Antimicrobial activity of ceftobiprole against Gram-negative and Gram-positive pathogens: results from INVITA-A-CEFTO Brazilian study

ABSTRACT

Ceftobiprole is a broad-spectrum cephalosporin with potent activity against staphylococci, including those resistant to oxacillin, as well as against most Gram-negative bacilli including *Pseudomonas aeruginosa*. In this study, the in vitro activity of ceftobiprole and comparator agents was tested against bacterial isolates recently collected from Brazilian private hospitals. A total of 336 unique bacterial isolates were collected from hospitalized patients between February 2008 and August 2009. Each hospital was asked to submit 100 single bacterial isolates responsible for causing blood, lower respiratory tract or skin and soft tissue infections. Bacterial identification was confirmed and antimicrobial susceptibility testing was performed using CLSI microdilution method at a central laboratory. The CLSI M100-S21 (2011) was used for interpretation of the antimicrobial susceptibility results. Among the 336 pathogens collected, 255 (75.9%) were Gram-negative bacilli and 81 (24.1%) were Gram-positive cocci. Although ceftobiprole MIC_{50} values for oxacillin resistant strains were two-fold higher than for methicillin susceptible *S. aureus*, ceftobiprole inhibited 100% of tested *S. aureus* at MICs ≤ 4 μg/mL. Polymyxin B was the only agent to show potent activity against *Acinetobacter* spp. ($MIC_{50/90}$, 0.5/1 μg/mL), and *P. aeruginosa* ($MIC_{50/90}$, 1/2 μg/mL). Resistance to broad-spectrum cephalosporins varied from 55.3-68.5% and 14.3-28.5% among *E. coli* and *Klebsiella* spp. isolates, respectively; with ceftobiprole MIC_{50} > 6 μg/mL for both species. Our results showed that ceftobiprole has potent activity against staphylococci and *E. faecalis*, which was superior to that of vancomycin. Our data also indicates that ceftobiprole demonstrated potency comparable to that of cefepime and ceftazidime against key Gram-negative species.

Keywords: cephalosporins; Brazil; Gram-negative aerobic bacteria; methicillin-resistant *Staphylococcus aureus*.

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INTRODUCTION

Fourth-generation cephalosporins represent a valuable addition to the therapeutic armamentarium since they have demonstrated activity against Gram-negative bacilli, including *Enterobacteriaceae* and, as well as Gram-positive cocci such as *Streptococcus pneumoniae* and methicllin-suceptible staphylococci. However, the lack of activity against methicillin-resistant staphylococci and extended-spectrum beta-lactamases (ESBL)-producing isolates has limited wider clinical use.[1,2] According to the most recent SENTRY data report, *Staphylococcus aureus* (20.2%) and coagulase-negative staphylococci (CoNS; 14.5%) ranked as the first and second cause of bloodstream infections in Brazilian hospitals between 2005 and 2008.[3] *S. aureus* was also the most common cause of skin and soft tissue infections (28.1%) and was isolated from 24.9% of patients with pneumonia. In that study, 31.0% and 78.7% of *S. aureus* and CoNS showed resistance to methicillin. The limited number of approved drugs with activity against multidrug-resistant bacteria such as methicillin-resistant *S. aureus* (MRSA) has increased the demand for new agents with a novel mechanism of action or an ability to overcome bacterial resistance.

Ceftobiprole is a pyrrolidinone-3-ylidenemethyl cephalosporin with a broad-spectrum of activity against Gram-positive cocci and Gram-negative bacilli.[4-6] The binding of ceftobiprole to penicillin-binding proteins

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(PBPs) is a critical determinant of its antibacterial activity.[4] Ceftobiprole demonstrated potent binding to PBPs from Gram-positive bacteria, including those with decreased β-lactam sensitivity, such as PBP2a in MRSA and PBP2x in penicillin-resistant *S. pneumoniae* (PRSP), in contrast to ceftriaxone. In *Escherichia coli*, ceftobiprole exhibited strong binding to the essential PBPs, PBP2 and PBP3. It also exhibited a binding profile similar to those of cefepime and ceftazidime in *P. aeruginosa* but with enhanced binding to PBP2. These binding profiles explain the broad-spectrum activity for ceftobiprole.[5] In addition, in single-step and serial passage *in vitro* resistance development studies, ceftobiprole demonstrated a low propensity to select for resistant subpopulations.[7,8] The purpose of this study was to assess the *in vitro* activity of ceftobiprole and comparator agents against Gram-positive cocci and Gram-negative bacilli, recently isolated from patients of Brazilian private hospitals.

MATERIAL AND METHODS

Participant medical centers

Four private hospitals participated of the INVITA-A-CEFTO Brazilian Study. The medical centers were located in four distinct Brazilian cities, Belo Horizonte, São Paulo, Rio de Janeiro and São Luís. Selection of the participant medical centers was based on the criteria that they should have preferentially ≥ 200 beds, at least one adult intensive care unit and located in cities with more than one million inhabitants.

Bacterial isolates

A total of 336 consecutive isolates of Gram-positive cocci and Gram-negative bacilli was submitted between February 2008 and August 2009. Each medical center was guided by protocol to submit Gram-positive cocci and Gram-negative bacilli collected from patients with diagnosis of pneumonia (40 isolates being from 20 ventilator-assisted patients), bloodstream infections (40 isolates) and skin and soft-tissue infections (20 isolates), according to the Centers for Disease Control and Prevention (CDC) definitions.[9] One isolate per patient was evaluated. All isolates were identified at the participating institution by routine methodologies in use at each laboratory. Upon receipt at the central laboratory (UNIFESP, São Paulo), isolates were subcultured to ensure viability and purity. Confirmation of species identification was performed with the BD Phoenix™ Automated Microbiology System (BD Diagnostics, MD, USA) or conventional methods, as required.

Susceptibility testing

Antimicrobial susceptibility testing was performed by the broth microdilution method, following recommendations of the Clinical and Laboratory Standards Institute (CLSI).[10] Antimicrobial powders were obtained from the respective manufacturers and microdilution plates were prepared by TREK Diagnostics (West Sussex, England). Susceptibility results were interpreted according to CLSI document M100-S21[11] for all comparison agents except for doripenem,[12] tigecycline[13] and ceftobiprole.[14] Quality control was performed by testing *E. coli* ATCC 25922; *P. aeruginosa* ATCC 27853; *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212.

RESULTS

A total of 336 isolates were collected as part of the INVITA-A-CEFTO Brazilian Study between February 2008 and August 2009. Of those, 225 (75.9%) and 81 (24.1%) were classified as Gram-negative and Gram-positive, respectively. The bacterial isolates were collected mainly from patients diagnosed with bloodstream (38.4%), lower respiratory tract (39.9%) and skin and soft tissue (21.7%) infections. The frequency of isolates collected, according to infection type and medical centers is shown in Table 1. The most frequent genera/species collected were

Table 1. Frequencies of isolates collected by the INVITA-A-CEFTO study according to type of infection and medical center

Medical center (city/state)	Bloodstream infections	Respiratory tracts infections	Skin and soft tissue infection	Total
01 (São Paulo, SP)	40	34	20	94 (28.0%)
02 (Rio de Janeiro, RJ)	38	39	20	97 (28.9%)
03 (Belo Horizonte, MG)	24	21	15	60 (17.9%)
04 (São Luis, MA)	27	40	18	85 (25.3%)
Total	129 (38.4%)	134 (39.9%)	73 (21.7%)	336 (100%)

Table 2. Frequency of isolates collected by the INVITA-A-CEFTO Brazilian Study

Microorganism	Number of isolates (%)
Pseudomonas spp.[a]	96 (28.6)
Klebsiella spp.[b]	41 (12.2)
Staphylococcus aureus	36 (10.7)
Acinetobacter baumannii	30 (8.9)
Escherichia coli	28 (8.3)
Staphylococcus coagulase negativa[c]	23 (6.8)
Enterobacter spp.[d]	21 (6.3)
Enterococcus faecalis	18 (5.4)
Serratia spp.[e]	17 (5.1)
Morganella morgannii	4 (1.2)
Proteus mirabilis	4 (1.2)
Providencia stuartii	4 (1.2)
Streptococcus spp.[f]	4 (1.2)
Stenotrophomonas maltophilia	3 (0.9)
Burkholderia cepacea	2 (0.6)
Achromobacter xylosoxidans	1 (0.3)
Aeromonas hydrophila	1 (0.3)
Citrobacter koseri	1 (0.3)
Cryseobacterium gleum	1 (0.3)
Moraxella spp.	1 (0.3)
Total	336

[a]*P. aeruginosa* (94), *P. putida* (1), *P. fluorescens* (1).
[b]*K. pneumoniae* (38), *K. oxytoca* (3).
[c]*S. epidermidis* (15), *S. haemolyticus* (2), *S. hominis* (2), *S. capitis* (1), *Staphylococcus* spp. (3).
[d]*E. cloacae* (10), *E. aerogenes* (9), *E. cancerogenus* (1), *E. sakazakii* (1). Recentely, *E. sakazakii* was called *Cronobacter sakazakii.*
[e]*S. marcescens* (14), *S. plymuthica* (3).
[f]*S. mitis* (1), *S. agalactiae* (3).

Pseudomonas spp. (28.6%); *Klebsiella* spp. (12.2%); *S. aureus* (10.7%); *Acinetobacter* spp. (8.9%); *E. coli* (8.3%) and coagulase negative staphylococci (CoNS, 6.8%). The frequency of occurrence of all pathogens collected is shown in Table 2.

Antimicrobial activity of the tested agents and the susceptibility profile of the most frequent Gram-negative isolates are shown in Table 3. Ceftobiprole showed similar activity to that displayed by cefepime against *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, *E. coli* and *Enterobacter* spp.

P. aeruginosa showed the highest rates of susceptibility towards polymyxin B (98.9%), amikacin (59.1%) and piperacillin/tazobactam (58.1%) (Table 3). Among the cephalosporins, slightly greater percentage of isolates was inhibited at MICs ≤ 8 μg/mL by ceftazidime (48.4%) or cefepime (47.8%) than by ceftobiprole (36.8%). Ceftobiprole and ceftriaxone inhibited 36.8% of *K. pneumoniae* isolates at concentrations ≤ 8 μg/mL. Against this species, ceftobiprole activity was comparable to that displayed by cefepime (39.5%), but lower than that of ceftazidime (44.7%, Table 4). Among the carbapenems, meropenem (76.3% susceptibility) and doripenem (73.7% susceptibility) showed remarkable susceptibility rates, followed by imipenem (68.4% susceptibility). Moreover, imipenem (MIC_{90}, 4 μg/mL) was two-fold more potent than meropenem (MIC_{90}, 8 μg/mL) and doripenem (MIC_{90}, 8 μg/mL) against *K. pneumoniae* isolates. All tested *K. pneumoniae* isolates were susceptible to tigecycline. Levofloxacin resistance was observed in 47.4% of *K. pneumoniae* isolates.

All tested *A. baumannii* isolates were susceptible to tigecycline (MIC_{90}, 0.5 μg/mL) and polymyxin B (MIC_{90}, ≤ 0.5 μg/mL). Ceftobiprole had $MIC_{50/90}$, > 6 μg/mL as did cefepime and ceftazidime.

The potency of ceftobiprole (MIC_{50}, 0.5 μg/mL) was identical to those displayed by ceftazidime (MIC_{50}, 0.5 μg/mL) and cefepime (MIC_{50}, 0.5 μg/mL) among *E. coli* isolates. Against *Enterobacter* spp., cefepime (MIC_{50}, ≤ 0.12 μg/mL) was at least two-fold and four-fold more active than ceftobiprole (MIC_{50}, 0.25 μg/mL) and ceftazidime (MIC_{50}, 0.5 μg/mL), respectively. Nevertheless, the highest *in vitro* activity for ceftobiprole was observed for this genus. Approximately 68% and 76% of *E. coli* and *Enterobacter* spp., respectively, were inhibited by ceftobiprole at 8 μg/mL (Table 4).

The activity of ceftobiprole and other antimicrobial agents tested against Gram-positive isolates is shown in Tables 5 and 6. Overall, 33.3% of *S. aureus* isolates were resistant to oxacillin. Ceftobiprole was two-fold more potent against oxacillin-susceptible *S. aureus* (MIC_{50}, 0.5 μg/mL) than oxacillin-resistant *S. aureus* (MIC_{50}, 1 μg/mL). All *S. aureus* strains were inhibited by concentrations of ceftobiprole ≤ 4 μg/mL. Agents providing the highest coverage against all *S. aureus* included vancomycin (MIC_{50}, 1 μg/mL; 100% susceptible), teicoplanin (MIC_{50}, ≤ 2 μg/mL; 100% susceptible), linezolid (MIC_{50}, 4 μg/mL; 97.2% susceptible) and tigecycline (MIC_{50}, 0.25 μg/mL; 97.2% susceptible). Tigecycline (MIC_{50}, 0.25 μg/mL; 100% susceptibility) followed by ceftobiprole ($MIC_{50/90}$, 1 and 8 μg/mL) were the most active agents tested against CoNS isolates. At 2 μg/mL, ceftobiprole inhibited 95.7% of CoNS isolates (Table 6). Only a single CoNS isolate showed a ceftobiprole MIC of 8 μg/mL.

Ceftobiprole ($MIC_{50/90}$, 0.5 and 16 μg/mL) inhibited the growth of 88.9% of the *E. faecalis* isolates at concentrations

Table 3. **In vitro** ***activity of ceftobiprole in comparison to selected antimicrobial agents tested against the main Gram negative pathogens collected by the INVITA-A-CEFTO Brazilian Study***

Organism/ Antimicrobial agents[a]	MIC (µg/mL) MIC_{50}	MIC_{90}	Susceptible (%)	Resistant (%)
P. aeruginosa **(94)**				
Ceftobiprole	> 16	> 16	15.1[c]	84.9[c]
Ceftazidime	16	> 16	48.4	45.2
Cefepime	16	> 16	47.3	43.0
Aztreonam	16	> 16	32.3	50.5
Piperaracillin/Tazobactam	64	> 64	58.1	41.9
Doripenem[b]	4	> 16	40.9	-[f]
Meropenem	8	> 8	43.6	46.8
Imipenem	8	> 8	43.0	44.1
Ciprofloxacin	> 2	> 2	37.6	59.1
Levofloxacin	> 4	> 4	34.4	59.1
Amikacin	16	> 32	59.1	37.6
Polymyxin B	1	2	98.9	1.1
K. pneumoniae **(38)**				
Ceftobiprole	> 16	> 16	31.6[c]	68.5[c]
Cefoxitin	8	> 16	60.5	31.6
Ceftriaxone	> 32	> 32	28.9	68.5
Ceftazidime	> 16	> 16	42.1	55.3
Cefepime	> 16	> 16	39.5	57.9
Aztreonam	> 16	> 16	42.1	55.3
Piperaracillin/Tazobactam	64	> 64	39.5	52.6
Doripenem[b]	0.25	8	73.7	23.6
Meropenem	0.12	8	76.3	21.1
Imipenem	1	4	68.4	13.2
Ciprofloxacin	> 2	> 2	34.2	63.2
Levofloxacin	4	> 4	39.5	47.4
Amikacin	8	32	84.2	2.6
Polymyxin B[e]	≤ 0.5	1	100.0	0.0
Tigecycline[b]	1	2	100.0	0.0
A. baumannii **(30)**				
Ceftobiprole	> 16	> 16	20.0[c]	80.0[c]
Ceftriaxone	> 32	> 32	6.7	66.7
Ceftazidime	> 16	> 16	40.0	56.7
Cefepime	> 16	> 16	26.7	73.3
Piperaracillin/Tazobactam	> 64	> 64	16.7	76.7
Doripenem[b]	> 16	> 16	23.3	-[f]
Meropenem	> 8	> 8	23.3	76.7
Imipenem	> 8	> 8	23.3	76.7
Ciprofloxacin	> 2	> 2	20.0	80.0
Levofloxacin	> 4	> 4	20.0	76.7
Amikacin	> 32	> 32	43.3	56.7
Polymyxin B	≤ 0.5	1	100.0	0.0
Tigecycline[b]	0.5	2	100.0	0.0

(Cont.)

Table 3. **In vitro** *activity of ceftobiprole in comparison to selected antimicrobial agents tested against the main Gram negative pathogens collected by the INVITA-A-CEFTO Brazilian Study*

Organism/ Antimicrobial agents[a]	MIC (µg/mL) MIC_{50}	MIC_{90}	Susceptible (%)	Resistant (%)
E. coli **(28)**				
Ceftobiprole	0.5	> 16	57.1[c]	39.2[c]
Cefoxitin	≤ 4	> 16	82.1	14.3
Ceftriaxone	1	> 32	64.3	28.5
Ceftazidime	0.5	16	78.6[d]	17.8
Cefepime	0.5	> 16	78.6	14.3
Aztreonam	≤ 1	> 16	75.0	14.3
Piperaracillin/Tazobactam	4	16	92.9	7.1
Doripenem[b]	≤ 0.12	1	96.4	3.57
Meropenem	≤ 0.12	0.25	100.0	0.0
Imipenem	0.25	2	89.3	0.0
Ciprofloxacin	2	> 2	46.4	50.0
Levofloxacin	2	> 4	50.0	46.4
Amikacin	≤4	> 32	85.7	10.7
Polymyxin B[e]	≤ 0.25	1	100.0	0.0
Tigecycline[b]	0.25	1	100.0	0.0
Enterobacter **spp. (21)**				
Ceftobiprole	0.25	> 16	76.2[c]	23.8[c]
Ceftriaxone	1	> 32	71.4	28.6
Ceftazidime	0.5	> 16	76.2	23.8
Cefepime	≤ 0.12	> 16	76.2	23.8
Aztreonam	≤ 1	> 16	66.7	28.6
Piperaracillin/Tazobactam	4	> 64	76.2	19.0
Doripenem[b]	0.5	2	85.7	9.52
Meropenem	0.12	1	90.5	0.0
Imipenem	4	4	28.6	57.2
Ciprofloxacin	≤ 0.25	> 2	81.0	19.0
Levofloxacin	≤ 0.5	> 4	81.0	19.0
Amikacin	≤ 4	16	90.5	9.5
Polymyxin B[e]	1	> 4	71.4	23.8
Tigecycline[b]	0.5	2	95.2	0.0

[a]MIC determined according CLSI (2009) recommendations.
[b]Resistance rates calculated according CLSI M100-S21 document (2011), except for doripenem and tigecycline, which were calculated according the FDA criteria.
[c]Interpretative criteria according to Rossolini et al.[14]
[d]According to breakpoints established by CLSI for *P. aeruginosa* (≤ 2 µg/mL for susceptibility and ≥ 8 µg/mL for resistance).
[e]According *P. aeruginosa* breakpoint, CLSI 2009 recommendations.
[f]Interpretative criteria not established by CLSI or FDA.

Table 4. Comparisons of cephalosporins tested against the major Gram-negative isolates collected by the INVITA-A-CEFTO Brazilian Study

Organism (n)	Antimicrobial agents	Cumulative % inhibited at MIC (µg/mL)								
		0.12	0.25	0.5	1	2	4	8	16	32
***P. aeruginosa* (94)**	Ceftobiprole			1.1	2.1	6.3	14.7	36.8	45.3	100.0
	Cefepime					5.3	30.5	47.8	56.8	100.0
	Ceftazidime				2.1	7.4	35.8	48.4	54.7	100.0
***K. pneumoniae* (38)**	Ceftobiprole	21.1	28.9		31.6			36.8		100.0
	Cefepime		28.9	34.2		36.8		39.5	42.1	100.0
	Ceftazidime		21.1	28.9	34.2	39.5	42.1	44.7	100.0	
	Ceftriaxone	26.3		28.9		31.6		36.8	100.0	
***A. baumannii* (30)**	Ceftobiprole		10.0	16.7		20.0			30.0	100.0
	Cefepime		3.3		10.0	20.0	23.3	26.7		100.0
	Ceftazidime				3.3	6.7	26.7	40.0	43.3	100.0
	Ceftriaxone					3.3		6.7	33.3	40.0
***E. coli* (28)**	Ceftobiprole		7.1	50.0	57.1		60.7	67.9		100.0
	Cefepime		46.4	50.0		64.3	71.4	78.6	85.7	100.0
	Ceftazidime		39.3	57.1	64.3	71.4	78.6	82.1	92.9	100.0
	Ceftriaxone	7.1	60.7	89.3	92.9	100.0				
***Enterobacter* spp. (21)**	Ceftobiprole		66.7	76.2						100.0
	Cefepime		61.9	71.4				76.2		100.0
	Ceftazidime		38.1	71.4	76.2					100.0
	Ceftriaxone		47.6		71.4		76.2			100.0

of 1 µg/mL even though enterococci are generally not inhibited by cephalosporins. Only two (20.2%) *E. faecalis* strains isolated from a single medical center presented ceftobiprole MICs ≥ 16 µg/mL (data not shown). Among the *E. faecalis* isolates tested, 94.4% were susceptible to ampicillin, vancomycin and teicoplanin, representing the highest susceptible rates (Table 5). One linezolid-resistant *E. faecalis* isolate (5.6%) was isolated from a patient diagnosed with skin and soft tissue infection.

DISCUSSION

The aim of this study was to assess the activity of ceftobiprole, a new broad-spectrum cephalosporin, against contemporary Gram-positive and Gram-negative pathogens collected from patients hospitalized at four distinct Brazilian medical centers, as part of the INVITA-A-CEFTO Brazilian Study.

Ceftobiprole was highly potent against all staphylococcal isolates, inhibiting 100% of CoNS and *S. aureus* at MICs ≤ 8 µg/mL and ≤ 4 µg/mL, respectively. MIC_{90} values for MRSA were eight-fold higher than those for MSSA isolates (Table 5). These results were similar to those previously reported.[7,15,16] Although cephalosporins are generally inactive against *E. faecalis*, ceftobiprole inhibited 88.9% at MICs ≤ 4 µg/mL.

Ceftobiprole showed similar potency to those of 3th- and 4th-generation cephems (MIC_{50} values, 0.25 ≥ 16 µg/mL) for the main Enterobacteriaceae species. All cephaloporins demonstrated poor activity against *K. pneumoniae* (28.9-42.1% susceptible). This fact could be explained by the probable high rate of ESBL-producing *K. pneumoniae* isolates in Brazilian hospitals and since ceftobiprole is hydrolyzed by class A, B, and D extended-spectrum beta-lactamases, but not by class C enzymes, as previously reported.[17] Ceftobiprole, like cefepime, is a weak inducer and a poor substrate for AmpC β-lactamases.[1,17]

Ceftobiprole like ceftazidime and cefepime ($MIC_{50/90}$ ≥ 16 µg/mL, Table 3) showed poor *in vitro* activity against *P. aeruginosa* and *Acinetobacter* spp. isolates. Polymyxin was the only antimicrobial agent to show good activity against both *P. aeruginosa* and *Acinetobacter* spp. isolates. The elevated carbapenem resistance rates noticed among *P. aeruginosa* and *Acinetobacter* spp. tested in this study could be possibly attributed to the spread of clones that produce SPM-1 and OXA-23, respectively, in Brazilian hospitals, as noticed before.[18,19]

Despite the low number of isolates collected, the resistance rates to oxacillin among staphylococci appeared to be similar to those previously reported in a Brazilian study.[3] Curiously, the antimicrobial resistance rates

Table 5. In vitro *activity of ceftobiprole in comparison to selected antimicrobial agents tested against the main Gram-positive pathogens collected by the INVITA-A-CEFTO Brazilian Study*

Organism/ Antimicrobial agent	MIC (µg/mL)[a]			
	MIC_{50}	MIC_{90}	Susceptible (%)[b]	Resistant (%)[b]
Enterococcus faecalis **(18)**				
Ceftobiprole	0.5	16	88.9[d]	11.1[d]
Penicillin	4	> 8	88.9	11.1
Ampicillin	1	2	94.4	5.6
Erythromycin	> 4	> 4	5.6	61.1
Gentamicin	> 8	> 8	66.7[c]	33.3[c]
Linezolid	2	> 4	83.3	5.6
Levofloxacin	4	> 4	44.4	44.4
Tigecycline	0.25	0.5	66.7	-[e]
Vancomycin	2	4	94.4	5.6
Teicoplanin	≤ 2	≤ 2	94.4	5.6
CoNS (23)				
Ceftobiprole	1	8	95.7[d]	4.3[d]
Penicillin	> 8	> 8	8.7	91.3
Ampicillin	8	> 8	8.7	91.3
Oxacillin	> 2	> 2	8.7	91.3
Cephalothin	8	> 16	56.5	39.1
Ceftriaxone	> 32	> 32	26.1	60.9
Cefepime	> 16	> 16	39.1	52.2
Levofloxacin	> 4	> 4	21.7	73.9
Clindamycin	> 2	> 2	26.1	69.6
Erythromycin	> 4	> 4	17.4	73.9
Gentamicin	2	> 8	56.5	39.1
Linezolid	2	> 4	82.6	17.4
Teicoplanin	4	> 16	82.6	17.4
Vancomycin	2	4	95.7	4.3
Tigecycline	0.25	0.5	100.0	-[e]
S. aureus **(36)**				
Ceftobiprole	0.5	2	100.0[d]	0.0[d]
Penicillin	> 8	> 8	22.2	77.8
Ampicillin	> 8	> 8	19.4	80.6
Cephalothin	≤ 4	> 16	77.8	16.7
Ceftriaxone	4	> 32	69.4	13.9
Cefepime	4	> 16	75.0	13.9
Clindamycin	≤ 0.25	> 2	77.8	22.2
Erythromycin	1	> 4	50.0	44.4
Gentamicin	≤ 1	> 8	77.8	19.4
Levofloxacin	≤ 0.5	> 4	77.8	22.2
Linezolid	4	4	97.2	2.8

(Cont.)

Table 5. **In vitro** ***activity of ceftobiprole in comparison to selected antimicrobial agents tested against the main Gram-positive pathogens collected by the INVITA-A-CEFTO Brazilian Study***

Organism/ Antimicrobial agent	MIC (µg/mL)[a]			
	MIC_{50}	MIC_{90}	Susceptible (%)[b]	Resistant (%)[b]
S. aureus **(36)**				
Vancomycin	1	2	100.0	0.0
Teicoplanin	≤ 2	> 16	100.0	0.0
Tigecycline	0.25	0.5	97.2	-[e]
Oxacillin	0.5	> 2	66.7	33.3
S. aureus **oxacillin-resistant (12)**				
Ceftobiprole	1	4	100.0[d]	0.0[d]
Penicillin	> 8	> 8	8.3	91.7
Ampicillin	> 8	> 8	0	100
Cephalothin	8	> 16	50.0	41.7
Ceftriaxone	32	> 32	8.3	41.7
Cefepime	16	> 16	25.0	41.7
Clindamycin	> 2	> 2	33.3	66.7
Erythromycin	> 4	> 4	8.3	83.3
Gentamicin	2	> 8	66.7	25.0
Levofloxacin	> 4	> 4	33.3	66.7
Linezolid	4	4	91.7	8.3
Vancomycin	2	2	100.0	0.0
Teicoplanin	≤ 2	> 16	100.0	0.0
Tigecycline	0.25	0.5	91.7	-[e]
S. aureus **oxacillin-susceptible (24)**				
Ceftobiprole	0.5	0.5	100.0[d]	0.0[d]
Penicillin	> 8	> 8	29.2	70.8
Ampicillin	> 8	> 8	29.2	70.8
Cephalothin	≤ 4	≤ 4	91.7	4.2
Ceftriaxone	4	4	100.0	0.0
Cefepime	2	4	100.0	0.0
Clindamycin	≤ 0.25	≤ 0.25	95.8	4.2
Erythromycin	≤ 0.5	> 4	70.8	25.0
Gentamicin	≤ 1	> 8	79.2	16.7
Levofloxacin	≤ 0.5	≤ 0.5	100.0	0.0
Linezolid	4	4	100.0	0.0
Tigecycline	0.25	0.5	100.0	-[e]
Vancomycin	1	2	100.0	0.0
Teicoplanin	≤ 2	≤ 2	100.0	0.0

[a]MIC determined according CLSI (2009) recommendations.
[b]Resistance rates calculated according CLSI M100-S21 (2011) document, except for tigecycline, for which the FDA criteria was used.
[c]Susceptible rates calculated considering the high level of gentamicin and streptomicin resistance.
[d]Interpretative criteria according to Rossolini et al.[14]
[e]Interpretative criteria not established by CLSI or FDA.

Table 6. Antimicrobial activity of ceftobiprole tested against **E. faecalis, S. aureus,** *and CoNS isolates collected from hospitalized patients as part of the INVITA-A-CEFTO Brazilian Study*

Organism (No. tested)	Cumulative % inhibited at MIC (µg/mL)							
	≤ 0.12	0.25	0.5	1	2	4	8	≥ 16
E. faecalis (18)		33.3	61.1	88.9	88.9	88.9	88.9	100.0
CoNS (23)	4.3	17.4	30.4	52.2	95.7	95.7	100.0	
Staphylococcus aureus (SA, 36)		16.7	72.2	83.3	94.4	100.0		
Oxacillin-susceptible SA (24)		25.0	100.0					
Oxacillin-resistant SA (12)			16.7	50.0	83.3	100.0		

observed among Gram-negative bacilli isolates collected from private hospitals were higher than those previously reported by other surveillance studies that evaluated bacterial isolates mostly collected from public/teaching hospitals.[20]

There has been a dramatic rise in antibiotic resistance in the hospital setting in the past decade. MRSA and carbapenem-resistant Gram-negative bacilli are of particular concern.[6] There is an urgent need to expand treatment options for treating infections caused by these pathogens. The activity of ceftobiprole against the *S. aureus* and CoNS isolates studied was good and warrant continued evaluation of ceftobiprole as therapy for severe infections, including skin and soft tissue infections, especially in those institutions/regions where MRSA is highly prevalent.

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