




# Ceftobiprole Activity against Bacteria from Skin and Skin Structure Infections in the United States from 2016 through 2018

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**ABSTRACT** Ceftobiprole medocartil is an advanced-generation cephalosporin pro-drug that has qualified infectious disease product status granted by the US FDA and is currently being evaluated in phase 3 clinical trials in patients with acute bacterial skin and skin structure infections (ABSSSIs) and in patients with *Staphylococcus aureus* bacteremia. In this study, the activity of ceftobiprole and comparators was evaluated against more than 7,300 clinical isolates collected in the United States from 2016 through 2018 from patients with skin and skin structure infections. The major species/pathogen groups were *S. aureus* (53%), *Enterobacterales* (23%), *Pseudomonas aeruginosa* (7%), beta-hemolytic streptococci (6%), *Enterococcus* spp. (4%), and coagulase-negative staphylococci (2%). Ceftobiprole was highly active against *S. aureus* (MIC<sub>50/90</sub>, 0.5/1 mg/liter; 99.7% susceptible by EUCAST criteria; 42% methicillin-resistant *S. aureus* [MRSA]). Ceftobiprole also exhibited potent activity against other Gram-positive cocci. The overall susceptibility of *Enterobacterales* to ceftobiprole was 84.8% (>99.0% susceptible for isolate subsets that exhibited a non-extended-spectrum  $\beta$ -lactamase [ESBL] phenotype). A total of 74.4% of *P. aeruginosa*, 100% of beta-hemolytic streptococci and coagulase-negative staphylococci, and 99.6% of *Enterococcus faecalis* isolates were inhibited by ceftobiprole at  $\leq 4$  mg/liter. As expected, ceftobiprole was largely inactive against *Enterobacterales* that contained ESBL genes and *Enterococcus faecium*. Overall, ceftobiprole was highly active against most clinical isolates from the major Gram-positive and Gram-negative skin and skin structure pathogen groups collected at U.S. medical centers participating in the SENTRY Antimicrobial Surveillance Program during 2016 to 2018. The broad-spectrum activity of ceftobiprole, including potent activity against MRSA, supports its further evaluation for a potential ABSSSI indication.

**KEYWORDS** ABSSSI, MRSA, SSTI, ceftobiprole, cephalosporin, skin, surveillance

Skin and skin structure infections (SSSIs) frequently occur in outpatient and inpatient settings (1–6). In the United States, an estimated 3.4 million patients received emergency room treatments for SSSIs in 2005 (2) and hospital admissions for SSSIs totaled more than 640,000 each year from 2000 to 2011 (7, 8). Gram-positive organisms—in particular, *Staphylococcus aureus* and beta-hemolytic streptococci—are the most common pathogens causing SSSIs; however, Gram-negative bacteria are also isolated as infection-causing pathogens (1–4, 6, 9, 10). Community-associated methicillin-resistant *S. aureus* (MRSA) isolates have emerged and are problematic in inpatient and outpatient settings, sometimes representing >50% of *S. aureus* isolates in the United States (1–6, 9, 10). In 2019, the CDC report on antibiotic resistance listed MRSA as a serious public health threat (11). Since 2010, six antimicrobial agents with

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MRSA activity have been approved in the United States for treatment of acute bacterial skin and skin structure infections (ABSSSIs): ceftaroline fosamil, dalbavancin, delafloxacin, omadacycline, oritavancin, and tedizolid phosphate. Three of these agents (delafloxacin, omadacycline, and tedizolid phosphate) are available in both intravenous and oral forms (12–15).

Ceftobiprole medocaril is an advanced-generation parenteral cephalosporin pro-drug that has been approved in 17 European and 8 non-European countries for the treatment of adults with community-acquired (CAP) and hospital-acquired pneumonia (excluding ventilator-associated pneumonia) (16–19). Ceftobiprole, the active moiety of ceftobiprole medocaril, was designed to inhibit penicillin-binding protein 2A, which confers methicillin (oxacillin) resistance in *S. aureus* (20–23), in addition to other essential penicillin-binding proteins. This agent exhibits potent *in vitro* antimicrobial activity against important Gram-positive pathogens like *S. aureus*, including MRSA isolates, and *Streptococcus pneumoniae* (24–28). Additionally, ceftobiprole exhibits antimicrobial activity against *Enterobacteriales* and *Pseudomonas aeruginosa* that is similar to other advanced cephalosporins like cefepime (24–31).

Ceftobiprole medocaril is not approved for use in the United States but has qualified infectious disease product status for the potential treatment of ABSSSIs and *S. aureus* bacteremia; it is being evaluated in 2 phase 3 clinical trials for patients with ABSSSIs (TARGET study, completed April 2019; ClinicalTrials.gov identifier NCT03137173) (32) and *S. aureus* bacteremia, including infective endocarditis (ERADICATE study, expected completion in 2021; ClinicalTrials.gov identifier: NCT03138733) (33). In this *in vitro* study, we report on the activity of ceftobiprole and comparators when tested against recent clinical isolates collected in the United States through the SENTRY Antimicrobial Surveillance Program (2016 to 2018) (34) from patients with SSSIs.

## RESULTS

**Pathogens in skin and skin structure infections.** The most common isolate type from SSSIs was *S. aureus* (53% overall; 42% of which were MRSA) (Table 1 and Fig. 1). Beta-hemolytic streptococci (6%) and *Enterococcus* spp. (4%) were the next most frequently isolated Gram-positive bacteria (Fig. 1). *Enterobacteriales* represented 23% of isolates, with *Escherichia coli* (29%), *Proteus mirabilis* (15%), *Enterobacter cloacae* species complex (14%), *Klebsiella pneumoniae* (11%), and *Serratia marcescens* (8%) as the most common species (Table 1). A total of 7% of isolates were *P. aeruginosa* (Table 1 and Fig. 1).

**Ceftobiprole activity against Gram-positive clinical isolates.** Ceftobiprole was highly active against the major groups of Gram-positive cocci associated with SSSIs (Table 1). The agent exhibited potent activity against *S. aureus* from SSSIs (MIC<sub>50/90</sub>, 0.5/1 mg/liter; 99.7% susceptible at the EUCAST breakpoint of 2 mg/liter) (Table 1). The MIC<sub>50/90</sub> values were only 2-fold higher for MRSA (99.4% susceptible) (Table 1). All MRSA isolates were susceptible to daptomycin, tigecycline, and vancomycin, and 97.1% were susceptible to ceftaroline (Table 2). Ceftobiprole also exhibited potent activity against beta-hemolytic streptococci (MIC<sub>50/90</sub>, 0.015/0.03 mg/liter; 100% inhibited at ≤0.12 mg/liter [4 mg/liter is the EUCAST pharmacokinetic/pharmacodynamic non-species-related breakpoint]), *Enterococcus faecalis* (MIC<sub>50/90</sub>, 0.5/2 mg/liter; 99.6% inhibited at ≤4 mg/liter), and coagulase negative staphylococci (MIC<sub>50/90</sub>, 0.5/1 mg/liter; 100% inhibited at ≤4 mg/liter) (Tables 1 and 2). As expected, ceftobiprole was inactive against *Enterococcus faecium* (MIC<sub>50/90</sub>, >4/>4 mg/liter; data not shown).

**Ceftobiprole activity against Gram-negative clinical isolates.** *Enterobacteriales* isolates overall exhibited 84.8% susceptibility to ceftobiprole (Table 3), which was similar to the susceptibility exhibited to other expanded-spectrum cephalosporins like cefepime (89.7%) and ceftazidime (85.0%) (Table 3). Most *E. coli* and *K. pneumoniae* isolates exhibited a non-extended-spectrum β-lactamase (ESBL) phenotype (77.6% for each species). The potent activity of ceftobiprole against *E. coli* (MIC<sub>50/90</sub>, 0.03/0.06 mg/liter; 99.7% susceptible) and *K. pneumoniae* (MIC<sub>50/90</sub>, 0.03/0.06 mg/liter; 99.3% susceptible) isolates that exhibited a non-ESBL phenotype contrasts with its inactivity against

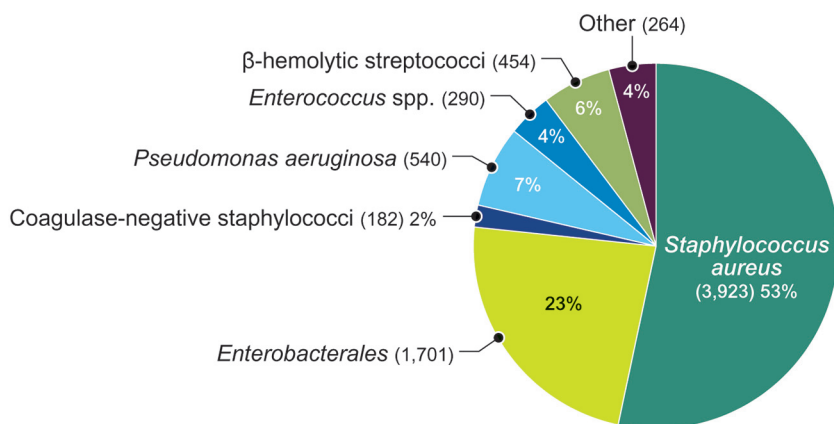
**TABLE 1** Antimicrobial activity of ceftobiprole tested against the main species and groups from skin and skin structure infections

Organism/organism group (no. of isolates) <sup>a</sup>	No. (cumulative %) of isolates inhibited at MIC (mg/liter) of:													MIC <sub>50</sub>	MIC <sub>90</sub>			
	≤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	> <sup>b</sup>
<i>Staphylococcus aureus</i> (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
Enterobacteriales (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			
<i>Escherichia coli</i> (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			
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			
ESBL genotype (88) <sup>c</sup>	0 (0.0)	23 (8.9)	195 (84.5)	30 (96.1)	2 (96.9)	0 (96.9)	0 (0.0)	1 (1.1)	0 (1.1)	0 (1.1)	0 (1.1)	0 (1.1)	87 (100.0)	>16	>16			
<i>Proteus mirabilis</i> (258)	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			
<i>Klebsiella pneumoniae</i> (192)	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			
Non-ESBL phenotype (149)	0 (0.0)	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)				>16	>16			
ESBL genotype (29) <sup>c</sup>	0 (0.0)	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	0.12			
<i>Serratia marcescens</i> (135)														0.06	0.12			
<i>Enterobacter cloacae</i> species complex (244)														0.06	2			
<i>Pseudomonas aeruginosa</i> (540)	0 (0.0)	5 (1.1)	7 (2.6)	198 (46.3)	142 (77.5)	98 (99.1)	3 (99.8)	0 (0.0)	1 (100.0)					2	16			
β-hemolytic streptococci (454)														0.015	0.03			
<i>Enterococcus faecalis</i> (223)														0.5	2			
Coagulase-negative staphylococci (182)														0.5	1			

<sup>a</sup>ESBL<sub>ext</sub> extended-spectrum β-lactamase.

<sup>b</sup>Greater than the highest concentration tested.

<sup>c</sup>The isolates met the MIC criteria for screening of β-lactamase-encoding genes (36) and contained an ESBL gene in the absence of a carbapenemase gene (see Materials and Methods).



**FIG 1** Species, groups, and numbers of U.S. isolates from skin and skin structure infections (2016 to 2018).

*Enterobacteriales* that contained ESBL genes (0% susceptible for *E. coli* and *K. pneumoniae* isolates with an ESBL-positive genotype) (Tables 1 and 3). Ceftobiprole also exhibited potent activity against other commonly isolated *Enterobacteriales* such as *P. mirabilis* (MIC<sub>50/90</sub>, 0.03/0.06 mg/liter; 96.9% susceptible), *S. marcescens* (MIC<sub>50/90</sub>, 0.06/0.12 mg/liter; 96.3% susceptible), and *E. cloacae* species complex isolates (MIC<sub>50/90</sub>, 0.06/2 mg/liter; 84.0% susceptible) (Table 1). A total of 74.4% of *P. aeruginosa* isolates were inhibited by ceftobiprole at  $\leq 4$  mg/liter (Table 1).

## DISCUSSION

Consistent with studies documenting that *S. aureus* is the leading bacterial pathogen in SSSIs (1–4, 6, 9, 10), *S. aureus* (42% MRSA) was the most commonly isolated pathogen in this surveillance study. The concern about the increasing occurrence of MRSA in the community and the inpatient setting is well documented (1–4, 6, 9). These data from a current U.S. bacterial surveillance program support the concern about MRSA and the need for antimicrobials that can successfully treat these organisms. Surveillance isolates collected from hospitalized patients also demonstrated that Gram-negative bacteria should be considered, at least for certain infections. Approximately 23% of the isolates were *Enterobacteriales*, with 78% of the *E. coli* and *K. pneumoniae* exhibiting a non-ESBL phenotype. An agent such as ceftobiprole that exhibits antimicrobial activity against MRSA and *Enterobacteriales* provides the opportunity for a broader spectrum of coverage. However, ceftobiprole is not active against certain subsets of *Enterobacteriales*, such as ESBLs.

Fortunately, a number of agents tested in this study demonstrated a high level of activity against *S. aureus*. For ceftobiprole, susceptibility was 99.7% (99.4% for MRSA and 100% for methicillin-susceptible *S. aureus* [MSSA]) when tested against *S. aureus*. Susceptibility to daptomycin and tigecycline was 100% for both MRSA and MSSA. Susceptibility to linezolid was 99.9% for MRSA and 100% for MSSA. All MSSA isolates were susceptible to ceftaroline, while 97.1% of MRSA isolates were susceptible. Of the agents listed, two (daptomycin and linezolid) are active only against Gram-positive bacteria. Ceftobiprole, tigecycline, and ceftaroline also have activity against *Enterobacteriales*.

In summary, ceftobiprole has been shown to have broad-spectrum activity, including potent activity against MRSA (24–30). It has been approved for marketing in many European and non-European countries for the treatment of adults with CAP and hospital-acquired pneumonia (excluding ventilator-associated pneumonia). In this study, the broad-spectrum activity of ceftobiprole against isolates from SSSIs collected in the United States as part of the SENTRY Antimicrobial Surveillance Program was shown. These data support ceftobiprole's further evaluation for the potential treatment of ABSSSIs.

**TABLE 2** Activity of ceftobiprole and comparator agents when tested against the major groups of Gram-positive bacteria from skin and skin structure infections in the United States (2016–2018)<sup>a</sup>

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI <sup>i</sup>			EUCAST <sup>i</sup>		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	%I	%R	%S	%I	%R
<b>MRSA (1,643)</b>									
Ceftobiprole	1	2	0.25 to 4				99.4		0.6
Ceftaroline	0.5	1	0.25 to 2	97.1 <sup>b</sup>	2.9	0.0	97.1 <sup>c</sup>	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 <sup>d</sup>			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
<b>MSSA (2,280)</b>									
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 <sup>b</sup>	0.0	0.0	100.0 <sup>c</sup>	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 <sup>d</sup>			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
<b>β-hemolytic streptococci (454)<sup>e</sup></b>									
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
<b>Enterococcus faecalis (223)</b>									
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	1.8	0.0			
Levofloxacin	1	>4	≤0.03 to >4	75.8	0.0	24.2	75.8 <sup>f</sup>		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 <sup>g</sup>			100.0		0.0
Vancomycin	1	2	0.25 to >16	96.9	0.0	3.1	96.9		3.1
<b>Coagulase-negative staphylococci (182)<sup>h</sup></b>									
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

(Continued on next page)

TABLE 2 (Continued)

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI <sup>f</sup>			EUCAST <sup>f</sup>		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	%I	%R	%S	%I	%R
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

<sup>a</sup>S, susceptible; I, intermediate; R, resistant; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

<sup>b</sup>Intermediate interpreted as susceptible-dose dependent.

<sup>c</sup>Using other than pneumonia breakpoints.

<sup>d</sup>FDA breakpoints accessed January 2019.

<sup>e</sup>Organisms include: *Streptococcus agalactiae* (142), *Streptococcus canis* (3), *Streptococcus dysgalactiae* (41), *Streptococcus pyogenes* (268).

<sup>f</sup>Uncomplicated urinary tract infections only.

<sup>g</sup>FDA breakpoints accessed January 2019 applied to all *E. faecalis* but approved for vancomycin-susceptible isolates only.

<sup>h</sup>Organisms include: *Staphylococcus capitis* (2), *Staphylococcus caprae* (2), *Staphylococcus epidermidis* (63), *Staphylococcus haemolyticus* (7), *Staphylococcus hominis* (3), *Staphylococcus intermedius* (1), *Staphylococcus lugdunensis* (90), *Staphylococcus pseudintermedius* (5), *Staphylococcus saprophyticus* (1), *Staphylococcus schleiferi* (1), *Staphylococcus simulans* (5), *Staphylococcus warneri* (1), *Staphylococcus xylosum* (1).

<sup>i</sup>Interpretive criteria as published by CLSI 2019 and EUCAST 2019.

## MATERIALS AND METHODS

**Bacterial isolates.** A total of 7,354 clinical isolates were collected from patients with SSSIs at 32 U.S. medical centers across the nine census divisions from 2016 through 2018. Nonduplicate consecutive isolates, one per patient infection episode, were submitted to the central laboratory (JMI Laboratories, North Liberty, Iowa, USA). Bacterial isolates were identified following the standard methods of the participating surveillance laboratory, and identification was confirmed by JMI Laboratories using matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany) or other methods when needed (35). *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, and *P. mirabilis* isolates that exhibited an MIC value of ≥2 mg/liter for ceftriaxone, ceftazidime, and/or aztreonam met the criteria for performance of ESBL tests (36). *S. aureus* strains were classified as MRSA according to their oxacillin MIC values (resistant MIC, ≥4 mg/liter) (36).

**Genotypic analysis of β-lactamase genes.** Ninety-five percent of the *E. coli* and *K. pneumoniae* isolates that met the MIC criteria for screening of β-lactamase-encoding genes, including ESBLs (36), were subjected to genome sequencing and analysis. Total genomic DNA was extracted using the Thermo Fisher Scientific KingFisher Flex magnetic particle processor (Cleveland, Ohio, USA) and used as input material for library construction. DNA libraries were prepared using the NexteraXT library construction protocol (Illumina, San Diego, California, USA) following the manufacturer's instructions and were sequenced on a MiSeq Sequencer (JMI Laboratories). FASTQ format sequencing files for each sample set were assembled independently using the *de novo* assembler SPAdes 3.9.0, and a JMI Laboratories-designed software workflow was applied to the assembled sequences to align against a database containing known β-lactamase-encoding genes. The *E. coli* and *K. pneumoniae* ESBL-genotype subsets consisted of isolates containing ESBL genes (primarily CTX-M) and lacking carbapenemase genes.

**Susceptibility testing.** Susceptibility to ceftobiprole and comparator agents was tested using current CLSI methods (36, 37). JMI prepared frozen-form broth microdilution panels for susceptibility testing. Ceftobiprole was supplied by Basilea Pharmaceutica International Ltd., and comparator agents were acquired from Sigma-Aldrich Chemical Co. (St. Louis, Missouri, USA) or similar suppliers. Interpretive criteria were those of CLSI and EUCAST (36, 38), where applicable. Only EUCAST interpretive criteria were applied to ceftobiprole, because corresponding interpretive criteria have not been published by CLSI. FDA criteria were used as an alternative breakpoint source for tigecycline (39). JMI Laboratories followed current CLSI quality assurance practices when performing the susceptibility tests (36). MIC values were validated by concurrently testing CLSI-recommended American Type Culture Collection (ATCC) quality control reference strains (36) that included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922 and ATCC 35218, *P. aeruginosa* ATCC 27853, and *S. pneumoniae* ATCC 49619 (36). The susceptibilities of pathogen groups without specific published interpretive criteria for ceftobiprole were evaluated using the EUCAST non-species-specific breakpoint of 4 mg/liter (38).

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**TABLE 3** Activity of ceftobiprole and comparator agents when tested against the major groups of Gram-negative bacteria from skin and skin structure infections in the United States (2016–2018)<sup>a</sup>

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI <sup>e</sup>			EUCAST <sup>e</sup>		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	%I	%R	%S	%I	%R
<b>Enterobacteriales (1,701)<sup>b</sup></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 <sup>c</sup>	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 <sup>d</sup>	7.4	0.9			
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	79.9		20.1	79.9	0.6	19.4
<b>Non-ESBL-phenotype <i>Escherichia coli</i> (388)</b>									
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 <sup>c</sup>	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 <sup>d</sup>	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
<b>Non-ESBL-phenotype <i>Klebsiella pneumoniae</i> (149)</b>									
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 <sup>c</sup>	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 <sup>d</sup>	2.0	0.7			
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	94.6		5.4	94.6	0.0	5.4
<b><i>Pseudomonas aeruginosa</i> (540)</b>									
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

(Continued on next page)

TABLE 3 (Continued)

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI <sup>e</sup>			EUCAST <sup>e</sup>		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	%I	%R	%S	%I	%R
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						

<sup>a</sup>S, susceptible; I, intermediate; R, resistant; ESBL, extended-spectrum β-lactamase.

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

<sup>c</sup>Intermediate interpreted as susceptible-dose dependent.

<sup>d</sup>FDA breakpoints accessed January 2019.

<sup>e</sup>Interpretive criteria as published by CLSI 2019 and EUCAST 2019.

Sciences, Allegra Therapeutics, Allergan, AmpliPhi Biosciences Corp., Amplyx, Antabio, American Proficiency Institute, Arietis Corp., Arixa Pharmaceuticals, Inc., Astellas Pharma Inc., Athelas, Basilea Pharmaceutica International Ltd., Bayer AG, Becton, Dickinson and Company, bioMérieux SA, Boston Pharmaceuticals, Bugworks Research Inc., CEM-102 Pharmaceuticals, Cepheid, Cidara Therapeutics, Inc., CorMedix Inc., DePuy Synthes, Destiny Pharma, Discuva Ltd., Dr. Falk Pharma GmbH, Emery Pharma, Entasis Therapeutics, Eurofarma Laboratorios SA, US Food and Drug Administration, Fox Chase Chemical Diversity Center, Inc., Gateway Pharmaceutical LLC, GenePOC Inc., Geom Therapeutics, Inc., GlaxoSmithKline plc, Harvard University, Helperby, HiMedia Laboratories, F. Hoffmann-La Roche Ltd., ICON plc, Idorsia Pharmaceuticals Ltd., Iterum Therapeutics plc, Laboratory Specialists, Inc., Melinta Therapeutics, Inc., Merck & Co., Inc., Microchem Laboratory, Micromyx, MicuRx Pharmaceuticals, Inc., Mutabilis Co., Nabriva Therapeutics plc, NAEJA-RGM, Novartis AG, Oxoid Ltd., Paratek Pharmaceuticals, Inc., Pfizer, Inc., Polyphor Ltd., Pharmaceutical Product Development, LLC, Prokaryotics Inc., Qpex Biopharma, Inc., Ra Pharmaceuticals, Inc., Roivant Sciences, Ltd., Safeguard Biosystems, Scynexis, Inc., SeLux Diagnostics, Inc., Shionogi and Co., Ltd., SinSa Labs, Spero Therapeutics, Summit Pharmaceuticals International Corp., Synlogic, T2 Biosystems, Inc., Taisho Pharmaceutical Co., Ltd., TenNor Therapeutics Ltd., Tetrphase Pharmaceuticals, The Medicines Company, Theravance Biopharma, University of Colorado, University of Southern California-San Diego, University of North Texas Health Science Center, VenatoRx Pharmaceuticals, Inc., Vyome Therapeutics Inc., Wockhardt, Yukon Pharmaceuticals, Inc., Zai Lab, and Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

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