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Antimicrobial Activity of Ceftobiprole Tested against Staphylococci and Streptococci from European Countries and Israel (2013)

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ABSTRACT

Objectives: To evaluate the *in vitro* activity of the newly approved parenteral broad-spectrum antimicrobial agent ceftobiprole medocaril against contemporary staphylococci and streptococci from Europe and Israel. Ceftobiprole medocaril was approved in 12 European Union countries (October 2013) for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults.

Methods: The activity of ceftobiprole (active form of the prodrug ceftobiprole medocaril) and comparator agents were evaluated against 2,507 staphylococci, 1,121 streptococci, and 683 enterococci. Clinically relevant isolates were collected from patients at 39 medical centres in 17 European countries and Israel from a variety of infection sites to include bloodstream, respiratory, skin and soft tissue, urinary and others. Ceftobiprole and comparator agents were susceptibility tested according Clinical and Laboratory Standards Institute guidelines using validated dry-form broth microdilution panels. Quality control organisms were tested concurrently with clinical isolates and results were within published limits. EUCAST interpretive criteria were applied according to current guidelines.

Results: Ceftobiprole was active against *S. aureus* with a $MIC_{50/90}$ at 0.5/1 mg/L (99.9% susceptible, EUCAST criteria), respectively. For MSSA the $MIC_{50/90}$ were 0.25/0.5, respectively (100.0% susceptible). For MRSA the $MIC_{50/90}$ were 1/2 mg/L, respectively (99.6% susceptible). For coagulase-negative staphylococci the $MIC_{50/90}$ were 1/4 mg/L, respectively with 88.6% of isolates at ≤2 mg/L. Ceftobiprole was active against *Enterococcus faecalis* ($MIC_{50/90}$, 0.5/4 mg/L) but not active against *E. faecium* ($MIC_{50/90}$, >8/>8 mg/L). Ceftobiprole was active against β-hemolytic streptococci with the highest MIC at 0.06 mg/L ($MIC_{50/90}$, 0.015/0.03 mg/L, respectively). Susceptibility to ceftobiprole for *Streptococcus pneumoniae* was 100.0% ($MIC_{50/90}$, 0.015/0.25 mg/L, respectively). Ceftobiprole was highly active against penicillin-resistant *S. pneumoniae* (ceftobiprole $MIC_{50/90}$, 0.5/0.5 mg/L). Susceptibility to ceftriaxone for *S. pneumoniae* was 88.3%. All ceftriaxone-non-susceptible isolates of *S. pneumoniae* were susceptible to ceftobiprole (ceftobiprole $MIC_{50/90}$, 0.5/0.5 mg/L, respectively). Ceftobiprole was active against viridans group streptococci with a $MIC_{50/90}$ of 0.06/0.25 mg/L, respectively.

Conclusions: Ceftobiprole was active against clinically relevant Gram-positive isolates collected at medical centers during 2013 from 17 European countries and Israel. A total of 99.9% of *S. aureus* including MRSA were susceptible to ceftobiprole. Ceftobiprole also exhibited 100.0% susceptibility against *S. pneumoniae* including isolates that were resistant to penicillin (3.1%) and non-susceptible to ceftriaxone (11.7%).

INTRODUCTION

Ceftobiprole is a novel parenteral cephalosporin active against Gram-positive and Gram-negative bacteria. Its antibacterial activity is due to the ability to inhibit penicillin binding proteins (PBPs). Ceftobiprole has shown potent inhibition of PBPs from Gram-positive bacteria including those with decreased affinity to other β-lactams such as PBP2a in methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2X in penicillin-resistant *Streptococcus pneumoniae*. Against *E. coli*, ceftobiprole has its greatest activity for PBP3 (the primary target of cephalosporins and monobactams) and PBP2. For *Pseudomonas aeruginosa* it has a similar binding profile to ceftazidime and cefepime, but also exhibits increased binding to PBP2.

Ceftobiprole is administered as the prodrug ceftobiprole medocaril which is rapidly hydrolyzed *in vivo* to the active form, ceftobiprole. During its clinical development ceftobiprole medocaril has been studied in hospitalized community-acquired bacterial pneumonia, hospital-acquired bacterial pneumonia, and acute bacterial skin and skin structure infections. It was recently approved (October 2013) through the decentralized regulatory process in 12 European countries for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults. In this study, we evaluated the activity of ceftobiprole and comparator agents against a large collection of staphylococci, streptococci, and enterococci isolated from patients at 39 medical centres in 17 European countries and Israel in 2013. The aim of this study was to characterize the *in vitro* activity of ceftobiprole to produce a baseline measurement which can be used for comparison in future surveillance years.

METHODS

Clinically relevant isolates (1 per patient episode) were collected during 2013 from patients at 39 medical centres in 17 European countries and Israel. Isolates were collected from a variety of infection types to include bloodstream, respiratory, skin and soft tissue, urinary and others. More than 4,300 *S. aureus*, coagulase negative staphylococci (CoNS), β-haemolytic streptococci, *S. pneumoniae,* and viridans group streptococci were obtained.

Susceptibility testing was performed by reference broth microdilution (Clinical and Laboratory Standards Institute; CLSI) to determine the antimicrobial susceptibility of ceftobiprole and comparator agents. Validated MIC panels were manufactured by ThermoFisher Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). *S. aureus* and *Enterococcus* spp. strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). Streptococci were tested in CA-MHB supplemented with 2.5-5% lysed horse blood (M07-A9, 2012). Quality control (QC) testing was performed concurrently to assure proper test conditions and procedures. MIC QC strains included *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619. MIC QC results were within the published CLSI ranges. Susceptibility interpretive criteria were based on the CLSI guideline (M100-S24) and EUCAST (2014). Ceftobiprole interpretive criteria were based on information in the Zeftera summary of product characteristics (EMA).

RESULTS

- The ceftobiprole $MIC_{50/90}$ was 0.5/1 mg/L for *S. aureus* (MIC range, 0.015-4 mg/L; **Tables 1** and **2**). A total of 99.9% of isolates were inhibited at a MIC of ≤2 mg/L (99.9% susceptible). Ceftobiprole was four-fold more active against MSSA ($MIC_{50/90}$, 0.25/0.5 mg/L) than MRSA ($MIC_{50/90}$, 1/2 mg/L; **Tables 1** and **2**). All MSSA and 99.6% of MRSA (2 isolates with a MIC at 4 mg/L) exhibited a MIC at ≤2 mg/L. There was 100.0% susceptibility to vancomycin and daptomycin (**Table 2**). There was one MRSA that was linezolid-resistant. A total of 1.7% of MRSA and 0.1% of MSSA were resistant to trimethoprim/sulfamethoxazole (**Table 2**). 87.7% of MRSA and 3.9% of MSSA were resistant to levofloxacin. Against CoNS, ceftobiprole exhibited a $MIC_{50/90}$ of 1/4 mg/L (**Tables 1** and **2**). A total of 85.8% of methicillin-resistant CoNS and all methicillin-susceptible CoNS were inhibited at a MIC ≤2 mg/L (**Table 1**).
- Ceftobiprole MIC values were lower against penicillin-susceptible (Pen-S, ≤0.06 mg/L) than for penicillin-resistant (Pen-R; MIC ≥2 mg/L) *S. pneumoniae* isolates (ceftobiprole $MIC_{50/90}$, 0.008/0.015 and 0.5/0.5 mg/L, respectively; **Table 1**). Against pneumococci, ceftobiprole ($MIC_{50/90}$, 0.015/0.25 mg/L) was four-fold more active than ceftriaxone ($MIC_{50/90}$, ≤0.06/1 mg/L) and cefepime ($MIC_{50/90}$, ≤0.5/1 mg/L; **Table 3**). A total of 29.3% of Pen-R strains and 3.1% of all strains were non-susceptible to ceftriaxone (CLSI criteria); 94.8 and 11.7%, respectively by EUCAST criteria. All *S. pneumoniae* isolates, regardless of penicillin or ceftriaxone susceptibility status, were susceptible to ceftobiprole. The $MIC_{50/90}$ values for ceftobiprole against ceftriaxone-non-susceptible *S. pneumoniae* (MIC ≥1 mg/L) isolates were both at 0.5 mg/L; **Table 1**).
- Ceftobiprole was active against β-haemolytic and viridans group streptococci with $MIC_{50/90}$ values of 0.015/0.03 and 0.06/0.25 mg/L, respectively (**Tables 1** and **3**). All β-haemolytic streptococci MIC values for ceftobiprole were ≤0.06 mg/L and 99.4% of viridans group streptococci were inhibited at a MIC ≤1 mg/L (**Table 1**).
- Ceftobiprole was inactive against *E. faecium* ($MIC_{50/90}$ at >8/>8 mg/L) but demonstrated activity against *E. faecalis* ($MIC_{50/90}$ at 0.5/4 mg/L; **Tables 1** and **4**). A total of 95.0% of *E. faecalis* isolates were inhibited by ceftobiprole at a MIC of ≤4 mg/L (**Table 1**).

CONCLUSIONS

Ceftobiprole, approved in October 2013 through the decentralized regulatory process in Europe, is a parenteral broad-spectrum anti-MRSA cephalosporin with Gram-negative activity that demonstrated potent activity against a large collection of clinically relevant isolates of staphylococcal, streptococcal, and enterococcal species from patients in 39 medical centres in 17 European countries and Israel. Included in the spectrum of ceftobiprole *in vitro* activity were *S. aureus* including MRSA, CoNS, *S. pneumoniae* including penicillin- and ceftriaxone-non-susceptible *S. pneumoniae,* β-haemolytic streptococci, and viridans streptococci.

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Table 1. Summary of ceftobiprole activity tested against staphylococci and streptococci from European medical centers (2013).

Organism (no. tested)	No. of organisms (cumulative %) inhibited at ceftobiprole MIC in mg/L of:												
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
Staphylococcus aureus (2,033)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	3 (0.2)	5 (0.4)	868 (43.1)	730 (79.0)	272 (92.4)	152 (99.9)	2 (100.0)	--	--	0.5	1
MSSA (1,554)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.1)	3 (0.3)	5 (0.6)	866 (56.3)	679 (100.0)	--	--	--	--	--	0.25	0.5
MRSA (479)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	51 (11.1)	272 (67.8)	152 (99.6)	2 (100.0)	--	--	1	2
Coagulase-negative staphylococci (474)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.2)	9 (2.1)	36 (9.7)	66 (23.6)	104 (45.6)	151 (77.4)	53 (88.6)	53 (99.8)	1 (100.0)	--	1	4
MSCoNS (95)	0 (0.0)	0 (0.0)	1 (1.1)	0 (1.1)	9 (10.5)	33 (45.3)	50 (97.9)	2 (100.0)	--	--	--	--	--	0.25	0.25
MRCoNS (379)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	16 (5.0)	102 (31.9)	151 (71.8)	53 (85.8)	53 (99.7)	1 (100.0)	--	1	4
Enterococcus spp. (693)	0 (0.0)	1 (0.1)	0 (0.1)	1 (0.3)	1 (0.4)	12 (2.2)	112 (18.3)	182 (44.6)	22 (47.8)	49 (54.8)	27 (58.7)	17 (61.2)	269 (100.0)	2	>8
Enterococcus faecalis (403)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.5)	12 (3.5)	111 (31.0)	179 (75.4)	19 (80.1)	37 (89.3)	23 (95.0)	17 (99.3)	3 (100.0)	0.5	4
Enterococcus faecium (280)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	9 (3.9)	4 (5.4)	0 (5.4)	265 (100.0)	>8	>8
Beta-haemolytic streptococci (396)	4 (1.0)	189 (48.7)	68 (65.9)	134 (99.7)	1 (100.0)	--	--	--	--	--	--	--	--	0.015	0.03
Group A *Streptococcus* (149)	3 (2.0)	129 (88.6)	13 (97.3)	4 (100.0)	--	--	--	--	--	--	--	--	--	0.008	0.015
Group B *Streptococcus* (168)	0 (0.0)	0 (0.0)	38 (22.6)	129 (99.4)	1 (100.0)	--	--	--	--	--	--	--	--	0.03	0.03
other streptococci (79)	1 (1.3)	60 (77.2)	17 (98.7)	1 (100.0)	--	--	--	--	--	--	--	--	--	0.008	0.015
Streptococcus pneumoniae (548)	12 (2.2)	245 (46.9)	173 (78.5)	20 (82.1)	13 (84.5)	7 (85.8)	44 (93.8)	34 (100.0)	--	--	--	--	--	0.015	0.25
Pen-S (MIC, ≤0.06 mg/L; 408)	11 (2.7)	239 (61.3)	150 (98.0)	6 (99.5)	2 (100.0)	--	--	--	--	--	--	--	--	0.008	0.015
Pen-I (MIC, 0.12 – 1 mg/L; 82)	1 (1.2)	6 (8.5)	23 (36.6)	14 (53.7)	11 (67.1)	7 (75.6)	20 (100.0)	--	--	--	--	--	--	0.03	0.25
Pen-R (MIC, ≥2 mg/L;58)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (41.4)	34 (100.0)	--	--	--	--	--	0.5	0.5
Pen-S (MIC, ≤2 mg/L;531)	12 (2.3)	245 (48.4)	173 (81.0)	20 (84.7)	13 (87.2)	7 (88.5)	42 (96.4)	19 (100.0)	--	--	--	--	--	0.015	0.25
Pen-I (MIC, 4 mg/L; 17)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	15 (100.0)	--	--	--	--	--	0.5	0.5
CRO-non-S (MIC, ≥1 mg/L; 64)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (46.9)	34 (100.0)	--	--	--	--	--	0.5	0.5
CRO-non-S (MIC, 2 mg/L; 17)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (23.5)	13 (100.0)	--	--	--	--	--	0.5	0.5
Viridans group streptococci (177)	1 (0.6)	13 (7.9)	35 (27.7)	27 (42.9)	31 (60.5)	44 (85.3)	14 (93.2)	3 (94.9)	8 (99.4)	0 (99.4)	0 (99.4)	1 (100.0)	--	0.06	0.25

Table 2. Activity of ceftobiprole and comparator antimicrobial agents when tested against staphylococci from European medical centres (2013).

Organism group (no. tested)/ antimicrobial agent	MIC (mg/L)			%Susc. / %Resistant	
	50%	90%	Range	CLSI[a]	EUCAST[a]
All *S. aureus* (2,033)					
Ceftobiprole	0.5	1	0.015 – 4	- / -	99.9 /0.1
Oxacillin	0.5	>2	≤0.25 – >2	76.4 / 23.6	76.4 / 23.6
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	0.25	>4	≤0.12 – >4	75.8 / 23.7	75.8 / 23.7
Linezolid	1	1	≤0.12 – 8	>99.9 / <0.1	>99.9 / <0.1
Tetracycline	0.25	0.25	0.06 – >32	94.3 / 5.1	93.9 / 5.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	99.5 / 0.5	99.5 / 0.4
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (479)					
Ceftobiprole	1	2	0.25 – 4	- / -	99.6 /0.4
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	>4	>4	≤0.12 – >4	11.3 / 87.7	11.3 / 87.7
Linezolid	1	1	≤0.12 – 8	99.8 / 0.2	99.8 / 0.2
Tetracycline	0.25	2	0.06 – >32	90.6 / 8.4	89.6 / 9.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	98.3 / 1.7	98.3 / 1.7
Vancomycin	0.5	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (1,554)					
Ceftobiprole	0.25	0.5	0.015 – 0.5	- / -	100.0 /0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	0.25	0.25	≤0.12 – >4	95.8 / 3.9	95.8 / 3.9
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.12	0.25	0.06 – >32	95.5 / 4.1	95.2 / 4.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	99.9 / 0.1	99.9 / 0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
CoNS (474)					
Ceftobiprole	1	4	0.015 – 8	- / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	20.0 / 80.0	20.0 / 80.0
Daptomycin	0.25	0.5	≤0.06 – 4	99.6 / -	99.6 / 0.4
Levofloxacin	4	>4	≤0.12 – >4	45.4 / 51.3	45.4 / 51.3
Linezolid	0.5	1	0.25 – >8	99.6 / 0.4	99.6 / 0.4
Tetracycline	0.5	32	0.06 – >32	81.6 / 16.5	76.8 / 20.5
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	64.1/ 35.9	64.1 / 18.6
Vancomycin	1	2	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI (2014) and EUCAST (2014).

Table 4. Activity of ceftobiprole and comparator antimicrobial agents when tested against enterococci from European medical centres (2013).

Organism group (no. tested)/ antimicrobial agent	MIC (mg/L)			%Susc. / %Resistant	
	50%	90%	Range	CLSI[a]	EUCAST[a]
Enterococcus faecalis (403)					
Ceftobiprole	0.5	4	0.03 – >8	- / -	- / -
Ampicillin	1	2	0.5 – 8	100.0 / 0.0	99.8 / 0.0
Daptomycin	1	1	≤0.06 – 2	100.0 / -	- / -
Imipenem	1	2	0.5 – >8	99.8 / -	99.8/ 0.2
Levofloxacin	1	>4	0.5 – >4	72.1 / 27.4	- / -
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – >16	99.5 / 0.5	99.5 / 0.5
Vancomycin	1	2	0.5 – >16	99.3 / 0.5	99.3 / 0.7
Enterococcus faecium (280)					
Ceftobiprole	>8	>8	1 – >8	- / -	- / -
Ampicillin	>8	>8	1 – >8	5.0 / 95.0	4.3 / 95.0
Daptomycin	2	2	≤0.06 – 4	100.0 / -	- / -
Imipenem	>8	>8	1 – >8	- / -	3.9 / 95.7
Levofloxacin	>4	>4	1 – >4	5.0 / 92.5	- / -
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	>16	≤2 – >16	74.6 / 22.1	74.3 / 25.7
Vancomycin	1	>16	0.5 – >16	70.4 / 29.3	70.4 / 29.6

a. Criteria as published by the CLSI (2014) and EUCAST (2014).

Table 3. Activity of ceftobiprole and comparator antimicrobial agents when tested against streptococci from European medical centres (2013).

Organism group/Antimicrobial agent (no. tested)	MIC (mg/L)			%Susc. / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Streptococcus pneumoniae (548)					
Ceftobiprole	0.015	0.25	≤0.004 – 0.5	- / -	100.0 / 0.0
Cefepime	≤0.5	1	≤0.5 – 2	96.2 / 0.0	96.2 / 0.0
Ceftriaxone	≤0.06	1	≤0.06 – 2	96.9 / 0.0	88.3 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	85.8 / 14.2	85.8 / 14.2
Erythromycin	≤0.12	>16	≤0.12 – >16	77.1 / 22.0	77.1 / 22.0
Imipenem	≤0.12	0.25	≤0.12 – 1	89.8 / 0.2	100.0 / 0.0
Levofloxacin	1	1	0.25 – >4	98.9 / 0.9	98.9 / 1.1
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Penicillin[b]	≤0.06	2	≤0.06 – 4	96.9 / 0.0	- / -
Penicillin[c]	≤0.06	2	≤0.06 – 4	74.5 / 10.6	74.5 / 3.1
Tetracycline	0.25	32	0.06 – >32	80.8 / 18.8	80.8 / 18.8
Trimethoprim/sulfamethoxazole	≤0.5	4	≤0.5 – >4	76.2 / 13.6	82.7 / 13.6
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-resistant (MIC, ≥2 mg/L; 58)					
Ceftobiprole	0.5	0.5	0.25 – 0.5	- / -	100.0/0.0
Cefepime	1	2	≤0.5 – 2	65.5 / 0.0	65.5 / 0.0
Ceftriaxone	1	2	0.5 – 2	70.7 / 0.0	5.2 / 0.0
Clindamycin	1	>2	≤0.25 – >2	48.3 / 51.7	48.3 / 51.7
Erythromycin	>16	>16	≤0.12 – >16	27.6 / 72.4	27.6 / 72.4
Imipenem	0.25	0.5	≤0.12 – 1	10.3 / 1.7	100.0 / 0.0
Levofloxacin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Penicillin[b]	2	4	2 – 4	70.7 / 0.0	- / -
Penicillin[c]	2	4	2 – 4	0.0 /100.0	0.0 / 29.3
Tetracycline	32	>32	0.12 – >32	36.2 / 63.8	36.2 / 63.8
Trimethoprim/sulfamethoxazole	2	>4	≤0.5 – >4	26.3 / 49.1	47.4 / 49.1
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-susceptible (MIC, ≤0.06 mg/L; 408)					
Ceftobiprole	0.008	0.015	≤0.004 – 0.06	- / - / -	100.0/0.0
Cefepime	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.8 / 4.2	95.8/ 4.2
Erythromycin	≤0.12	0.25	≤0.12 – >16	90.9 / 7.9	90.9 / 7.9
Imipenem	≤0.12	≤0.12	≤0.12 – 0.25	99.8 / 0.0	100.0 / 0.0
Levofloxacin	1	1	0.25 – >4	99.0 / 1.0	99.0/ 1.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Penicillin[b]	≤0.06	≤0.06	≤0.06	100.0 / 0.0	- / -
Penicillin[c]	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.25	0.5	0.06 – >32	91.9 / 7.6	91.9/ 7.6
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5 – >4	89.7 / 4.2	93.6/ 4.2
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (396)					
Ceftobiprole	0.015	0.03	≤0.004 – 0.06	- / -	- / -
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Cefepime	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	86.6 / 12.6	87.4 / 12.6
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.12	>16	≤0.12 – >16	77.5 / 20.5	77.5 / 20.5
Levofloxacin	0.5	1	0.25 – >4	99.5 / 0.5	95.7 / 0.5
Linezolid	1	1	0.25 – 1	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (177)					
Ceftobiprole	0.06	0.25	≤0.004 – 8	- / -	- / -
Cefepime	≤0.5	1	≤0.5 – 4	92.0 / 4.0	83.5 / 16.5
Ceftriaxone	0.25	0.5	≤0.06 – >8	93.8 / 4.0	90.4 / 9.6
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.9 / 8.0	92.0/ 8.0
Daptomycin	0.25	1	≤0.06 – 2	99.4 / -	- / -
Erythromycin	≤0.12	4	≤0.12 – >16	63.0 / 33.5	- / -
Levofloxacin	1	2	0.25 – >4	98.9 / 0.6	- / -
Linezolid	0.5	1	≤0.12 – 1	100.0 / -	- / -
Penicillin	≤0.06	1	≤0.06 – 8	73.9 / 4.0	83.5/ 4.0
Vancomycin	0.5	1	≤0.12 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI (2014) and EUCAST (2014).
b. Criteria as published by the CLSI (2014) for Penicillin (parenteral (non-meningitis).
c. Criteria as published by the CLSI (2014) for Penicillin (oral penicillin V).