AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

SUSCEPTIBILITY

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

Robert K. Flamm,[a] Leonard R. Duncan,[a] Kamal A. Hamed,[b] Jennifer I. Smart,[b] Rodrigo E. Mendes,[a] Michael A. Pfaller[a,c]

[a]JMI Laboratories, North Liberty, Iowa, USA
[b]Basilea Pharmaceutica International Ltd., Basel, Switzerland
[c]University of Iowa, Iowa City, Iowa, USA

ABSTRACT Ceftobiprole medocaril is an advanced-generation cephalosporin prodrug 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* ($MIC_{50/90}$, 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 β-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 ≤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

Citation Flamm RK, Duncan LR, Hamed KA, Smart JI, Mendes RE, Pfaller MA. 2020. Ceftobiprole activity against bacteria from skin and skin structure infections in the United States from 2016 through 2018. Antimicrob Agents Chemother 64:e02566-19. https://doi.org/10.1128/AAC.02566-19.

Address correspondence to Leonard R. Duncan, leonard-duncan@jmilabs.com.

Received 23 December 2019
Returned for modification 22 January 2020
Accepted 9 March 2020
Accepted manuscript posted online 16 March 2020
Published 21 May 2020

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 prodrug 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 *Enterobacterales* 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). *Enterobacterales* 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 ($MIC_{50/90}$, 0.5/1 mg/liter; 99.7% susceptible at the EUCAST breakpoint of 2 mg/liter) (Table 1). The $MIC_{50/90}$ 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 ($MIC_{50/90}$, 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* ($MIC_{50/90}$, 0.5/2 mg/liter; 99.6% inhibited at ≤4 mg/liter), and coagulase negative staphylococci ($MIC_{50/90}$, 0.5/1 mg/liter; 100% inhibited at ≤4 mg/liter) (Tables 1 and 2). As expected, ceftobiprole was inactive against *Enterococcus faecium* ($MIC_{50/90}$, >4/>4 mg/liter; data not shown).

Ceftobiprole activity against Gram-negative clinical isolates. *Enterobacterales* 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* ($MIC_{50/90}$, 0.03/0.06 mg/liter; 99.7% susceptible) and *K. pneumoniae* ($MIC_{50/90}$, 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)[a]	No. (cumulative %) of isolates inhibited at MIC (mg/liter) of:																	
	≤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	>[b]	MIC_{50}	MIC_{90}
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
Enterobacterales (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
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)[c]										0 (0.0)	1 (1.1)	0 (1.1)	0 (1.1)	0 (1.1)	0 (1.1)	87 (100.0)	>16	>16
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
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
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
ESBL genotype (29)[c]										0 (0.0)	2 (6.9)	0 (6.9)	1 (10.3)	0 (10.3)	0 (10.3)	26 (100.0)	>16	>16
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
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

[a]ESBL, extended-spectrum β-lactamase.

[b]Greater than the highest concentration tested.

[c]These 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).

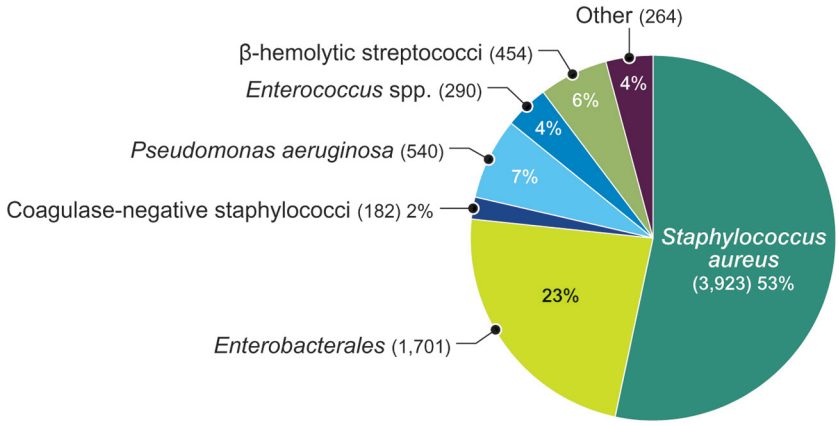

FIG 1 Species, groups, and numbers of U.S. isolates from skin and skin structure infections (2016 to 2018).

Enterobacterales 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 *Enterobacterales* such as *P. mirabilis* ($MIC_{50/90}$, 0.03/0.06 mg/liter; 96.9% susceptible), *S. marcescens* ($MIC_{50/90}$, 0.06/0.12 mg/liter; 96.3% susceptible), and *E. cloacae* species complex isolates ($MIC_{50/90}$, 0.06/2 mg/liter; 84.0% susceptible) (Table 1). A total of 74.4% of *P. aeruginosa* isolates were inhibited by ceftobiprole at ≤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 *Enterobacterales*, 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 *Enterobacterales* provides the opportunity for a broader spectrum of coverage. However, ceftobiprole is not active against certain subsets of *Enterobacterales*, 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 *Enterobacterales*.

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)[a]

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI[i]			EUCAST[i]		
	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	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

(Continued on next page)

TABLE 2 (Continued)

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI[i]			EUCAST[i]		
	MIC_{50}	MIC_{90}	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

[a]S, susceptible; I, intermediate; R, resistant; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.
[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), *Streptococcus canis* (3), *Streptococcus dysgalactiae* (41), *Streptococcus pyogenes* (268).
[f]Uncomplicated urinary tract infections 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), *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 xylosus* (1).
[i]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).

ACKNOWLEDGMENTS

This project was funded in part with federal funds from the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under contract no. HHSO100201600002C, and in part by Basilea Pharmaceutica International Ltd., Basel, Switzerland. This includes funding for services related to preparing the manuscript.

This study was performed by JMI Laboratories. JMI Laboratories contracted to perform services in 2018 for Achaogen, Inc., Albany College of Pharmacy and Health

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)[a]

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI[e]			EUCAST[e]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R
Enterobacterales (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

(Continued on next page)

TABLE 3 (Continued)

Species or group (no. of isolates) and antimicrobial agent	MIC (mg/liter)			CLSI[e]			EUCAST[e]		
	MIC_{50}	MIC_{90}	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						

[a]S, susceptible; I, intermediate; R, resistant; ESBL, extended-spectrum β-lactamase.
[b]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).
[c]Intermediate interpreted as susceptible-dose dependent.
[d]FDA breakpoints accessed January 2019.
[e]Interpretive criteria as published by CLSI 2019 and EUCAST 2019.

Sciences, Allecra 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., Tetraphase 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.

REFERENCES

1. Pallin DJ, Espinola JA, Leung DY, Hooper DC, Camargo CA. Jr., 2009. Epidemiology of dermatitis and skin infections in United States physicians' offices, 1993–2005. Clin Infect Dis 49:901–907. https://doi.org/10.1086/605434.
2. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA. Jr., 2008. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. Ann Emerg Med 51:291–298. https://doi.org/10.1016/j.annemergmed.2007.12.004.
3. Dryden MS. 2010. Complicated skin and soft tissue infection. J Antimicrob Chemother 65 Suppl 3:iii35–iii44. https://doi.org/10.1093/jac/dkq302.
4. Lipsky BA, Moran GJ, Napolitano LM, Vo L, Nicholson S, Kim M. 2012. A prospective, multicenter, observational study of complicated skin and soft tissue infections in hospitalized patients: clinical characteristics, medical treatment, and outcomes. BMC Infect Dis 12:227. https://doi.org/10.1186/1471-2334-12-227.
5. Leong HN, Kurup A, Tan MY, Kwa ALH, Liau KH, Wilcox MH. 2018. Management of complicated skin and soft tissue infections with a special focus on the role of newer antibiotics. Infect Drug Resist 11:1959–1974. https://doi.org/10.2147/IDR.S172366.
6. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. 2014. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 59:e10–e52. https://doi.org/10.1093/cid/ciu296.
7. Edelsberg J, Taneja C, Zervos M, Haque N, Moore C, Reyes K, Spalding J, Jiang J, Oster G. 2009. Trends in US hospital admissions for skin and soft tissue infections. Emerg Infect Dis 15:1516–1518. https://doi.org/10.3201/eid1509.081228.
8. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. 2015. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. PLoS One 10:e0143276. https://doi.org/10.1371/journal.pone.0143276.
9. Ray GT, Suaya JA, Baxter R. 2013. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a

retrospective population-based study. BMC Infect Dis 13:252. https://doi.org/10.1186/1471-2334-13-252.
10. Moet GJ, Jones RN, Biedenbach DJ, Stilwell MG, Fritsche TR. 2007. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). Diagn Microbiol Infect Dis 57:7–13. https://doi.org/10.1016/j.diagmicrobio.2006.05.009.
11. Centers for Disease Control. 2019. Antibiotic resistance threats in the United States. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed November 2019.
12. Paratek Pharmaceuticals, Inc. 2018. NUZYRA™ (omadacycline) package insert. Paratek Pharmaceuticals, Inc, Boston, MA, USA.
13. Melinta Therapeutics, Inc. 2017. Baxdela label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208610s000,208611s000lbl.pdf. Accessed August 2017.
14. Cubist Pharmaceuticals U.S. 2014. SIVEXTRO™ (tedizolid phosphate) label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205435s000lbl.pdf. Accessed June 2019.
15. Jaffa RK, Pillinger KE, Roshdy D, Isip JA, Pasquale TR. 2019. Novel developments in the treatment of acute bacterial skin and skin structure infections. Expert Opin Pharmacother 20:1493–1502. https://doi.org/10.1080/14656566.2019.1617851.
16. Basilea Medical Ltd. 2014. Zevtera label. https://www.medicines.org.uk/emc/product/9164/smpc. Accessed August 06, 2019.
17. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, Scheeren TW, Sanchez AS, Zhou X, Saulay M, Engelhardt M. 2014. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis 59:51–61. https://doi.org/10.1093/cid/ciu219.
18. Liapikou A, Cilloniz C, Torres A. 2015. Ceftobiprole for the treatment of pneumonia: a European perspective. Drug Des Devel Ther 9:4565–4572. https://doi.org/10.2147/DDDT.S56616.
19. Syed YY. 2014. Ceftobiprole medocaril: a review of its use in patients with hospital- or community-acquired pneumonia. Drugs 74:1523–1542. https://doi.org/10.1007/s40265-014-0273-x.
20. Page MG. 2004. Cephalosporins in clinical development. Expert Opin Invest Drugs 13:973–985. https://doi.org/10.1517/13543784.13.8.973.
21. Page MG. 2007. Ceftobiprole—a case study. Expert Opin Drug Discov 2:115–129. https://doi.org/10.1517/17460441.2.1.115.
22. Hebeisen P, Heinze-Krauss I, Angehrn P, Hohl P, Page MG, Then RL. 2001. In vitro and in vivo properties of Ro 63-9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. Antimicrob Agents Chemother 45:825–836. https://doi.org/10.1128/AAC.45.3.825-836.2001.
23. Davies TA, Page MG, Shang W, Andrew T, Kania M, Bush K. 2007. Binding of ceftobiprole and comparators to the penicillin-binding proteins of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. Antimicrob Agents Chemother 51:2621–2624. https://doi.org/10.1128/AAC.00029-07.
24. Fritsche TR, Sader HS, Jones RN. 2008. Antimicrobial activity of ceftobiprole, a novel anti-methicillin-resistant *Staphylococcus aureus* cephalosporin, tested against contemporary pathogens: results from the SENTRY Antimicrobial Surveillance Program (2005–2006). Diagn Microbiol Infect Dis 61:86–95. https://doi.org/10.1016/j.diagmicrobio.2008.02.008.
25. Rossolini GM, Dryden MS, Kozlov RS, Quintana A, Flamm RK, Lauffer JM, Lee E, Morrissey I, Group CS. 2011. Comparative activity of ceftobiprole against Gram-positive and Gram-negative isolates from Europe and the Middle East: the CLASS study. J Antimicrob Chemother 66:151–159. https://doi.org/10.1093/jac/dkq397.
26. Pfaller MA, Flamm RK, Mendes RE, Streit JM, Smart JI, Hamed KA, Duncan LR, Sader HS. 2018. Ceftobiprole activity against Gram-positive and -negative pathogens collected from the United States across a decade: 2006 and 2016. Antimicrob Agents Chemother 63:e01566. https://doi.org/10.1128/AAC.01566-18.
27. Pfaller MA, Flamm RK, Duncan LR, Shortridge D, Smart JI, Hamed KA, Mendes RE, Sader HS. 2019. Ceftobiprole activity when tested against contemporary bacteria causing bloodstream infections in the United States (2016–2017). Diagn Microbiol Infect Dis 94:304–313. https://doi.org/10.1016/j.diagmicrobio.2019.01.015.
28. Karlowsky JA, Decorby M, Hoban DJ, Zhanel GG. 2009. In vitro activities of ceftobiprole and doripenem tested against frequently encountered aerobic and facultative Gram-positive and Gram-negative bacterial pathogens isolated from patients in Canadian hospitals in 2007. Can J Infect Dis Med Microbiol 20:59a–66a. https://doi.org/10.1155/2009/183843.
29. Walkty A, Adam HJ, Laverdiere M, Karlowsky JA, Hoban DJ, Zhanel GG, Canadian Antimicrobial Resistance Alliance (CARA). 2011. In vitro activity of ceftobiprole against frequently encountered aerobic and facultative Gram-positive and Gram-negative bacterial pathogens: results of the CANWARD 2007–2009 study. Diagn Microbiol Infect Dis 69:348–355. https://doi.org/10.1016/j.diagmicrobio.2010.10.032.
30. Zhanel GG, Lam A, Schweizer F, Thomson K, Walkty A, Rubinstein E, Gin AS, Hoban DJ, Noreddin AM, Karlowsky JA. 2008. Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. Am J Clin Dermatol 9:245–254. https://doi.org/10.2165/00128071-200809040-00004.
31. Pfaller MA, Flamm RK, Duncan LR, Streit JM, Castanheira M, Sader HS. 2018. Antimicrobial activity of ceftobiprole and comparator agents when tested against contemporary Gram-positive and -negative organisms collected from Europe (2015). Diagn Microbiol Infect Dis 91:77–84. https://doi.org/10.1016/j.diagmicrobio.2017.12.020.
32. ClinicalTrials.gov. 2019. Ceftobiprole in the treatment of patients with acute bacterial skin and skin structure infections. Trial NCT03137173. https://clinicaltrials.gov/ct2/show/NCT03137173. Accessed August 31, 2019.
33. ClinicalTrials.gov. 2019. Ceftobiprole in the treatment of patients with Staphylococcus aureus bacteremia. Trial NCT03138733. https://clinicaltrials.gov/ct2/show/NCT03138733. Accessed August 30, 2019.
34. Fuhrmeister AS, Jones RN. 2019. The importance of antimicrobial resistance monitoring worldwide and the origins of SENTRY Antimicrobial Surveillance Program. Open Forum Infect Dis 6(Suppl 1):S1–S4. https://doi.org/10.1093/ofid/ofy346.
35. Castanheira M, Deshpande LM, Mendes RE, Canton R, Sader HS, Jones RN. 2019. Variations in the occurrence of resistance phenotypes and carbapenemase genes among *Enterobacteriaceae* isolates in 20 years of the SENTRY Antimicrobial Surveillance Program. Open Forum Infect Dis 6(Suppl 1):S23–S33. https://doi.org/10.1093/ofid/ofy347.
36. Clinical and Laboratory Standards Institute. 2019. Performance standards for antimicrobial susceptibility testing: 29th informational supplement: M100Ed29. Clinical and Laboratory Standards Institute, Wayne, PA.
37. Clinical and Laboratory Standards Institute. 2018. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition: M07Ed11. Clinical and Laboratory Standards Institute, Wayne, PA.
38. European Committee on Antimicrobial Susceptibility Testing. 2019. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, January 2019. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf. Accessed January 2019.
39. U.S. Food and Drug Administration. 2019. Antibacterial susceptibility test interpretive criteria. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. Accessed 05 May 2019.