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Ceftobiprole Activity against over 60,000 Clinical Bacterial Pathogens Isolated in Europe, Turkey, and Israel from 2005 to 2010

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Ceftobiprole medocaril is a newly approved drug in Europe for the treatment of hospital-acquired pneumonia (HAP) (excluding patients with ventilator-associated pneumonia but including ventilated HAP patients) and community-acquired pneumonia in adults. The aim of this study was to evaluate the *in vitro* antimicrobial activity of ceftobiprole against prevalent Gram-positive and -negative pathogens isolated in Europe, Turkey, and Israel during 2005 through 2010. A total of 60,084 consecutive, nonduplicate isolates from a wide variety of infections were collected from 33 medical centers. Species identification was confirmed, and all isolates were susceptibility tested using reference broth microdilution methods. Ceftobiprole had high activity against methicillin-susceptible *Staphylococcus aureus* (MSSA) (100.0% susceptible), methicillin-susceptible coagulase-negative staphylococci (CoNS), beta-hemolytic streptococci, and *Streptococcus pneumoniae* (99.3% susceptible), with MIC_{90} values of 0.25, 0.12, ≤0.06, and 0.5 μg/ml, respectively. Ceftobiprole was active against methicillin-resistant *S. aureus* (MRSA) (98.3% susceptible) and methicillin-resistant CoNS, having a MIC_{90} of 2 μg/ml. Ceftobiprole was active against *Enterococcus faecalis* ($MIC_{50/90}$, 0.5/4 μg/ml) but not against most *Enterococcus faecium* isolates. Ceftobiprole was very potent against the majority of *Enterobacteriaceae* (87.3% susceptible), with >80% inhibited at ≤0.12 μg/ml. The potency of ceftobiprole against *Pseudomonas aeruginosa* ($MIC_{50/90}$, 2/>8 μg/ml; 64.6% at MIC values of ≤4 μg/ml) was similar to that of ceftazidime ($MIC_{50/90}$, 2/>16 μg/ml; 75.4% susceptible), but limited activity was observed against *Acinetobacter* spp. and *Stenotrophomonas maltophilia*. High activity was also observed against all *Haemophilus influenzae* (MIC_{90}, ≤0.06 μg/ml) and *Moraxella catarrhalis* ($MIC_{50/90}$, ≤0.06/0.25 μg/ml) isolates. Ceftobiprole demonstrated a wide spectrum of antimicrobial activity against this very large longitudinal sample of contemporary pathogens.

Ceftobiprole medocaril (BAL5788, formerly Ro-65-5788) is the prodrug form of ceftobiprole (BAL9141, formerly Ro-63-9141), which is an extended-spectrum anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) parenteral cephalosporin with potent activity against Gram-positive and -negative bacterial pathogens. Ceftobiprole has been evaluated in several phase III clinical trials focusing on skin and skin structure infections (SSSI) (1, 2), community-acquired pneumonia (CAP) requiring hospitalization (3), and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) (4), and has recently obtained regulatory approval in Europe for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults. Ceftobiprole is relatively stable toward AmpC β-lactamases and has a strong affinity for penicillin binding proteins (PBPs), including PBP 2A, which mediates resistance to β-lactams in MRSA and methicillin (oxacillin)-resistant coagulase-negative staphylococci (CoNS) (5). PBP assay experiments have confirmed the remarkably high affinity of ceftobiprole to PBP 2A and showed that this β-lactam in low concentrations was also able to saturate PBPs 1, 3, and 4, a new property not shared by other β-lactams (6). Ceftobiprole also has high affinity against *Streptococcus pneumoniae* PBP 2x in penicillin-resistant and ceftriaxone-resistant strains and retains good *in vitro* activity against them (7, 8). In time-kill analysis, ceftobiprole was bactericidal against community-acquired and hospital-acquired MRSA strains (9).

Ceftobiprole also displays potent activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates that is similar to those of advanced-generation cephalosporins such as cefepime (10–13). In addition, ceftobiprole has demonstrated activity against *Haemophilus influenzae*, *Moraxella catarrhalis* (7), and *Enterococcus faecalis* (8). These characteristics make ceftobiprole an attractive therapeutic candidate, given its broad spectrum (including MRSA and penicillin-resistant *S. pneumoniae*) and its potent bactericidal action.

The objective of the current study was to examine the susceptibility profiles and antibiograms of ceftobiprole and comparator agents tested by a standardized reference methodology against 60,084 clinical isolates collected during the years 2005 through 2010 from European region medical centers, Turkey, and Israel.

MATERIALS AND METHODS

Bacterial strains tested. From the ceftobiprole SENTRY Antibiotic Surveillance Program in Europe (2005 to 2010), a total of 60,084 nonduplicate, consecutive clinical isolates were submitted from 33 medical centers in the following countries (number of sites): Belgium (1), France (5), Germany (4), Greece (2), Ireland (2), Israel (1), Italy (3), Poland (1), Portugal (1), Russia (2), Spain (3), Sweden (2), Switzerland (1), Turkey (2), the United Kingdom (2), and Ukraine (1). All organisms were isolated from documented infections, and only one strain per patient infection episode was included in the surveillance collection. The isolates were derived primarily from hospitalized pa-

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TABLE 1 Frequency of occurrence and cumulative percent distribution of ceftobiprole MICs for all European organisms tested (2005 to 2010)

Organism(s) (no. of isolates tested)	No. (cumulative %) of isolates inhibited at a ceftobiprole MIC (μg/ml) of:									MIC_{50}	MIC_{90}
	≤0.06	0.12	0.25	0.5	1	2	4	8	>8		
Gram-positive bacteria											
Staphylococcus aureus (15,426)	30 (0.2)	163 (1.3)	6,338 (42.3)	5,302 (76.7)	2,372 (92.1)	1,149 (99.5)	72 (100.0)			0.5	1
MSSA (11,279)	30 (0.3)	162 (1.7)	6,316 (57.7)	4,738 (99.7)	29 (100.0)	4 (100.0)				0.25	0.5
MRSA (4,147)	0 (0.0)	1 (0.0)	22 (0.6)	564 (14.2)	2,343 (70.7)	1,145 (98.3)	72 (100.0)			1	2
Coagulase-negative staphylococci (5,563)	236 (4.2)	650 (15.9)	624 (27.1)	1,191 (48.6)	1,757 (80.1)	721 (93.1)	383 (100.0)	1 (100.0)		1	2
Methicillin-susceptible CoNS (1,317)	209 (15.9)	616 (62.6)	455 (97.2)	35 (99.8)	2 (100.0)					0.12	0.25
Methicillin-resistant CoNS (4,246)	27 (0.6)	34 (1.4)	169 (5.4)	1,156 (32.6)	1,755 (74.0)	721 (91.0)	383 (100.0)	1 (100.0)		1	2
Streptococcus pneumoniae (4,443)	3,428 (77.2)	109 (79.6)	369 (87.9)	508 (99.3)	23 (99.9)	6 (100.0)				≤0.06	0.5
Penicillin susceptible (4,223)	3,427 (81.2)	108 (83.7)	356 (92.1)	325 (99.8)	7 (100.0)					≤0.06	0.25
Penicillin nonsusceptible (217)	1 (0.5)	1 (0.9)	13 (6.8)	183 (90.0)	16 (97.3)	6 (100.0)				0.5	0.5
Penicillin intermediate (209)	1 (0.5)	1 (1.0)	13 (7.2)	179 (92.8)	12 (98.6)	3 (100.0)				0.5	0.5
Penicillin resistant (11)	0 (0.0)	0 (0.0)	0 (0.0)	4 (36.4)	4 (72.7)	3 (100.0)				1	2
Ceftriaxone nonsusceptible (202)	0 (0.0)	1 (0.5)	4 (2.5)	168 (85.6)	23 (97.0)	6 (100.0)				0.5	1
Ceftriaxone resistant (20)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	12 (75.0)	5 (100.0)				1	2
Beta-hemolytic streptococci (2,981)	2,957 (99.2)	22 (99.9)	2 (100.0)							≤0.06	≤0.06
S. pyogenes (1,170)	1,167 (99.7)	2 (99.9)	1 (100.0)							≤0.06	≤0.06
S. agalactiae (1,227)	1,222 (99.6)	4 (99.9)	1 (100.0)							≤0.06	≤0.06
Viridans group streptococci (1,264)	929 (73.5)	173 (87.2)	65 (92.3)	23 (94.1)	20 (95.7)	22 (97.5)	9 (98.2)	4 (98.5)	19 (100.0)	≤ 0.06	0.25
Enterococcus spp. (6,395)	37 (0.6)	476 (8.0)	883 (21.8)	1,321 (42.5)	374 (48.3)	634 (58.2)	401 (64.5)	145 (66.8)	2,124 (100.0)	2	>8
Enterococcus faecalis (3,968)	31 (0.8)	466 (12.5)	860 (34.2)	1,259 (65.9)	316 (73.9)	527 (87.2)	348 (95.9)	118 (98.9)	43 (100.0)	0.5	4
Enterococcus faecium (2,222)	0 (0.0)	5 (0.2)	3 (0.4)	4 (0.5)	24 (1.6)	71 (4.8)	45 (6.8)	16 (7.6)	2,054 (100.0)	>8	>8
Other enterococci (205)	6 (2.9)	5 (5.4)	20 (15.1)	58 (43.4)	34 (60.0)	36 (77.6)	8 (81.5)	11 (86.8)	27 (100.0)	1	>8
Gram-negative bacteria											
Enterobacteriaceae (17,480)	13,398 (76.6)	803 (81.2)	374 (83.4)	243 (84.8)	159 (85.7)	154 (86.6)	132 (87.3)	99 (87.9)	2,118 (100.0)	≤0.06	>8
Escherichia coli (9,609)	8,194 (85.3)	272 (88.1)	100 (89.1)	48 (89.6)	26 (89.9)	26 (90.2)	24 (90.4)	20 (90.6)	899 (100.0)	≤0.06	2
ESBL[a] phenotype (1,089)	73 (6.7)	16 (8.2)	23 (10.3)	12 (11.4)	14 (12.7)	19 (14.4)	24 (16.6)	19 (18.4)	889 (100.0)	>8	>8
Non-ESBL phenotype (8,520)	8,121 (95.3)	256 (98.3)	77 (99.2)	36 (99.7)	12 (99.8)	7 (99.9)	0 (99.9)	1 (99.9)	10 (100.0)	≤0.06	≤0.06
Klebsiella pneumoniae (2,625)	1,760 (67.0)	93 (70.6)	46 (72.3)	32 (73.6)	27 (74.6)	16 (75.2)	10 (75.6)	16 (76.2)	625 (100.0)	≤0.06	>8
ESBL phenotype (703)	14 (2.0)	7 (3.0)	7 (4.0)	7 (5.0)	16 (7.3)	16 (9.5)	10 (11.0)	16 (13.2)	610 (100.0)	>8	>8
Non-ESBL phenotype (1,922)	1,746 (90.8)	86 (95.3)	39 (97.4)	25 (98.7)	11 (99.2)	0 (99.2)	0 (99.2)	0 (99.2)	15 (100.0)	≤0.06	≤0.06
Proteus mirabilis (733)	666 (90.9)	13 (92.6)	7 (93.6)	4 (94.1)	3 (94.5)	1 (94.7)	0 (94.7)	3 (95.1)	36 (100.0)	≤0.06	≤0.06
Enterobacter spp. (1,909)	1,237 (64.8)	118 (71.0)	54 (73.8)	42 (76.0)	35 (77.8)	77 (81.9)	79 (86.0)	46 (88.4)	221 (100.0)	≤0.06	>8
Citrobacter spp. (414)	301 (72.7)	15 (76.3)	6 (77.8)	14 (81.2)	23 (86.7)	20 (91.5)	5 (92.8)	4 (93.7)	26 (100.0)	≤0.06	2
Serratia spp. (711)	405 (57.0)	140 (76.7)	51 (83.8)	46 (90.3)	23 (93.5)	8 (94.7)	7 (95.6)	4 (96.2)	27 (100.0)	≤0.06	0.5
Indole-positive *Proteus* spp. (479)	357 (74.5)	2 (74.9)	2 (75.4)	2 (75.8)	0 (75.8)	0 (75.8)	1 (76.0)	3 (76.6)	112 (100.0)	≤0.06	>8
Pseudomonas aeruginosa (3,434)	2 (0.1)	4 (0.2)	11 (0.5)	113 (3.8)	826 (27.8)	806 (51.3)	458 (64.6)	489 (78.9)	725 (100.0)	2	>8
Ceftazidime susceptible (2,588)	2 (0.1)	3 (0.2)	11 (0.6)	112 (4.9)	812 (36.3)	761 (65.7)	327 (78.4)	325 (90.9)	235 (100.0)	2	8
Ceftazidime nonsusceptible (846)	0 (0.0)	1 (0.1)	0 (0.1)	1 (0.2)	14 (1.9)	45 (7.2)	131 (22.7)	164 (42.1)	490 (100.0)	>8	>8
Acinetobacter spp. (1,146)	59 (5.1)	37 (8.4)	96 (16.8)	85 (24.2)	45 (28.1)	18 (29.7)	12 (30.7)	8 (31.4)	786 (100.0)	>8	>8
Stenotrophomonas maltophilia (420)	0 (0.0)	1 (0.2)	0 (0.2)	0 (0.2)	0 (0.2)	0 (0.2)	0 (0.2)	2 (0.7)	417 (100.0)	>8	>8
Haemophilus influenzae (2,052)	1,965 (95.8)	76 (99.5)	8 (99.9)	3 (100.0)						≤0.06	≤0.06
Moraxella catarrhalis (200)	107 (53.5)	70 (88.5)	20 (98.5)	3 (100.0)						≤0.06	0.25

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

tients with bloodstream infections, SSSI, pneumonias, urinary tract infections, and intra-abdominal infections, according to a common surveillance design (14). Species identification was performed at the participant medical center and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) using the Vitek 2 System (bioMérieux, Hazelwood, MO, USA), when necessary.

Susceptibility testing methods. All isolates were tested by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A9, 2012) (15) using validated commercially prepared panels (Thermo Fisher Scientific, Cleveland, OH, USA) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of fastidious streptococci or *Haemophilus* test medium [HTM] for testing of *H. influenzae*) against ceftobiprole and comparator antimicrobial agents. Susceptibility interpretations were based upon the CLSI M100-S23 and EUCAST breakpoints (16, 17) and the EUCAST breakpoints recently established for ceftobiprole for *S. aureus* (susceptible, ≤2 μg/ml; resistant, >2 μg/ml), *S. pneumoniae* (susceptible, ≤0.5 μg/ml; resistant, >0.5 μg/ml), and *Enterobacteriaceae* (susceptible, ≤0.25 μg/ml; resistant, >0.25 μg/ml) and non-species-specific breakpoints (susceptible, ≤4 μg/ml; resistant, >4 μg/ml) (18). Concurrent testing of ATCC quality control (QC) strains included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and ATCC 35218, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247. All QC results were observed to be within published limits (16, 19).

RESULTS

Ceftobiprole activity against staphylococci. Ceftobiprole was very active against 15,426 *S. aureus* isolates ($MIC_{50/90}$, 0.5/1 μg/ml; all MIC results at ≤4 μg/ml; 99.5% susceptible) (Tables 1 and 2). Ceftobiprole ($MIC_{50/90}$, 0.25/0.5 μg/ml) was at least 16-fold more potent than ceftriaxone ($MIC_{50/90}$, 4/>8 μg/ml) when tested against methicillin-susceptible *S. aureus* (MSSA) (Table 2). All *S. aureus* isolates were susceptible to vancomycin ($MIC_{50/90}$, 1/1 μg/ml), and >99.9% of isolates were susceptible to linezolid ($MIC_{50/90}$, 1/2 μg/ml), tigecycline ($MIC_{50/90}$, 0.12/0.25 μg/ml), and daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/ml) (Table 2). Among 11,279 MSSA isolates, the ceftobiprole susceptibility rate was 100.0% (Table 2). Overall, 4,147 (26.9%) isolates were MRSA, and ceftobiprole was very active against most strains ($MIC_{50/90}$, 1/2 μg/ml; 98.3% susceptible), with a potency most similar to those of vancomycin ($MIC_{50/90}$, 1/1 μg/ml) and linezolid ($MIC_{50/90}$, 1/2 μg/ml) (Table 2). High resistance rates among MRSA were observed for levofloxacin (88.6%), erythromycin (68.0%), and clindamycin (35.6/35.8%) (CLSI/EUCAST criteria), with lower rates observed for gentamicin (21.4/23.8%) and tetracycline (14.7/16.3%), while trimethoprim-sulfamethoxazole resistance was minimal (2.7%) (Table 2).

TABLE 2 Antimicrobial activities of ceftobiprole and comparator agents when tested against bacterial isolates from European medical centers (2005 to 2010)

Organism (no. of isolates tested) and antimicrobial agent	MIC			% of isolates susceptible/intermediate/resistant[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
S. aureus (15,426)					
Ceftobiprole	0.5	1	≤0.06–4	—[b]/—/—	99.5/0.0/0.5
Oxacillin	0.5	>2	≤0.25–>2	73.1/0.0/26.9	73.1/0.0/26.9
Cefepime	2	>16	≤0.12–>16	73.1/0.0/26.9	73.1/0.0/26.9
Ceftriaxone	4	>8	≤0.25–>8	73.1/0.0/26.9	73.1/0.0/26.9
Imipenem	≤0.12	8	≤0.12–>8	73.1/0.0/26.9	73.1/0.0/26.9
Clindamycin	≤0.25	>2	≤0.25–>2	88.6/0.1/11.3	88.1/0.5/11.4
Erythromycin	≤0.25	>2	≤0.25–>2	70.5/0.9/28.6	71.0/0.3/28.7
Daptomycin	0.25	0.5	≤0.06–2	>99.9/—/—	>99.9/0.0/<0.1
Gentamicin	≤2	≤2	≤2–>8	92.5/0.5/7.0	91.9/0.0/8.1
Levofloxacin	≤0.5	>4	≤0.5–>4	71.6/0.6/27.8	71.6/0.6/27.8
Linezolid	1	2	≤0.12–>8	>99.9/0.0/<0.1	>99.9/0.0/<0.1
Tetracycline	≤2	≤2	≤2–>8	91.7/0.6/7.7	91.4/0.0/8.6
Tigecycline[c]	0.12	0.25	≤0.03–1	>99.9/—/—	>99.9/0.0/<0.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	99.0/0.0/1.0	99.0/<0.1/1.0
Vancomycin	1	1	≤0.12–2	100.0/0.0/0.0	100.0/0.0/0.0
Oxacillin-susceptible *S. aureus* (11,279)					
Ceftobiprole	0.25	0.5	≤0.06–2	—/—/—	100.0/0.0/0.0
Cefepime	2	4	≤0.12–16	100.0/0.0/0.0	100.0/0.0/0.0
Ceftriaxone	4	4	≤0.25–>8	100.0/0.0/0.0	100.0/0.0/0.0
Imipenem	≤0.12	≤0.12	≤0.12–2	100.0/0.0/0.0	100.0/0.0/0.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	97.5/0.1/2.4	97.1/0.4/2.5
Erythromycin	≤0.25	>2	≤0.25–>2	85.1/0.8/14.1	85.4/0.4/14.2
Daptomycin	0.25	0.5	≤0.06–1	100.0/—/—	100.0/0.0/0.0
Gentamicin	≤2	≤2	≤2–>8	98.1/0.2/1.7	97.7/0.0/2.3
Levofloxacin	≤0.5	≤0.5	≤0.5–>4	94.1/0.4/5.5	94.1/0.4/5.5
Linezolid	1	2	≤0.12–2	100.0/0.0/0.0	100.0/0.0/0.0
Tetracycline	≤2	≤2	≤2–>8	94.5/0.4/5.1	94.2/<0.1/5.8
Tigecycline[c]	0.12	0.25	≤0.03–0.5	100.0/—/—	100.0/0.0/0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	99.6/0.0/0.4	99.6/<0.1/0.4
Vancomycin	1	1	≤0.12–2	100.0/0.0/0.0	100.0/0.0/0.0
Oxacillin-resistant *S. aureus* (4,147)					
Ceftobiprole	1	2	0.12–4	—/—/—	98.3/0.0/1.7
Clindamycin	≤0.25	>2	≤0.25–>2	64.2/0.2/35.6	63.6/0.6/35.8
Erythromycin	>2	>2	≤0.25–>2	30.9/1.1/68.0	31.6/0.4/68.0
Daptomycin	0.25	0.5	≤0.06–2	>99.9/—/—	>99.9/0.0/<0.1
Gentamicin	≤2	>8	≤2–>8	77.2/1.4/21.4	76.2/0.0/23.8
Levofloxacin	>4	>4	≤0.5–>4	10.4/1.0/88.6	10.4/1.0/88.6
Linezolid	1	2	0.25–>8	>99.9/0.0/<0.1	>99.9/0.0/<0.1
Tetracycline	≤2	>8	≤2–>8	84.0/1.3/14.7	83.6/0.1/16.3
Tigecycline[c]	0.12	0.25	≤0.03–1	>99.9/—/—	>99.9/0.0/<0.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	97.3/0.0/2.7	97.3/0.0/2.7
Vancomycin	1	1	≤0.12–2	100.0/0.0/0.0	100.0/0.0/0.0
Coagulase-negative staphylococci (5,563)[d]					
Ceftobiprole	1	2	≤0.06–8	—/—/—	—/—/—
Oxacillin	>2	>2	≤0.25–>2	23.7/0.0/76.3	23.7/0.0/76.3
Cefepime	4	>16	≤0.12–>16	23.7/0.0/76.3	23.7/0.0/76.3
Ceftriaxone	>8	>8	≤0.25–>8	23.7/0.0/76.3	23.7/0.0/76.3
Imipenem	0.25	>8	≤0.12–>8	23.7/0.0/76.3	23.7/0.0/76.3
Clindamycin	≤0.25	>2	≤0.25–>2	71.6/1.0/27.4	69.1/2.5/28.4
Erythromycin	>2	>2	≤0.25–>2	36.3/0.3/63.4	36.4/0.2/63.4
Daptomycin	0.25	0.5	≤0.06–4	99.8/—/—	99.8/0.0/0.2
Gentamicin	≤2	>8	≤2–>8	58.8/8.2/33.0	52.2/0.0/47.8
Levofloxacin	4	>4	≤0.5–>4	42.3/4.8/52.9	42.3/4.8/52.9
Linezolid	1	1	≤0.12–>8	99.8/0.0/0.2	99.8/0.0/0.2
Tetracycline	≤2	>8	≤2–>8	84.4/1.4/14.2	79.8/1.4/18.8
Tigecycline[c]	0.12	0.25	≤0.03–0.5	—/—/—	100.0/0.0/0.0
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5–>2	60.9/0.0/39.1	60.9/1.8/37.3
Vancomycin	1	2	≤0.12–4	100.0/0.0/0.0	100.0/0.0/0.0
Enterococcus faecalis (3,968)					
Ceftobiprole	0.5	4	≤0.06–>8	—/—/—	—/—/—
Ampicillin	≤1	2	≤1–>16	99.6/0.0/0.4	99.4/0.2/0.4
Daptomycin	1	1	≤0.06–4	100.0/—/—	—/—/—
Levofloxacin	1	>4	≤0.5–>4	65.4/0.6/34.0	—/—/—
Linezolid	1	2	0.12–>8	99.8/0.1/0.1	99.8/0.1/0.1
Tigecycline[c]	0.12	0.25	≤0.03–1	99.9/—/—	99.9/0.1/<0.1

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TABLE 2 (Continued)

Organism (no. of isolates tested) and antimicrobial agent	MIC			% of isolates susceptible/intermediate/resistant[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Teicoplanin	≤2	≤2	≤2–>8	99.1/<0.1/0.9	99.0/0.0/1.0
Vancomycin	1	2	0.25–>16	98.7/0.1/1.2	98.7/0.0/1.3
Enterococcus faecium (2,222)					
Ceftobiprole	>8	>8	0.12–>8	—/—/—	—/—/—
Ampicillin	>8	>8	≤1–>8	7.1/0.0/92.9	6.4/0.7/92.9
Daptomycin	2	2	≤0.06–4	100.0/—/—	—/—/—
Levofloxacin	>4	>4	≤0.5–>4	12.7/4.5/82.8	—/—/—
Linezolid	1	2	0.25–>8	99.6/0.2/0.2	99.8/0.0/0.2
Tigecycline[c]	0.06	0.12	≤0.03–0.5	99.9/0.1/—	99.9/0.1/0.0
Teicoplanin	≤2	>8	≤2–>8	81.0/1.5/17.5	79.8/0.0/20.2
Vancomycin	1	>16	≤0.12–>16	75.3/1.5/23.2	75.3/0.0/24.7
Streptococcus pneumoniae (4,443)					
Ceftobiprole	≤0.06	0.5	≤0.06–2	—/—/—	99.3/0.0/0.7
Penicillin[e]	≤0.03	2	≤0.03–>4	95.0/4.8/0.2	—/—/—
Penicillin[f]	≤0.03	2	≤0.03–>4	71.1/12.0/16.9	71.1/23.9/5.0
Amoxicillin-clavulanate	≤1	2	≤1–>16	93.9/3.1/3.0	—/—/—
Cefepime	≤0.12	1	≤0.12–16	95.7/4.0/0.3	95.7/4.0/0.3
Ceftriaxone	≤0.25	1	≤0.25–32	95.5/4.0/0.5	83.5/16.0/0.5
Erythromycin	≤0.25	>2	≤0.25–>2	69.0/0.4/30.6	69.0/0.4/30.6
Clindamycin	≤0.25	>1	≤0.25–>1	79.1/0.6/20.3	79.7/0.0/20.3
Levofloxacin	1	1	≤0.5–>4	98.3/0.2/1.5	98.3/0.0/1.7
Linezolid	1	1	≤0.12–2	100.0/—/—	100.0/0.0/0.0
Tetracycline	≤2	>8	≤2–>8	74.4/1.2/24.4	74.4/<0.1/25.6
Tigecycline[c]	≤0.03	0.06	≤0.03–1	91.0/—/—	—/—/—
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5–>2	70.2/11.0/18.8	77.1/4.1/18.8
Vancomycin	1	1	≤1–1	100.0/—/—	100.0/0.0/0.0
β-Hemolytic streptococci (2,981)[g]					
Ceftobiprole	≤0.06	≤0.06	≤0.06–0.25	—/—/—	—/—/—
Penicillin	≤0.03	0.06	≤0.03–0.12	100.0/—/—	100.0/0.0/0.0
Cefepime	≤0.12	≤0.12	≤0.12–2	99.9/—/—	100.0/0.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25–4	99.9/—/—	100.0/0.0/0.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	91.9/0.5/7.6	92.4/0.0/7.6
Erythromycin	≤0.25	>2	≤0.25–>2	82.0/1.0/17.0	82.0/1.0/17.0
Daptomycin	≤0.06	0.25	≤0.06–0.5	100.0/—/—	100.0/0.0/0.0
Levofloxacin	≤0.5	1	≤0.5–>4	99.6/0.0/0.4	95.6/4.0/0.4
Linezolid	1	1	0.25–2	100.0/—/—	100.0/0.0/0.0
Tetracycline	4	>8	≤2–>8	49.5/2.6/47.9	49.3/0.2/50.5
Tigecycline[c]	≤0.03	0.06	≤0.03–0.5	>99.9/—/—	>99.9/<0.1/0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	—/—/—	99.0/0.4/0.6
Vancomycin	0.25	0.5	≤0.12–1	100.0/—/—	100.0/0.0/0.0
Viridans group streptococci (1,264)[h]					
Ceftobiprole	≤0.06	0.25	≤0.06–>8	—/—/—	—/—/—
Penicillin	0.06	1	≤0.03–>4	77.5/17.0/5.5	84.3/10.2/5.5
Cefepime	≤0.12	1	≤0.12–>16	92.1/3.4/4.5	88.1/0.0/11.9
Ceftriaxone	≤0.25	1	≤0.25–>8	92.2/3.2/4.6	88.8/0.0/11.2
Daptomycin	0.25	0.5	≤0.06–2	99.8/—/—	—/—/—
Clindamycin	≤0.25	>2	≤0.25–>2	88.0/0.3/11.7	88.3/0.0/11.7
Erythromycin	≤0.25	>2	≤0.25–>2	61.6/2.2/36.2	—/—/—
Levofloxacin	1	2	≤0.5–>4	96.8/1.1/2.1	—/—/—
Linezolid	1	1	≤0.12–2	100.0/—/—	—/—/—
Tetracycline	≤2	>8	≤2–>8	62.2/2.2/35.6	—/—/—
Tigecycline[c]	≤0.03	0.06	≤0.03–0.5	99.9/—/—	—/—/—
Vancomycin	0.5	1	≤0.12–1	100.0/—/—	100.0/0.0/0.0
Enterobacteriaceae (17,480)[i]					
Ceftobiprole	≤0.06	>8	≤0.06–>8	—/—/—	83.4/0.0/16.6
Ampicillin	>8	>8	≤1–>8	28.5/3.8/67.7	28.5/0.0/71.5
Amoxicillin-clavulanate	8	>8	≤1–>8	62.6/10.9/26.5	62.6/0.0/37.4
Piperacillin-tazobactam	2	32	≤0.5–>64	88.0/5.9/6.1	84.3/3.7/12.0
Cefepime	≤0.5	2	≤0.5–>16	93.1/1.6/5.3	88.2/3.5/8.3
Ceftazidime	≤1	16	≤1–>16	87.6/1.8/10.6	83.5/4.1/12.4
Imipenem	0.25	1	≤0.12–>8	94.4/3.8/1.8	98.2/1.4/0.4
Aztreonam	≤0.12	16	≤0.12–>16	86.6/2.1/11.3	83.6/5.1/11.3
Colistin	≤0.5	>4	≤0.5–>4	—/—/—	87.3/0.0/12.7
Amikacin	≤4	≤4	≤4–>32	98.5/0.8/0.7	96.9/1.6/1.5
Gentamicin	≤2	8	≤2–>8	89.7/0.8/9.5	88.7/1.0/10.3
Levofloxacin	≤0.5	>4	≤0.5–>4	80.9/2.6/16.5	79.3/1.6/19.1

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TABLE 2 (Continued)

Organism (no. of isolates tested) and antimicrobial agent	MIC			% of isolates susceptible/intermediate/resistant[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Tetracycline	≤2	>8	≤2–>8	62.0/3.1/34.9	—/—/—
Tigecycline[c]	0.25	1	≤0.03–>4	98.7/1.2/0.1	95.0/3.7/1.3
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5–>2	71.9/0.0/28.1	71.9/22.4/5.7
Acinetobacter spp. (1,146)[j]					
Ceftobiprole	>8	>8	≤0.06–>8	—/—/—	—/—/—
Cefepime	16	>16	≤0.12–>16	36.5/14.1/49.4	—/—/—
Ceftazidime	>16	>16	≤1–>16	29.4/7.5/63.1	—/—/—
Piperacillin-tazobactam	>64	>64	≤0.5–>64	34.3/0.0/65.7	—/—/—
Imipenem	2	>8	≤0.12–>8	53.9/2.6/43.5	50.7/5.8/43.5
Aztreonam	>16	>16	≤0.12–>16	8.2/15.9/75.9	—/—/—
Colistin	≤0.5	1	≤0.5–>4	98.7/0.0/1.3	98.7/0.0/1.3
Amikacin	>32	>32	≤4–>32	42.7/3.6/53.7	40.5/2.2/57.3
Gentamicin	>8	>8	≤2–>8	35.8/3.2/61.0	35.8/0.0/64.2
Levofloxacin	>4	>4	≤0.5–>4	31.8/8.7/59.5	29.8/2.0/68.2
Tetracycline	>8	>8	≤2–>8	38.6/6.1/55.3	—/—/—
Trimethoprim-sulfamethoxazole	>2	>2	≤0.5–>2	37.0/0.0/63.0	37.0/53.7/9.3
Pseudomonas aeruginosa (3,434)					
Ceftobiprole	2	>8	≤0.06–>8	—/—/—	64.6[k]/—/35.4
Cefepime	4	16	≤0.12–>16	78.6/11.7/9.7	78.6/0.0/21.4
Ceftazidime	2	>16	≤1–>16	75.4/5.2/19.4	75.4/0.0/24.6
Piperacillin-tazobactam	8	>64	≤0.5–>64	72.4/11.1/16.5	72.4/0.0/27.6
Imipenem	2	>8	≤0.12–>8	70.2/4.8/25.0	75.0/7.8/17.2
Aztreonam	8	>16	≤0.12–>16	66.6/13.7/19.7	3.4/76.9/19.7
Colistin	1	2	≤0.5–>4	99.5/0.3/0.2	99.5/0.0/0.5
Amikacin	≤4	16	≤4–>32	91.2/3.3/5.5	86.2/5.0/8.8
Gentamicin	≤2	>8	≤2–>8	78.8/3.1/18.1	78.8/0.0/21.2
Levofloxacin	≤0.5	>4	≤0.5–>4	69.2/5.7/25.1	62.0/7.2/30.8

[a] Criteria as published by the CLSI (2013) (16) and EUCAST (2013) (17) and the EUCAST breakpoints recently established for ceftobiprole for *S. aureus* (susceptible, ≤2 μg/ml; resistant, >2 μg/ml), *S. pneumoniae* (susceptible, ≤0.5 μg/ml; resistant, >0.5 μg/ml), and *Enterobacteriaceae* (susceptible, ≤0.25 μg/ml; resistant, >0.25 μg/ml) and non-species-specific breakpoints (susceptible, ≤4 μg/ml; resistant, >4 μg/ml) (18).

[b] —, no breakpoint has been established.

[c] U.S. FDA breakpoints (26) were applied as CLSI criteria.

[d] Includes *S. auricularis* (16 strains), *S. capitis* (201 strains), *S. caprae* (six strains), *S. carnosus* (one strain), *S. chromogenes* (four strains), *S. cohnii* (12 strains), *S. epidermidis* (2,673 strains), *S. haemolyticus* (467 strains), *S. hominis* (492 strains), *S. intermedius* (six strains), *S. lentus* (three strains), *S. lugdunensis* (92 strains), *S. saprophyticus* (67 strains), *S. schleiferi* (nine strains), *S. sciuri* (12 strains), *S. simulans* (25 strains), *S. succinus* (one strain), *S. warneri* (115 strains), *S. xylosus* (79 strains), *Staphylococcus* of undetermined species (two strains), and coagulase-negative staphylococci of undetermined species (1,280 strains).

[e] Criteria as published by the CLSI (2013) (16) for "penicillin parenteral (nonmeningitis)."

[f] Criteria as published by the CLSI (2013) (16) for "penicillin (oral penicillin V)."

[g] Includes *S. dysgalactiae* (126 strains), *S. equi* (three strains), *S. equisimilis* (13 strains), *S. pyogenes* (1,170 strains), *S. agalactiae* (1,227 strains), group C *Streptococcus* (108 strains), group F *Streptococcus* (nine strains), group G *Streptococcus* (320 strains), and beta-hemolytic streptococci of undetermined species (five strains).

[h] Includes *S. acidominimus* (four strains), *S. alactolyticus* (one strain), *S. anginosus* (155 strains), *S. anginosus* group (57 strains), *S. bovis* group (103 strains), *S. canis* (one strain), *S. constellatus* (53 strains), *S. equinus* (eight strains), *S. gallolyticus* (22 strains), *S. gordonii* (12 strains), *S. infantis* (one strain), *S. intermedius* (27 strains), *S. mitis* group (218 strains), *S. mutans* (nine strains), *S. oralis* (134 strains), *S. parasanguinis* (39 strains), *S. porcinus* (one strain), *S. salivarius* (75 strains), *S. sanguinis* (75 strains), *S. sobrinus* (one strain), *S. thermophilus* (two strains), *S. uberis* (three strains), *S. vestibularis* (17 strains), *Streptococcus* of undetermined species (19 strains), alpha-hemolytic streptococci of undetermined species (19 strains), and viridans group streptococci of undetermined species (208 strains).

[i] Includes *Citrobacter amalonaticus* (three strains), *C. braakii* (11 strains), *C. farmeri* (two strains), *C. freundii* (236 strains), *C. koseri* (144 strains), *C. sedlakii* (one strain), *C. youngae* (one strain), *Enterobacter aerogenes* (384 strains), *E. amnigenus* (nine strains), *E. asburiae* (five strains), *E. cancerogenus* (three strains), *E. cloacae* (1,385 strains), *E. gergoviae* (one strain), *E. hormaechei* (two strains), *E. intermedius* (one strain), *E. sakazakii* (six strains), *E. taylorae* (one strain), *Escherichia coli* (9,609 strains), *E. vulneris* (one strain), *Hafnia alvei* (31 strains), *Klebsiella ornithinolytica* (nine strains), *K. oxytoca* (743 strains), *K. ozaenae* (seven strains), *K. planticola* (one strain), *K. pneumoniae* (2,625 strains), *K. terrigena* (two strains), *Leclercia adecarboxylata* (one strain), *Morganella morganii* (284 strains), *Pantoea agglomerans* (12 strains), *Proteus mirabilis* (733 strains), *P. penneri* (two strains), *P. vulgaris* (93 strains), *Providencia alcalifaciens* (1 strain), *P. rettgeri* (16 strains), *P. stuartii* (35 strains), *Rahnella aquatilis* (one strain), *Raoultella ornithinolytica* (two strains), *R. planticola* (one strain), *Salmonella* spp. (152 strains), *Serratia fonticola* (three strains), *S. liquefaciens* (31 strains), *S. marcescens* (637 strains), *S. odorifera* (four strains), *S. plymuthica* (six strains), *S. rubidaea* (one strain), *Shigella sonnei* (two strains), *Yersinia enterocolitica* (four strains), *Citrobacter* of undetermined species (16 strains), *Enterobacter* of undetermined species (112 strains), *Escherichia* of undetermined species (4 strains), *Klebsiella* of undetermined species (20 strains), *Kluyvera* of undetermined species (1 strain), *Morganella* of undetermined species (1 strain), *Pantoea* of undetermined species (4 strains), *Proteus* of undetermined species (32 strains), *Providencia* of undetermined species (17 strains), and *Serratia* of undetermined species (29 strains).

[j] Includes *Acinetobacter baumannii* (925 strains), *A. calcoaceticus* (19 strains), *A. haemolyticus* (eight strains), *A. junii* (three strains), *A. lwoffii* (58 strains), *A. nosocomialis* (one strain), *A. pittii* (seven strains), *A. radioresistens* (one strain), *A. ursingii* (three strains), and *Acinetobacter* of undetermined species (121 strains).

[k] EUCAST non-species-specific breakpoint (18).

Ceftobiprole activity against 5,563 coagulase-negative staphylococci (CoNS) was similar to that found against MRSA and reflects the greater proportion of CoNS than of *S. aureus* isolates that were oxacillin resistant (76.3% versus 26.9%) (Table 1). One notable difference is the much higher overall rate of trimethoprim-sulfamethoxazole resistance observed for CoNS (39.1%) than for *S. aureus* (1.0%) (Table 2).

Ceftobiprole activity against enterococci. Ceftobiprole demonstrated good activity against 3,968 *E. faecalis* isolates ($MIC_{50/90}$, 0.5/4 μg/ml) but was not active against 2,222 *Enterococcus faecium*

isolates (MIC_{50}, >8 μg/ml) (Table 1). This pattern correlated best to ampicillin susceptibility rates (Table 2). Vancomycin resistance was low for *E. faecalis* (1.2/1.3%) (CLSI/EUCAST criteria) but much higher for *E. faecium* (23.2/24.7%). Susceptibility rates of 99 to 100.0% were found for tigecycline, daptomycin, and linezolid tested against both *E. faecalis* and *E. faecium*.

Ceftobiprole activity against *S. pneumoniae*. Ceftobiprole was very active against *S. pneumoniae*, with MIC_{50} and MIC_{90} values of ≤0.06 and 0.5 μg/ml, respectively. All isolates were inhibited at a ceftobiprole MIC of 2 μg/ml or less, and 99.3% were susceptible to ceftobiprole (Tables 1 and 2). Overall, penicillin nonsusceptibility/resistance were 28.9/16.9% by CLSI criteria (16) (for oral penicillin V) and 28.9/5.0% by EUCAST criteria (17). Furthermore, ceftriaxone nonsusceptibility/resistance were 4.5/0.5% by CLSI criteria but 16.5/0.5% by EUCAST criteria; ceftobiprole susceptibility was 85.6% against the 202 ceftriaxone-nonsusceptible strains (Table 2). Erythromycin, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole resistances were 30.6, 20.3, 24.4, and 18.8%, respectively. All isolates were susceptible to linezolid (MIC_{90}, 1 μg/ml), and the majority of isolates were susceptible to levofloxacin (98.3%) (Table 2).

Ceftobiprole activity against other streptococci. Ceftobiprole was very active against all beta-hemolytic streptococci, including 1,170 isolates of *S. pyogenes* and 1,227 isolates of *S. agalactiae*, with a MIC_{50} and a MIC_{90} at ≤0.06 μg/ml. All isolates were inhibited at a ceftobiprole MIC of 0.25 μg/ml or less (Tables 1 and 2). Ceftobiprole ($MIC_{50/90}$, ≤0.06/0.25 μg/ml) was at least 4-fold more active than penicillin ($MIC_{50/90}$, 0.06/1 μg/ml; 22.5% nonsusceptible) and ceftriaxone (MIC_{90}, 1 μg/ml) against 1,264 viridans group streptococci (Table 2).

Ceftobiprole activity against *Enterobacteriaceae* and nonfermentative Gram-negative bacilli. The activity of ceftobiprole against *Enterobacteriaceae* had a bimodal distribution, with 83.4% of isolates being inhibited at a MIC of ≤0.25 μg/ml (the EUCAST susceptibility breakpoint) and 12.7% having MIC values of ≥8 μg/ml (Table 1). Similar potencies and MIC distributions were observed for ceftazidime, cefepime, and ceftriaxone (data not shown). This pattern, shown for all cephalosporin agents tested, is a reflection of their limited activity against extended-spectrum β-lactamase (ESBL) phenotype strains of *E. coli* (11.3%) and *Klebsiella* spp. (26.8%). Ceftobiprole potency against *P. aeruginosa* ($MIC_{50/90}$, 2/>8 μg/ml; 64.6% susceptible by the EUCAST nonspecies-specific susceptibility breakpoint of 4 μg/ml) was similar to those of cefepime ($MIC_{50/90}$, 4/16 μg/ml; 78.6% susceptible) and ceftazidime ($MIC_{50/90}$, 2/>16 μg/ml; 75.4% susceptible) (Table 2). Ceftobiprole had limited activity against *Acinetobacter* spp. (MIC_{50}, >8 μg/ml) and *Stenotrophomonas maltophilia* (MIC_{50}, >8 μg/ml) (Table 1).

Ceftobiprole activity against *H. influenzae* and *M. catarrhalis*. Ceftobiprole was the most potent (MIC_{90}, ≤0.06 μg/ml) antimicrobial agent tested against *H. influenzae*, inhibiting all isolates at ≤0.5 μg/ml (Table 1). Ceftobiprole was also very active against *M. catarrhalis*, inhibiting with $MIC_{50/90}$ values of ≤0.06/0.25 μg/ml, and all isolates were inhibited at MIC values of ≤0.5 μg/ml (Table 1).

DISCUSSION

HAP is associated with significant mortality and has been reported to account for ~25% of all infections in intensive care units (20, 21). Increasing multidrug resistance (MDR) has complicated empirical therapy for patients with HAP and VAP, especially in patients with risk factors for MDR pathogens, often necessitating a combination therapy approach (22). It has been recommended that monotherapy should be used whenever possible to reduce the risk of MDR development and adverse outcomes (22). CAP is a significant cause of morbidity and mortality in developed countries, especially in the elderly, with up to 60% of patients requiring hospitalization (23, 24). Resistance among the CAP pathogens is increasing and of major concern; an analysis of pneumococcal resistance rates in the United States spanning the years 1998 to 2009 demonstrated remarkable increases in nonsusceptibility to commonly used β-lactam agents (25).

In this very large (60,084 isolates) and longitudinal (2005 to 2010) European antimicrobial resistance surveillance study, ceftobiprole showed broad-spectrum activity against Gram-positive and Gram-negative pathogens causative of HAP and CAP. Ceftobiprole demonstrated high potency against staphylococci, including MRSA and methicillin-resistant CoNS. Ceftobiprole was also very potent against all beta-hemolytic and viridans streptococci and demonstrated activity against nearly all *E. faecalis* isolates but not *E. faecium*. The majority of *Enterobacteriaceae* (non-ESBL producing) were also inhibited by ceftobiprole, an activity most like those of cefepime, ceftriaxone, and ceftazidime. Activity against *P. aeruginosa* (64.6% susceptible by the EUCAST nonspecies-specific susceptibility breakpoint of 4 μg/ml) was lower than but similar to those of cefepime (78.6% susceptible) and ceftazidime (75.4% susceptible). Ceftobiprole had more limited activity against *Acinetobacter* spp., *S. maltophilia*, and ESBL phenotypes of *Enterobacteriaceae*, as noted with other marketed broad-spectrum cephalosporins.

Ceftobiprole continues to demonstrate high potency against the causative agents of CAP, with 99.3% of 4,443 *S. pneumoniae* isolates testing susceptible, as well as 2,052 strains of *H. influenzae* inhibited at MIC values of ≤0.5 μg/ml and 200 strains of *M. catarrhalis* inhibited at MIC values of ≤0.5 μg/ml. Ceftobiprole was especially potent against penicillin-susceptible (MIC, ≤2 μg/ml) strains of *S. pneumoniae*, which represented 95.0% of all isolates, and potencies (although lower) were retained against penicillin-resistant and ceftriaxone-resistant strains.

In summary, ceftobiprole exhibited excellent coverage of Gram-positive pathogens, including MRSA, and has a spectrum of activity against Gram-negative bacilli similar to those of third-generation and fourth-generation cephalosporins consistently over a period of 6 years. These *in vitro* results from an extensive European surveillance study evaluating 60,084 organisms confirm a large volume of earlier reports on the broad spectrum of activity of ceftobiprole and hence demonstrate its potential to be utilized as a single agent for the empirical therapy of pneumonia. Clinical data from patients with pneumonia enrolled in large phase III studies have demonstrated that ceftobiprole medocaril is noninferior to the combination of high-dose ceftazidime and linezolid for the treatment of HAP (excluding VAP) (4) and noninferior to high-dose ceftriaxone with or without linezolid for the treatment of CAP requiring hospitalization (3). Ceftobiprole offers a number of advantages in potency, spectrum, and β-lactamase stability compared to currently marketed third-generation cephems and other β-lactams, especially with its enhanced coverage of MDR *S. aureus* and CoNS, including methicillin-resistant strains.

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REFERENCES

1. **Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS.** 2008. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin. Infect. Dis. **46:**647–655. http://dx.doi.org/10.1086/526527.
2. **Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS.** 2008. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by Gram-positive bacteria. Antimicrob. Agents Chemother. **52:**37–44. http://dx.doi.org/10.1128/AAC.00551-07.
3. **Nicholson SC, Welte T, File TM, Strauss RS, Michiels B.** 2012. A randomized, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with our without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalization. Int. J. Antimicrob. Agents **39:**240–246. http://dx.doi.org/10.1016/j.ijantimicag.2011.11.005.
4. **Noel GJ, Strauss R, Shah A, Bagchi P.** 2008. Ceftobiprole versus ceftazidime combined with linezolid for treatment of patients with nosocomial pneumonia. Abstr. 48th Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, DC.
5. **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. http://dx.doi.org/10.1128/AAC.45.3.825-836.2001.
6. **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. http://dx.doi.org/10.1128/AAC.00029-07.
7. **Bogdanovich T, Clark C, Ednie L, Lin G, Smith K, Shapiro S, Appelbaum PC.** 2006. Activities of ceftobiprole, a novel broad-spectrum cephalosporin, against *Haemophilus influenzae* and *Moraxella catarrhalis*. Antimicrob. Agents Chemother. **50:**2050–2057. http://dx.doi.org/10.1128/AAC.00044-06.
8. **Arias CA, Singh KV, Panesso D, Murray BE.** 2007. Time-kill and synergism studies of ceftobiprole against Enterococcus faecalis, including beta-lactamase-producing and vancomycin-resistant isolates. Antimicrob. Agents Chemother. **51:**2043–2047. http://dx.doi.org/10.1128/AAC.00131-07.
9. **Leonard SN, Cheung CM, Rybak MJ.** 2008. Activities of ceftobiprole, linezolid, vancomycin, and daptomycin against community-associated and hospital-associated methicillin-resistant Staphylococcus aureus. Antimicrob. Agents Chemother. **52:**2974–2976. http://dx.doi.org/10.1128/AAC.00257-08.
10. **Deshpande L, Rhomberg PR, Fritsche TR, Sader HS, Jones RN.** 2004. Bactericidal activity of BAL9141, a novel parenteral cephalosporin against contemporary Gram-positive and Gram-negative isolates. Diagn. Microbiol. Infect. Dis. **50:**73–75. http://dx.doi.org/10.1016/j.diagmicrobio.2004.04.011.
11. **Lodise TP, Patel N, Renaud-Mutart A, Gorodecky E, Fritsche TR, Jones RN.** 2008. Pharmacokinetic and pharmacodynamic profile of ceftobiprole. Diagn. Microbiol. Infect. Dis. **61:**96–102. http://dx.doi.org/10.1016/j.diagmicrobio.2008.02.013.
12. **Rossolini GM, Dryden MS, Kozlov RS, Quintana A, Flamm RK, Lauffer JM, Lee E, Morrissey I, CLASS Study Group.** 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. http://dx.doi.org/10.1093/jac/dkq397.
13. **Pillar CM, Aranza MK, Shah D, Sahm DF.** 2008. In vitro activity profile of ceftobiprole, an anti-MRSA cephalosporin, against recent gram-positive and gram-negative isolates of European origin. J. Antimicrob. Chemother. **61:**595–602. http://dx.doi.org/10.1093/jac/dkm492.
14. **Jones RN, Masterton R.** 2001. Determining the value of antimicrobial surveillance programs. Diagn. Microbiol. Infect. Dis. **41:**171–175. http://dx.doi.org/10.1016/S0732-8893(01)00318-2.
15. **Clinical and Laboratory Standards Institute.** 2012. M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 9th ed. Clinical and Laboratory Standards Institute, Wayne, PA.
16. **Clinical and Laboratory Standards Institute.** 2013. M100-S23. Performance standards for antimicrobial susceptibility testing; 23rd informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
17. **EUCAST.** 2013. Breakpoint tables for interpretation of MICs and zone diameters, version 3.1, February 2013. http://www.eucast.org/clinical_breakpoints/.
18. **Zevtera.** 2013. Summary of product characteristics. Basilea Medical Ltd., Basel, Switzerland.
19. **Anderegg TR, Jones RN, Sader HS.** 2004. Quality control guidelines for BAL9141 (RO 63-9141), an investigational cephalosporin, when reference MIC and standardized disk diffusion susceptibility test methods are used. J. Clin. Microbiol. **42:**3356–3358. http://dx.doi.org/10.1128/JCM.42.7.3356-3358.2004.
20. **Torres A, Ferrer M, Badia JR.** 2010. Treatment guidelines and outcomes of hospital-acquired and ventilator-associated pneumonia. Clin. Infect. Dis. **51**(Suppl 1)**:**S48–S53. http://dx.doi.org/10.1086/653049.
21. **Barbier F, Andremont A, Wolff M, Bouadma L.** 2013. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. Curr. Opin. Pulm. Med. **19:**216–228. http://dx.doi.org/10.1097/MCP.0b013e32835f27be.
22. **American Thoracic Society and Infectious Disease Society of America.** 2005. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. **15:**388–416. http://dx.doi.org/10.1164/rccm.200405-644ST.
23. **Sligl WI, Marrie TJ.** 2013. Severe community-acquired pneumonia. Crit. Care Clin. **29:**563–601. http://dx.doi.org/10.1016/j.ccc.2013.03.009.
24. **Blasi F, Mantero M, Santus P, Tarsia P.** 2012. Understanding the burden of pneumococcal disease in adults. Clin. Microbiol. Infect. **18**(Suppl 5)**:**7–14. http://dx.doi.org/10.1111/j.1469-0691.2012.03937.x.
25. **Jones RN, Sader HS, Moet GJ, Farrell DJ.** 2010. Declining antimicrobial susceptibility of *Streptococcus pneumoniae* in the United States: report from the SENTRY Antimicrobial Surveillance Program (1998-2009). Diagn. Microbiol. Infect. Dis. **68:**334–336. http://dx.doi.org/10.1016/j.diagmicrobio.2010.08.024.
26. **Wyeth Pharmeceuticals Inc.** 2012. Tygacil package insert. Wyeth Pharmeceuticals Inc., New York, NY. www.tygacil.com.