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In Vitro Activity of Ceftobiprole Against 10,035 Pathogens Obtained from Patients in Canadian Hospitals: CANWARD 2007 and 2008

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REVISED ABSTRACT

Background: Ceftobiprole demonstrates broad spectrum activity against both Gram-positive and Gram-negative bacteria. The purpose of this study was to compare the in vitro activity of ceftobiprole with that of cefepime against hospital pathogens obtained across Canada.
Methods: From January 2007-December 2008, 12 sentinel Canadian hospitals (10 centres - 2008) were asked to submit pathogens (consecutive, one per patient/infection site) from blood (360), respiratory (200), urine (100), and wound/IV (50) infections. 7881 and 5282 isolates were collected for 2007 and 2008, respectively. Susceptibility testing was performed using CLSI broth microdilution.
Results: MIC50s and MIC90s (µg/ml) are displayed below:

Organism (# isolates)	Ceftobiprole MIC_{50}/MIC_{90}	Cefepime MIC_{50}/MIC_{90}
SPN-All (1182)	≤ 0.06/ 0.06	≤ 0.06/ 0.12
SPN-PenI (103)	≤ 0.06/ 0.12	≤ 0.06/ 0.25
SPN-Pen (34)	0.25/0.5	0.5/1
MSSA (1826)	≤ 1/≤1	4/4
MRSA (657)	1/2	128/>128
CA-MRSA (149)	1/1	32/>32
HA-MRSA (477)	1/2	>64/>64
MSSE (185)	≤ 1/1	4/16
MRSE (28)	1/2	>32/>32
E. faecalis (254)	≤ 1/1	>32/>32
E. faecium (107)	>32/>32	>32/>32
E. coli (2833)	≤ 1/1	≤ 1/≤1
E. cloacae (280)	≤ 1/4	≤ 1/2
K. pneumoniae (771)	≤ 1/≤1	≤ 1/≤1
P. aeruginosa (1006)	4/16	4/32
P. mirabilis (203)	≤ 1/≤1	≤ 1/≤1
A. baumannii (40)	≤ 1/1	4/8
H. influenzae (513)	≤ 0.06/ 0.12	≤ 0.25/ 0.25

SPN-*S. pneumoniae*, HA-healthcare-associated, CA-community-associated, SE-*S. epidermidis.*
Conclusions: Ceftobiprole was more active in vitro than cefepime versus *S. aureus* (MSSA, MRSA), *S. epidermidis* (MSSE, MRSE), SPN, *E. faecalis* and *A. baumannii.*

ACKNOWLEDGEMENTS

The authors would like to thank the participating centres, investigators and laboratory site staff for their continued support. Financial support for the CANWARD study was provided in part by Janssen Ortho/Ortho McNeil.

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INTRODUCTION

Ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity, has been approved in Canada for the treatment of complicated skin and skin structure infections (cSSSI) and is pending approval by the United States FDA for complicated skin and skin structure infections and nosocomial pneumonia.

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, and is being jointly developed by Basilea Pharmaceutica AG and Johnson and Johnson Pharmaceutical Research and Development L.L.C. [1]. Ceftobiprole has an anti-Gram-positive spectrum that includes MRSA, while maintaining broad anti-gram-negative activity [1], and possesses resistance to hydrolysis by certain beta-lactamases produced by gram-positive and gram-negative pathogens.

MATERIALS AND METHODS

CANWARD Study Design

From January 2007-December 2008, 12 sentinel Canadian hospitals (10 centres-2008) were asked to submit pathogens (consecutive, one per patient/infection site) from blood (360), respiratory (200), urine (100), and wound/IV (50) infections. 7881 and 5282 isolates were collected for 2007 and 2008, respectively. Isolates were received from twelve sentinel hospitals that were geographically distributed in a population-based fashion in seven of the ten Canadian provinces. Isolates were collected from Canadian patients attending hospital clinics, emergency rooms, medical/surgical wards and intensive care units. All organisms were identified at the originating centre using local site criteria and were deemed clinically significant. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) on Amies semi-solid transport media where they were subcultured onto appropriate media and stocked in skim milk at -80°C.

Antimicrobial Susceptibility Testing

Following two subcultures from frozen stock, the in vitro activities of cefazolin, ceftobiprole, ceftriaxone, cefepime, clarithromycin, clindamycin, ciprofloxacin, daptomycin, doxycycline, ertapenem, levofloxacin, linezolid, meropenem, moxifloxacin, penicillin, piperacillin-tazobactam, tigecycline, trimethoprim-sulfamethoxazole and vancomycin were determined by broth microdilution in accordance with CLSI guidelines (2). The minimum inhibitory concentrations (MICs) of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre panels. Quality control was performed using the following ATCC organisms: *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. MIC interpretive standards were defined according to CLSI breakpoints (3). The following interpretive breakpoint (FDA) was used for tigecycline susceptible: *S. aureus*, ≤0.5 µg/ml; and *E. faecalis*, ≤0.25 µg/ml.

RESULTS

TABLE 1. Ceftobiprole in vitro activity against 4482 aerobic gram-positive bacteria isolated from patients in Canadian hospitals in 2007-2008

Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	MIC Range (µg/ml)	% Susceptible
Methicillin-susceptible *S. aureus* (1,826)	Cefazolin	≤0.5	1	≤0.5-2	100
	Cefepime	4	4	≤1-8	100
	Ceftobiprole	**0.25**	**0.5**	**0.12-2**	**100[d]**
	Ceftriaxone	4	4	1-8	100
	Ertapenem	0.25	0.25	0.12-0.5	100
	Meropenem	≤0.06	0.12	≤0.06-1	100
Methicillin-resistant *S. aureus* (657)	Cefazolin	128	>128	32->128	0
	Cefepime	>256	>256	32->256	0
	Ceftobiprole	**1**	**2**	**0.25-4**	**100[d]**
	Ceftriaxone	>256	>256	>256	0
	Ertapenem	8	>32	8->32	0
	Meropenem	16	>32	16->32	0
Methicillin-susceptible *S. epidermidis* (185)	Cefazolin	1	4	≤0.5-8	100
	Cefepime	4	16	≤1-8	100
	Ceftobiprole	**0.25**	**0.5**	**≤0.06-2**	**NA**
	Ceftriaxone	8	8	≤0.25-8	100
	Ertapenem	0.5	8	0.12-2	100
	Meropenem	1	8	≤0.06-4	100
Methicillin-resistant *S. epidermidis* (28)	Cefazolin	64	128	32-128	0
	Cefepime	64	128	32-128	0
	Ceftobiprole	**1**	**2**	**≤1-2**	**NA**
	Ceftriaxone	256	>256	64->256	0
	Ertapenem	>32	>32	16->32	0
	Meropenem	32	>32	16->32	0
Penicillin-susceptible[a] *S. pneumoniae* (931)	Cefuroxime	≤0.25	≤0.25	≤0.25-0.5	100
	Ceftobiprole	**≤0.06**	**≤0.06**	**≤0.06**	**NA**
	Ceftriaxone	≤0.06	≤0.06	≤0.06-0.25	100
	Ertapenem	≤0.06	≤0.06	≤0.06-0.12	100
	Meropenem	≤0.06	≤0.06	≤0.06-0.12	100
Penicillin-intermediate[b] *S. pneumoniae* (180)	Cefuroxime	≤0.25	2	≤0.25-2	86.7
	Ceftobiprole	**≤0.06**	**0.12**	**≤0.06-0.5**	**NA**
	Ceftriaxone	≤0.06	0.25	≤0.06-2	100
	Ertapenem	≤0.06	0.25	≤0.06-0.25	100
	Meropenem	≤0.06	0.25	≤0.06-0.25	100
Penicillin-resistant[c] *S. pneumoniae* (56)	Cefuroxime	4	16	1->16	16.1
	Ceftobiprole	**0.25**	**0.5**	**≤0.06-0.5**	**NA**
	Ceftriaxone	0.5	1	0.25-4	91
	Ertapenem	0.5	1	≤0.06-2	98.2
	Meropenem	0.5	1	≤0.06-2	37.5
***S. pyogenes* (170)**	Cefuroxime	≤0.25	≤0.25	≤0.25	NA
	Ceftobiprole	**≤0.06**	**≤0.06**	**≤0.06**	**100[d]**
	Ceftriaxone	≤0.06	≤0.06	≤0.06	100
	Ertapenem	≤0.06	≤0.06	≤0.06-0.12	100
	Meropenem	≤0.06	≤0.06	≤0.06-0.12	100
***S. agalactiae* (88)**	Cefuroxime	≤0.25	≤0.25	≤0.25-0.5	NA
	Ceftobiprole	**≤0.06**	**≤0.06**	**≤0.06**	**100[d]**
	Ceftriaxone	≤0.06	≤0.06	≤0.06-0.25	100
	Ertapenem	≤0.06	≤0.06	≤0.06	100
	Meropenem	≤0.06	≤0.06	≤0.06	100
***E. faecalis* (254)**	Cefazolin	32	>128	0.5->128	NA
	Cefepime	128	128	≤0.25->128	NA
	Ceftobiprole	**0.5**	**1**	**≤0.06->32**	**NA**
	Ceftriaxone	>256	>256	≤0.25->256	NA
	Ertapenem	8	16	0.25->32	NA
	Meropenem	4	8	≤0.06->32	NA
***E. faecium* (107)**	Cefazolin	>128	>128	32->128	NA
	Cefepime	>128	>128	2->128	NA
	Ceftobiprole	**128**	**128**	**0.25-128**	**NA**
	Ceftriaxone	>256	>256	0.5->256	NA
	Ertapenem	>32	>32	2->32	NA
	Meropenem	>32	>32	2->32	NA

[a] Penicillin-susceptible, MIC ≤0.06 µg/ml.
[b] Penicillin-intermediate, MIC 0.12-1 µg/ml.
[c] penicillin-resistant, MIC ≥2 µg/ml.
[d] Ceftobiprole MICs interpreted using Health Canada approved breakpoints.

TABLE 2. Ceftobiprole in vitro activity against 5587 aerobic gram-negative bacteria isolated from patients in Canadian hospitals in 2007-2008

Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	MIC Range (µg/ml)	% Susceptible
***E. coli* ESBL-negative (2605)**	Amoxicillin-clavulanate	4	8	0.5-32	96.4
	Cefazolin	2	8	≤0.5->128	97.7
	Cefepime	≤1	≤1	≤1-32	99.8
	Cefoxitin	4	8	≤0.06->32	92.3
	Ceftobiprole	**≤0.06**	**≤0.06**	**≤0.06->128**	**99.5[d]**
	Ceftriaxone	≤0.25	≤0.25	≤0.25->256	98.4
	Ertapenem	≤0.06	≤0.06	≤0.06-1	100
	Meropenem	≤0.06	≤0.06	≤0.06-0.5	100
	Piperacillin-tazobactam	2	4	≤1->512	97.6
***E. coli* ESBL-positive (108)**	Amoxicillin-clavulanate	8	16	2-32	78.7
	Cefazolin	>128	>128	32->128	0
	Cefepime	16	>128	≤1->128	46.3
	Cefoxitin	8	16	0.5->128	82.4
	Ceftobiprole	**32**	**>128**	**0.12->128**	**1.9[d]**
	Ceftriaxone	>256	>256	2->256	8.3
	Ertapenem	≤0.06	0.12	≤0.06-0.25	100
	Meropenem	≤0.06	≤0.06	≤0.06	100
	Piperacillin-tazobactam	4	16	≤1->512	90.7
***K. pneumoniae* ESBL-negative (743)**	Amoxicillin-clavulanate	2	4	0.5-32	96.9
	Cefazolin	2	8	≤0.5->128	93.8
	Cefepime	≤1	≤1	≤1->128	100
	Cefoxitin	4	8	1->128	93
	Ceftobiprole	**≤0.06**	**≤0.06**	**≤0.06-32**	**99.1[d]**
	Ceftriaxone	≤0.25	≤0.25	≤0.25-64	99.3
	Ertapenem	≤0.06	≤0.06	≤0.06-1	100
	Meropenem	≤0.06	≤0.06	≤0.06-0.25	100
	Piperacillin-tazobactam	2	8	≤1->512	97.2
***K. pneumoniae* ESBL-positive (17)**	Amoxicillin-clavulanate	8	16	4-16	82.4
	Cefazolin	>128	>128	16->128	0
	Cefepime	8	>128	≤1->128	52.9
	Cefoxitin	8	64	2->128	70.6
	Ceftobiprole	**32**	**>128**	**≤0.06->128**	**10.0[d]**
	Ceftriaxone	>256	>256	≤0.5->256	35.3
	Ertapenem	≤0.06	0.25	≤0.06-0.25	100
	Meropenem	0.12	0.12	0.12-0.25	100
	Piperacillin-tazobactam	16	512	2->512	70.6
***K. oxytoca* (176)**	Amoxicillin-clavulanate	2	8	1-16	93.5
	Cefazolin	8	64	≤0.5->128	59.7
	Cefepime	≤0.25	≤0.25	≤0.25-16	99.4
	Cefoxitin	2	4	1-16	96.3
	Ceftobiprole	**≤0.06**	**2**	**≤0.06-128**	**89.2[d]**
	Ceftriaxone	≤0.25	1	≤0.25-32	95.5
	Ertapenem	≤0.06	≤0.06	≤0.06	100
	Meropenem	≤0.06	≤0.06	≤0.06-0.12	100
	Piperacillin-tazobactam	2	128	≤1-512	89.2
***E. cloacae* (280)**	Amoxicillin-clavulanate	16	>32	2->32	27.4
	Cefazolin	128	>128	1->128	5.7
	Cefepime	≤0.25	2	≤0.25-8	99.6
	Cefoxitin	>32	>32	4->32	22.6
	Ceftobiprole	**≤0.06**	**4**	**≤0.06-64**	**85.0[d]**
	Ceftriaxone	≤0.25	>256	≤0.25->256	81.4
	Ertapenem	≤0.06	0.5	≤0.06-2	98.9
	Meropenem	≤0.06	≤0.06	≤0.06-0.5	100
	Piperacillin-tazobactam	2	64	≤1-512	84.3
***P. mirabilis* (203)**	Amoxicillin-clavulanate	1	4	0.5->32	95.8
	Cefazolin	8	16	1-64	87.7
	Cefepime	≤0.25	≤0.25	≤0.25-2	100
	Cefoxitin	4	8	2-16	94.1
	Ceftobiprole	**≤0.06**	**0.12**	**≤0.06-2**	**99.0[d]**
	Ceftriaxone	≤0.25	≤0.25	≤0.25-4	99.5
	Ertapenem	≤0.06	≤0.06	≤0.06-0.12	100
	Meropenem	≤0.06	≤0.06	≤0.06-0.25	100
	Piperacillin-tazobactam	≤1	≤1	≤1-2	100
***S. marcescens* (176)**	Amoxicillin-clavulanate	32	>32	4->32	2.6
	Cefazolin	>128	>128	2->128	0.9
	Cefepime	≤0.25	≤0.25	≤0.25-8	100
	Cefoxitin	16	>32	4->32	20.4
	Ceftobiprole	**≤0.06**	**0.5**	**≤0.06-8**	**95.5[d]**
	Ceftriaxone	≤0.25	1	≤0.25->64	92.5
	Ertapenem	≤0.06	≤0.06	≤0.06-0.5	100
	Meropenem	≤0.06	≤0.06	≤0.06-2	100
	Piperacillin-tazobactam	2	8	≤1-128	94.4
***P. aeruginosa* (1006)**	Cefepime	4	32	≤0.25->128	72.4
	Ceftobiprole	**4**	**16**	**0.25->128**	**NA**
	Ceftriaxone	32	256	≤0.25->256	23
	Ertapenem	8	>32	0.12->32	NA
	Meropenem	0.5	8	≤0.06->64	88.8
	Piperacillin-tazobactam	4	64	≤1->512	92.5
***S. maltophilia* (163)**	Amoxicillin-clavulanate	>32	>32	4->32	NA
	Cefepime	64	128	≤0.25->128	NA
	Ceftobiprole	**128**	**128**	**0.5->128**	**NA**
	Ceftriaxone	256	256	8->256	NA
	Ertapenem	>32	>32	0.12->32	NA
	Meropenem	>64	>64	≤0.06->64	NA
	Piperacillin-tazobactam	256	>512	16->512	NA
***A. baumannii* (40)**	Amoxicillin-clavulanate	8	>32	2->32	NA
	Cefepime	4	8	≤0.25->128	90
	Ceftobiprole	**1**	**1**	**0.12-128**	**NA**
	Ceftriaxone	16	32	4->256	32.5
	Ertapenem	4	16	2->32	NA
	Meropenem	0.5	2	≤0.06-32	97.5
	Piperacillin-tazobactam	4	32	≤1->512	82.5
***M. catarrhalis* (70)**	Amoxicillin-clavulanate	0.12	0.25	≤0.06-0.5	100
	Cefazolin	128	>128	1->128	NA
	Cefepime	≤0.25	2	≤0.25-8	NA
	Ceftobiprole	**0.12**	**0.5**	**≤0.06-1**	**NA**
	Ceftriaxone	≤0.25	1	≤0.25-1	100
	Ertapenem	≤0.06	≤0.06	≤0.06-0.12	NA
	Meropenem	≤0.06	≤0.06	≤0.06	NA
	Piperacillin-tazobactam	≤1	≤1	≤1	NA

ESBL = extended spectrum ß-lactamase
[d] Ceftobiprole MICs interpreted using Health Canada approved breakpoints.
NA = not available
M45 used to interpret *M. catarrhalis* MICs.

CONCLUSIONS

1. Against methicillin-susceptible and methicillin-resistant *S. aureus* (including both community- and nosocomial-associated strains), ceftobiprole was more active than cefepime.
2. Against methicillin-susceptible and methicillin-resistant *S. epidermidis* ceftobiprole was more active than cefepime.
3. Against penicillin-resistant *S. pneumoniae* and *E. faecalis*, ceftobiprole was more active than cefepime.
4. Ceftobiprole was more active than cefepime versus *P. aeruginosa*.
5. Ceftobiprole was more active than cefepime versus *A. baumannii*.

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