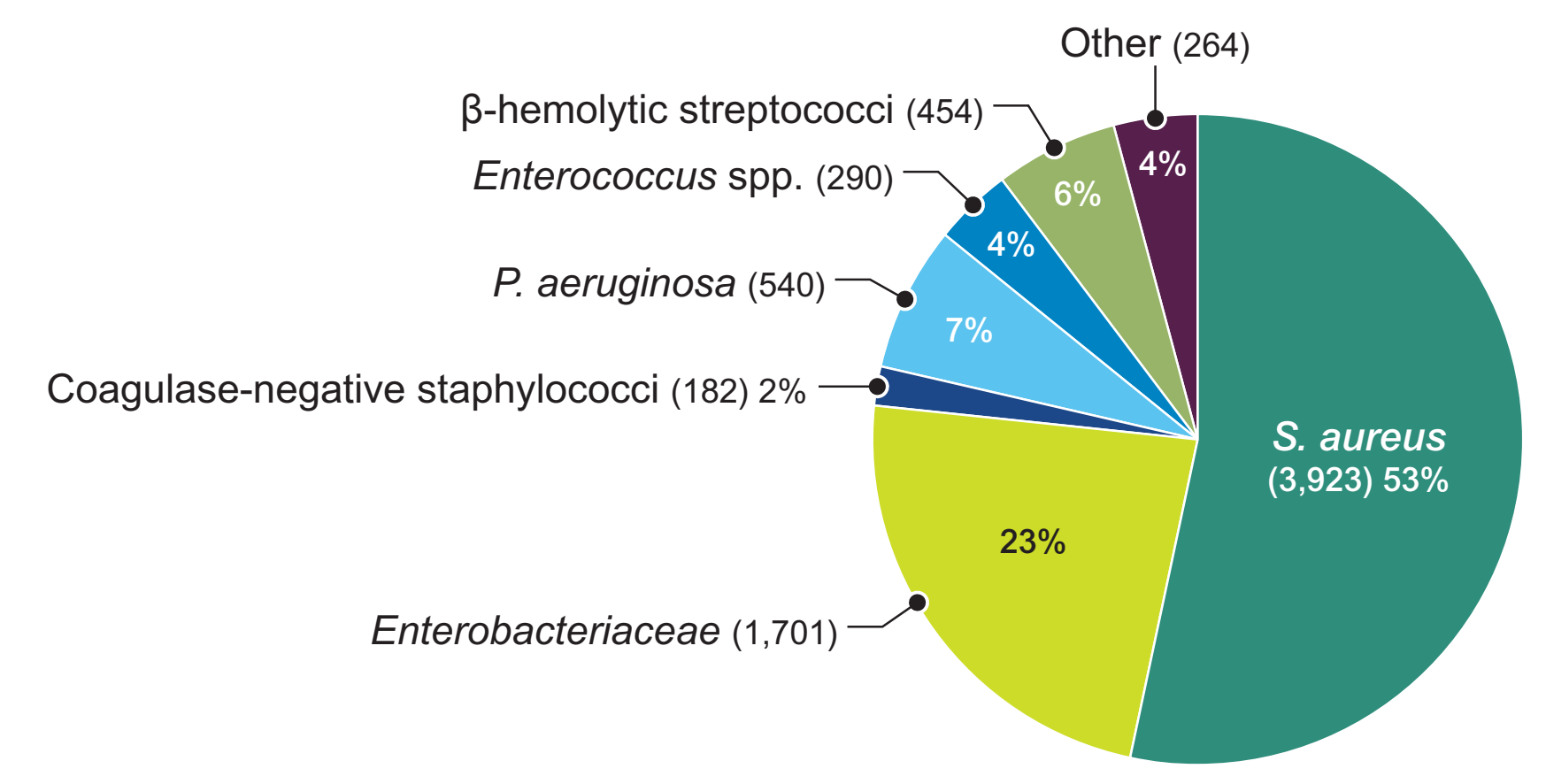


Table 1 Antimicrobial activity of ceftobiprole tested against the main species and groups from skin and skin structure infections

Organism/organism group (no. of isolates)	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	> [a]	MIC$_{50}$	MIC$_{90}$
	No. and cumulative % of isolates inhibited at MIC (mg/L) of:																	
Staphylococcus aureus (3,923)						1 <0.1	0 <0.1	13 0.4	572 14.9	1,758 59.8	1,215 90.7	354 99.7	10 100.0				0.5	1
Methicillin-susceptible (2,280)						1 <0.1	0 <0.1	13 0.6	570 25.6	1,688 99.6	8 100.0						0.5	0.5
Methicillin-resistant (1,643)								0 0.0	2 0.1	70 4.4	1,207 77.8	354 99.4	10 100.0				1	2
Enterobacteriaceae (1,701)				16 0.9	48 3.8	862 54.4	394 77.6	83 82.5	40 84.8	27 86.4	22 87.7	18 88.8	12 89.5	4 89.7	4 89.9	171 100.0	0.03	>16
Escherichia coli (500)				0 0.0	10 2.0	291 60.2	83 76.8	10 78.8	6 80.0	4 80.8	2 81.2	1 81.4	1 81.6	0 81.6	2 82.0	90 100.0	0.03	>16
ESBL-phenotype (112)					0 0.0	3 2.7	4 6.2	2 8.0	4 11.6	3 14.3	2 16.1	1 17.0	1 17.9	0 17.9	2 19.6	90 100.0	>16	>16
Non-ESBL-phenotype (388)				0 0.0	10 2.6	288 76.8	79 97.2	8 99.2	2 99.7	1 100.0							0.03	0.06
Proteus mirabilis (258)				0 0.0	23 8.9	195 84.5	30 96.1	2 96.9	0 96.9	1 97.3	0 97.3	0 97.3	0 97.3	0 97.3	1 97.7	6 100.0	0.03	0.06
ESBL-phenotype (8)						0 0.0	1 12.5	0 12.5	0 12.5	0 12.5	0 12.5	0 12.5	0 12.5	0 12.5	1 25.0	6 100.0	>16	
Non-ESBL-phenotype (250)				0 0.0	23 9.2	195 87.2	29 98.8	2 99.6	0 99.6	1 100.0							0.03	0.06
Klebsiella pneumoniae (192)				0 0.0	4 2.1	108 58.3	32 75.0	5 77.6	0 77.6	2 78.6	4 80.7	2 81.8	1 82.3	0 82.3	0 82.3	34 100.0	0.03	>16
ESBL-phenotype (43)						0 0.0	1 2.3	0 2.3	0 2.3	1 4.7	4 14.0	2 18.6	1 20.9	0 20.9	0 20.9	34 100.0	>16	>16
Non-ESBL-phenotype (149)				0 0.0	4 2.7	108 75.2	31 96.0	5 99.3	0 99.3	1 100.0							0.03	0.06
Serratia marcescens (135)					0 0.0	2 1.5	91 68.9	30 91.1	7 96.3	2 97.8	2 99.3	0 99.3	1 100.0				0.06	0.12
Enterobacter cloacae species complex (244)					0 0.0	100 41.0	90 77.9	14 83.6	1 84.0	4 85.7	5 87.7	9 91.4	8 94.7	4 96.3	1 96.7	8 100.0	0.06	2
Pseudomonas aeruginosa (540)								0 0.0	1 0.2	13 2.6	109 22.8	191 58.1	88 74.4	57 85.0	56 95.4	25 100.0	2	16
β-hemolytic streptococci (454)	0 0.0	5 1.1	7 2.6	198 46.3	142 77.5	98 99.1	3 99.8	1 100.0									0.015	0.03
Streptococcus pyogenes (268)	0 0.0	5 1.9	5 3.7	187 73.5	68 98.9	2 99.6	1 100.0										0.008	0.015
Streptococcus agalactiae (142)				0 0.0	43 30.3	96 97.9	2 99.3	1 100.0									0.03	0.03
Enterococcus faecalis (223)						4 1.8	4 3.6	17 11.2	41 29.6	101 74.9	21 84.3	30 97.8	4 99.6			1 100.0	0.5	2
Coagulase-negative staphylococci (182)						3 1.6	2 2.7	27 17.6	28 33.0	63 67.6	48 94.0	8 98.4	3 100.0				0.5	1

ESBL, extended-spectrum β-lactamase

[a] Greater than the highest concentration tested.

Table 2 Activity of ceftobiprole and comparator agents when tested against the major groups of Gram-positive bacteria from SSSIs (USA; 2016–2018)

Species or group (no. of isolates) Antimicrobial agent	MIC (mg/L)			CLSI[a]			EUCAST[a]		
	MIC$_{50}$	MIC$_{90}$	Range	%S	%I	%R	%S	%I	%R
MRSA (1,643)									
Ceftobiprole	1	2	0.25 to 4				99.4		0.6
Ceftaroline	0.5	1	0.25 to 2	97.1[b]	2.9	0.0	97.1[c]	2.9	0.0
Ceftriaxone	>8	>8	4 to >8	0.0		100.0			
Clindamycin	≤0.25	>2	≤0.25 to >2	80.8	0.3	18.9	80.7	0.1	19.2
Daptomycin	0.25	0.5	≤0.12 to 1	100.0			100.0		0.0
Erythromycin	>8	>8	≤0.06 to >8	14.2	2.9	82.8	14.5	0.9	84.6
Gentamicin	≤1	≤1	≤1 to >8	97.5	0.2	2.3	97.4		2.6
Levofloxacin	4	>4	0.06 to >4	40.4	1.3	58.3	40.4		59.6
Linezolid	1	2	≤0.12 to >8	99.9		0.1	99.9		0.1
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	93.2	1.1	5.7	91.8	0.9	7.2
Tigecycline	0.06	0.12	≤0.015 to 0.5	100.0[d]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	97.3		2.7	97.3	0.0	2.7
Vancomycin	1	1	0.25 to 2	100.0	0.0	0.0	100.0		0.0
MSSA (2,280)									
Ceftobiprole	0.5	0.5	≤0.03 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]	0.0	0.0
Ceftriaxone	4	8	0.5 to 8	100.0		0.0			
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	96.3	0.0	3.7	96.1	0.1	3.7
Daptomycin	0.25	0.5	≤0.12 to 1	100.0			100.0		0.0
Erythromycin	0.25	>8	≤0.06 to >8	66.9	6.3	26.8	67.5	2.2	30.3
Gentamicin	≤1	≤1	≤1 to >8	99.0	0.2	0.8	98.9		1.1
Levofloxacin	0.25	2	0.06 to >4	90.0	0.6	9.5	90.0		10.0
Linezolid	1	2	0.25 to 4	100.0		0.0	100.0		0.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.4	1.5	3.2	93.8	0.3	6.0
Tigecycline	0.06	0.12	0.03 to 0.5	100.0[d]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	99.5		0.5	99.5	0.0	0.5
Vancomycin	1	1	≤0.12 to 2	100.0	0.0	0.0	100.0		0.0
β-hemolytic streptococci (454)[e]									
Ceftobiprole	0.015	0.03	0.002 to 0.12						
Ceftaroline	≤0.008	0.015	≤0.008 to 0.03	100.0			100.0		0.0
Ceftriaxone	0.03	0.06	≤0.015 to 0.12	100.0			100.0		0.0
Clindamycin	≤0.25	>2	≤0.25 to >2	84.6	0.7	14.8	85.2		14.8
Daptomycin	≤0.06	0.25	≤0.06 to 0.5	100.0			100.0		0.0
Erythromycin	0.03	>16	≤0.015 to >16	71.6	0.9	27.5	71.6	0.9	27.5
Levofloxacin	0.5	1	0.12 to >4	99.8	0.0	0.2	99.8		0.2
Linezolid	1	2	0.5 to 2	100.0			100.0	0.0	0.0
Meropenem	≤0.008	0.06	≤0.008 to 0.06	100.0			100.0		0.0
Penicillin	0.015	0.06	≤0.008 to 0.06	100.0			100.0		0.0
Tetracycline	0.5	>4	≤0.25 to >4	59.4	1.3	39.3	58.7	0.7	40.6
Vancomycin	0.5	0.5	0.12 to 1	100.0			100.0		0.0
***Enterococcus faecalis* (223)**									
Ceftobiprole	0.5	2	≤0.03 to >4						
Ampicillin	1	1	≤0.5 to 2	100.0		0.0	100.0	0.0	0.0
Ceftaroline	2	8	≤0.06 to >8						
Daptomycin	0.5	1	≤0.25 to 4	98.2[b]	1.8	0.0			
Levofloxacin	1	>4	≤0.03 to >4	75.8	0.0	24.2	75.8[f]		24.2
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	97.3	0.0	2.7	96.9		3.1
Tigecycline	0.06	0.12	≤0.015 to 0.12	100.0[g]			100.0		0.0
Vancomycin	1	2	0.25 to >16	96.9	0.0	3.1	96.9		3.1
Coagulase-negative staphylococci (182)[h]									
Ceftobiprole	0.5	1	≤0.03 to 4						
Ceftaroline	0.25	0.5	≤0.06 to 2						
Ceftriaxone	4	>8	≤0.25 to >8	67.6		32.4			
Clindamycin	≤0.25	>2	≤0.25 to >2	82.4	2.2	15.4	81.3	1.1	17.6
Daptomycin	0.25	0.5	≤0.12 to 1	100.0			100.0		0.0
Erythromycin	0.12	>8	≤0.06 to >8	57.7	0.5	41.8	58.2	0.0	41.8
Gentamicin	≤1	2	≤1 to >8	90.1	0.5	9.3	89.6		10.4
Levofloxacin	0.25	>4	≤0.03 to >4	83.0	0.5	16.5	83.0		17.0
Linezolid	0.5	1	≤0.12 to 2	100.0		0.0	100.0		0.0
Oxacillin	1	>2	≤0.25 to >2	67.6		32.4	68.1		31.9
Tetracycline	≤0.5	1	≤0.5 to >8	92.9	1.1	6.0	90.1	2.7	7.1
Tigecycline	0.06	0.12	≤0.015 to 0.5				100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	4	≤0.5 to >4	83.0		17.0	83.0	7.1	9.9
Vancomycin	1	2	≤0.12 to 2	100.0	0.0	0.0	100.0		0.0

SSSIs, skin and skin structure infections; S, susceptible; I, intermediate; R, resistant; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*

[a] Criteria as published by CLSI 2019 and EUCAST 2019.

[b] Intermediate interpreted as susceptible-dose dependent.

[c] Using other than pneumonia breakpoints.

[d] FDA breakpoints accessed January 2019.

[e] Organisms include: *Streptococcus agalactiae* (142), *S. canis* (3), *S. dysgalactiae* (41), *S. pyogenes* (268).

[f] Uncomplicated urinary tract infection only.

[g] FDA breakpoints accessed January 2019 applied to all *E. faecalis* but approved for vancomycin-susceptible isolates only.

[h] Organisms include: *Staphylococcus capitis* (2), *S. caprae* (2), *S. epidermidis* (63), *S. haemolyticus* (7), *S. hominis* (3), *S. intermedius* (1), *S. lugdunensis* (90), *S. pseudintermedius* (5), *S. saprophyticus* (1), *S. schleiferi* (1), *S. simulans* (5), *S. warneri* (1), *S. xylosus* (1)

Table 3 Activity of ceftobiprole and comparator agents when tested against the major groups of Gram-negative bacteria from SSSIs (USA; 2016–2018)

Species or group (no. of isolates) Antimicrobial agent	MIC (mg/L)			CLSI[a]			EUCAST[a]		
	MIC$_{50}$	MIC$_{90}$	Range	%S	%I	%R	%S	%I	%R
***Enterobacteriaceae* (1,701)[b]**									
Ceftobiprole	0.03	>16	≤0.008 to >16				84.8		15.2
Ampicillin-sulbactam	16	>32	≤0.5 to >32	44.9	17.4	37.7	44.9		55.1
Aztreonam	0.12	16	≤0.03 to >16	87.6	1.6	10.8	85.6	2.0	12.4
Cefepime	≤0.12	2	≤0.12 to >16	90.8[c]	2.2	7.0	89.7	2.4	7.9
Ceftaroline	0.12	>16	≤0.03 to >16	75.9	6.0	18.1	75.9		24.1
Ceftazidime	0.25	16	0.03 to >32	88.7	1.2	10.1	85.0	3.8	11.3
Ceftriaxone	0.12	>8	≤0.06 to >8	83.7	1.5	14.8	83.7	1.5	14.8
Colistin	0.25	>8	≤0.06 to >8				67.3		32.7
Gentamicin	0.5	2	≤0.12 to >8	92.5	0.6	6.8	91.7	0.9	7.5
Imipenem	0.25	2	≤0.12 to >8	84.6	11.8	3.6	78.0	21.6	0.5
Levofloxacin	0.06	>4	≤0.03 to >4	79.7	1.8	18.5	79.7	1.8	18.5
Meropenem	0.03	0.06	≤0.015 to >32	99.4	0.0	0.6	99.4	0.5	0.2
Piperacillin-tazobactam	2	8	≤0.5 to >64	94.0	2.1	3.9	91.5	2.5	6.0
Tigecycline	0.5	2	≤0.06 to 8	91.7[d]	7.4	0.9			
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	79.9		20.1	79.9	0.6	19.4
Non-ESBL-phenotype *Escherichia coli* (388)									
Ceftobiprole	0.03	0.06	0.015 to 0.5				99.7		0.3
Ampicillin-sulbactam	8	>32	0.5 to >32	52.8	21.6	25.5	52.8		47.2
Aztreonam	0.12	0.25	≤0.03 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Cefepime	≤0.12	≤0.12	≤0.12 to 1	100.0[c]	0.0	0.0	100.0	0.0	0.0
Ceftaroline	0.12	0.5	≤0.03 to 8	95.6	2.1	2.3	95.6		4.4
Ceftazidime	0.25	0.5	0.06 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	≤0.06 to 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Colistin	0.12	0.25	≤0.06 to 1				100.0		0.0
Gentamicin	1	2	0.12 to >8	92.5	0.0	7.5	92.3	0.3	7.5
Imipenem	≤0.12	≤0.12	≤0.12 to 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	≤0.03	>4	≤0.03 to >4	75.8	1.0	23.2	75.8	1.0	23.2
Meropenem	≤0.015	0.03	≤0.015 to 0.06	100.0	0.0	0.0	100.0	0.0	0.0
Piperacillin-tazobactam	2	4	≤0.5 to >64	99.2	0.3	0.5	98.7	0.5	0.8
Tigecycline	0.12	0.25	≤0.06 to 1	100.0[d]	0.0	0.0	99.7		0.3
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	73.1		26.9	73.1	0.5	26.4
Non-ESBL-phenotype *Klebsiella pneumoniae* (149)									
Ceftobiprole	0.03	0.06	0.015 to 0.5				99.3		0.7
Ampicillin-sulbactam	8	16	≤0.5 to >32	82.6	12.1	5.4	82.6		17.4
Aztreonam	0.06	0.12	≤0.03 to 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Cefepime	≤0.12	≤0.12	≤0.12 to 0.5	100.0[c]	0.0	0.0	100.0	0.0	0.0
Ceftaroline	0.12	0.25	≤0.03 to 1	99.3	0.7	0.0	99.3		0.7
Ceftazidime	0.12	0.5	0.03 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	≤0.06 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Colistin	0.12	0.25	≤0.06 to >8				98.6		1.4
Gentamicin	0.25	0.5	≤0.12 to >16	99.3	0.0	0.7	99.3	0.0	0.7
Imipenem	≤0.12	0.25	≤0.12 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	0.06	0.25	≤0.03 to 8	95.9	2.7	1.4	95.9	2.7	1.4
Meropenem	0.03	0.03	≤0.015 to 0.06	100.0	0.0	0.0	100.0	0.0	0.0
Piperacillin-tazobactam	2	8	≤0.5 to 16	100.0	0.0	0.0	91.9	8.1	0.0
Tigecycline	0.5	1	≤0.06 to 8	97.3[d]	2.0	0.7			
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	94.6		5.4	94.6	0.0	5.4
***Pseudomonas aeruginosa* (540)**									
Ceftobiprole	2	16	0.25 to >16						
Amikacin	4	8	≤0.25 to >32	98.7	0.4	0.9	94.6	4.1	1.3
Ampicillin-sulbactam	>32	>32	≤0.25 to >32						
Aztreonam	8	>16	0.06 to >16	68.3	13.0	18.7	81.3		18.7
Cefepime	2	16	0.25 to >16	85.9	10.7	3.3	85.9		14.1
Ceftaroline	16	>16	0.5 to >16						
Ceftazidime	2	32	0.12 to >32	84.3	5.6	10.2	84.3		15.7
Colistin	1	1	0.12 to >8	99.4		0.6	99.4		0.6
Gentamicin	2	4	≤0.12 to >8	90.6	5.7	3.7	90.6		9.4
Imipenem	1	8	≤0.12 to >8	81.9	3.5	14.6	85.4		14.6
Levofloxacin	0.5	>4	≤0.03 to >4	69.4	8.7	21.9	69.4		30.6
Piperacillin-tazobactam	4	64	≤0.5 to >64	80.5	9.8	9.6	80.5		19.5
Tigecycline	8	>8	0.5 to >8						
Trimethoprim-sulfamethoxazole	4	>4	≤0.5 to >4						

S, susceptible; I, intermediate; R, resistant; ESBL, extended-spectrum β-lactamase

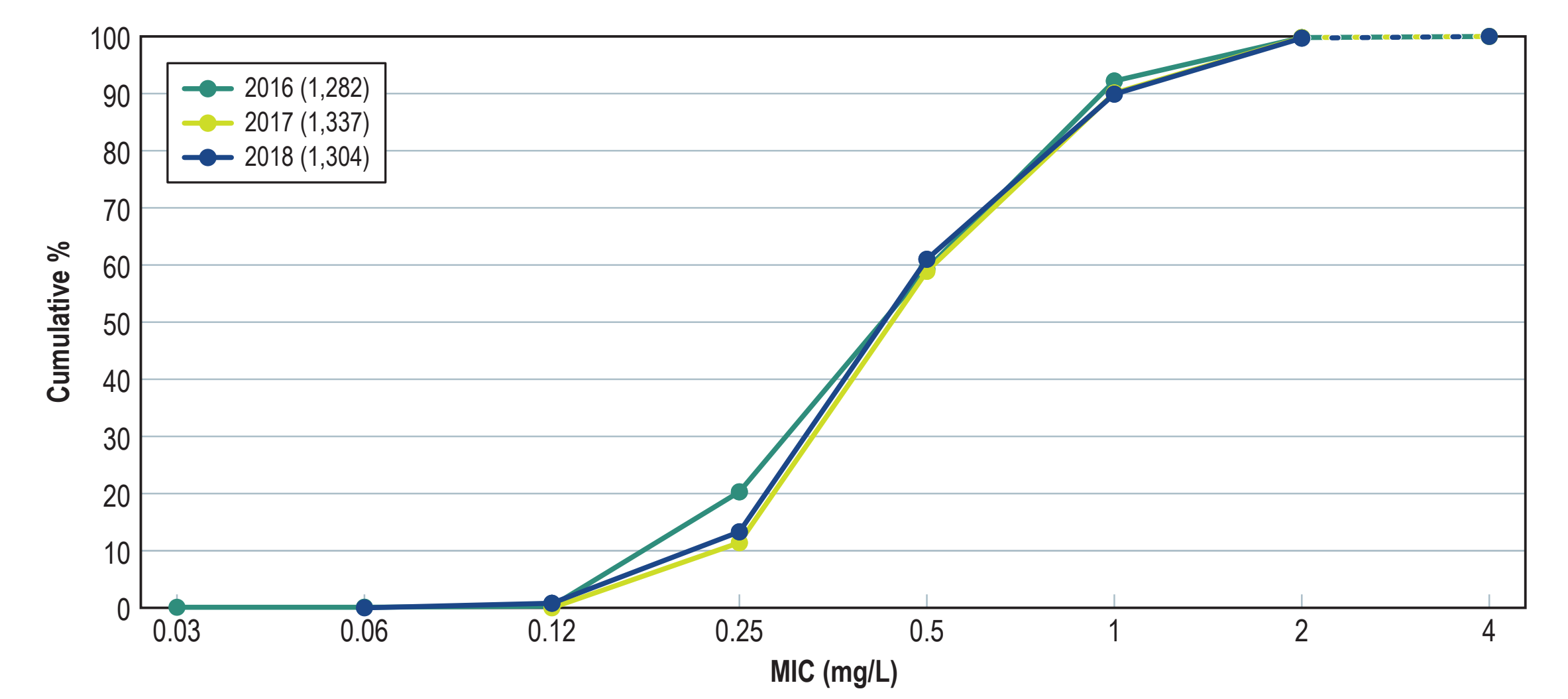
[a] Criteria as published by CLSI 2019 and EUCAST 2019.

[b] Organisms include: *Citrobacter amalonaticus* (1), *C. amalonaticus/farmeri* (3), *C. farmeri* (1), *C. freundii* (8), *C. freundii* species complex (43), *C. koseri* (31), *Cronobacter sakazakii* (1), *Edwardsiella tarda* (1), *Enterobacter aerogenes* (57), *E. cloacae* (115), *E. cloacae* species complex (129), *Escherichia coli* (500), *E. hermannii* (1), *Klebsiella oxytoca* (90), *K. pneumoniae* (192), *Leclercia adecarboxylata* (1), *Lelliottia amnigena* (1), *Metakosakonia massiliensis* (1), *Morganella morganii* (73), *Pantoea agglomerans* (2), *P. calida* (1), *P. eucrina* (1), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (258), *P. vulgaris* (3), *P. vulgaris* group (16), *Providencia rettgeri* (14), *P. stuartii* (7), *Serratia fonticola* (1), *S. liquefaciens* (7), *S. liquefaciens* complex (1), *S. marcescens* (135), unspeciated *Pantoea* (2), unspeciated *Providencia* (1), unspeciated *Raoultella* (2)

[c] Intermediate interpreted as susceptible-dose dependent.

[d] FDA breakpoints accessed January 2019.

Figure 2 Ceftobiprole activity against US *S. aureus* SSSI isolates by year



SSSI, skin and skin structure infection

Conclusions

- Ceftobiprole was highly active *in vitro* against a large percentage of the clinical isolates from the major Gram-positive and Gram-negative SSSI pathogen groups collected at US medical centers during 2016–2018
- 76% of the SSSI pathogens was composed of *S. aureus* and *Enterobacteriaceae* isolates
  - Overall, the *S. aureus* SSSI isolate set was 99.7% susceptible to ceftobiprole
  - The *Enterobacteriaceae* SSSI isolate set was 84.8% susceptible to ceftobiprole
- The broad-spectrum activity of ceftobiprole, including potent activity against MRSA, supports its further evaluation for this potential indication

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