In Vitro Activities of Ceftobiprole and Comparators versus *Streptococcus pneumoniae* (SPN) Isolated in Hospital Laboratories across Canada: CANWARD 2007 and 2008

E-196

University of Manitoba

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ABSTRACT

Background: Ceftobiprole (BPR) is a broad-spectrum cephalosporin with activity against MRSA and penicillin-resistant (PR) SPN. The purpose of this study was to compare the activity of BPR to ceftriaxone (CTR) and cefuroxime (CXM) against SPN with various penicillin resistance phenotypes obtained from Canadian hospitals.
Methods: From Jan- 2007- Dec 2008, 12 sentinel Canadian hospitals (10 centres - 2008) submitted pathogens from patients attending hospital clinics, emergency room, medical and surgical wards and intensive care units. 7881 and 5282 isolates were collected for 2007 and 2008, respectively. Susceptibility testing was performed using CLSI broth microdilution.
Results: The activity of BPR, CTR and CXM against blood (n=335) and respiratory (n=847) SPN is shown in the table.

Specimen Phenotype (n)	MIC 50/90 µg/ml Ceftobiprole	Ceftriaxone	Cefuroxime
Blood			
All (335)	≤0.06/≤0.06	≤0.06/≤0.06	≤0.25/≤0.25
Pen S (280)	≤0.06/≤0.06	≤0.06/≤0.06	≤0.25/≤0.25
Pen I (41)	≤0.06/0.12	≤0.06/0.25	≤0.25/2
Pen R (9)	0.25/0.25	0.5/1	4/8
MDR (4)	0.25/0.25	0.5/1	4/8
Respiratory			
All (847)	≤0.06/0.12	≤0.06/0.12	≤0.25/0.5
Pen S (652)	≤0.06/≤0.06	≤0.06/≤0.06	≤0.25/≤0.25
Pen I (139)	≤0.06/0.12	≤0.06/0.25	≤0.25/2
Pen R (47)	0.25/0.5	0.5/2	4/16
MDR (25)	0.25/0.5	1/2	8/16

Pen S- penicillin susceptible, ≤0.06µg/ml; Pen I-penicillin intermediate, 0.12-1µg/ml; Pen-R-penicillin resistant, ≥ 2µg/ml.MDR penicillin-resistant; ≥2µg/ml and clarithromycin-resistant, ≥1µg/ml.

Conclusions: Ceftobiprole was more active than both ceftriaxone and cefuroxime against penicillin-intermediate, penicillin-resistant and MDR (penicillin-resistant and macrolide-resistant) *S. pneumoniae*.

INTRODUCTION

Streptococcus pneumoniae is an important cause of both invasive and non-invasive infections in the community and also in the hospital. *S. pneumoniae* is the most common pathogen, responsible for at least 15% of community-acquired pneumonia (CAP) cases, 20% of which are thought to become bacteremic and require hospitalization. Fatality rates for pneumonia due to *S. pneumoniae* remain high, in the range of 15-36%, and are highest among bacteremic pneumococcal pneumonia. *S. pneumoniae* is also an important cause of meningitis, otitis media and bacteremia.
β-lactams and macrolides are among the principal therapeutic agents used for the empiric treatment of CAP, however this choice is complicated by the increasing prevalence of antimicrobial resistance. During the 1980s infections due to penicillin non-susceptible pneumococci became widespread. Today, *S. pneumoniae* has acquired resistance to several classes of antimicrobial agents, including penicillins, macrolides, trimethoprimsulfa-methoxazole, and flouroquinlones and by variety of mechanisms. Although recent introduction of pneumococcal conjugate vaccine led to a decrease in invasive pneumococcal disease, multidrug resistant strains of *S. pneumoniae* not covered by the vaccine have emerged and are increasing which may result in treatment failure.

Ceftobiprole medocaril is the parenteral prodrug of ceftobiprole, a novel pyrrolidinone broad-spectrum cephalosporin with in vitro and in vivo bactericidal activities against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Ceftobiprole exerts its antibacterial activity by inhibiting the penicillin-binding proteins (PBPs) involved in cell wall synthesis. It has an established stability against hydrolysis by many gram-positive beta-lactamases and a higher affinity for various PBPs (such as PBP2a of MRSA or PBP2x of *Streptococcus pneumoniae*), which leads to a wider spectrum of activity compared with older beta-lactams. Ceftobiprole, a cephalosporin, is currently in Phase III clinical development in the USA and UK, but has recently been approved for use in patients in both Canada and Switzerland. Ceftobiprole is a broad-spectrum cephalosporin with demonstrated in vitro activity against Gram-positive cocci, including MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae*, *Enterococcus faecalis*, Gram-negative bacilli including AmpC-producing *Escherichia coli* and *Pseudomonas aeruginosa* but excluding extendedspectrum b-lactamase (ESBL)-producing strains.

PURPOSE

The purpose of this study was to compare the in vitro activity of BPR to CTR and CXM against blood and respiratory SPN with various penicillin and multidrug - resistant phenotypes.

MATERIALS AND METHODS

Bacterial Isolates:

The CANWARD 2007 and CANWARD 2008 study included 12 and 10 medical centres, respectively, from all regions of Canada (www.can-r.com). Each centre collected and submitted clinical isolates from patients attending hospital clinics (HS), emergency rooms (ER), medical (MED) and surgical (SUR) wards, and intensive care units (ICUs). During 2007 and 2008, respectively each centre was asked to submit clinical isolates, consecutive, one organism/infection site per patient from blood (n=30/month, n=20/month), respiratory (n=200, n=150), urine (n=100, n=100), and wound/intravenous infections (n=50, n=50). All organisms were identified at the originating centre using local site criteria and were deemed clinically significant. A total of 7881 and 5282 isolates, including 664 (445 respiratory), and 522 (405 respiratory) SPN were collected in 2007 and 2008 respectively. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Manitoba, Canada) on Amis charcoal swabs. All received isolates were subcultured onto appropriate media, and stocked in skim milk at -80°C until antimicrobial susceptibility tested was carried out.

Antimicrobial Susceptibilities:

Susceptibility testing was carried out using microbroth dilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. Antimicrobial agents were obtained as laboratory grade powders from their respective manufactures. Stock solutions were prepared and dilutions made as described by CLSI guidelines. The MICs of the antimicrobial agents were determined using a custom designed 96-well microtitre plates containing doubling antimicrobial dilutions in 100µl/well Cation Adjusted Mueller-Hinton Broth (CAMHB) with 2.5-5% Laked Horse Blood (LHB), inoculated to a final concentration of approximately 5 x105 CFU/ml and incubated at 37°C in 5% CO2 for 20-24hr. Colony counts were performed periodically to confirm inocula counts. Quality control was performed using ATCC QC *S. pneumoniae* 49619.

CONCLUSIONS

Ceftobiprole was 2 and 16-fold more active than ceftriaxone and cefuroxime, respectively against penicillin-intermediate blood and respiratory *S. pneumoniae.*

Ceftobiprole was 4 and 32-fold more active than ceftriaxone and cefuroxime, respectively against penicillin-resistant blood and respiratory *S. pneumoniae.*

Ceftobiprole was 2 and 8-fold and 4 and 16-fold more active than ceftriaxone and cefuroxime, against macrolide-resistant blood and respiratory *S. pneumoniae,* respectively.

Ceftobiprole was 4 and 16-fold and 2 and 16-fold more active than ceftriaxone and cefuroxime, against MDR blood and respiratory *S. pneumoniae.*

0.5µg/ml was the highest ceftobiprole MIC observed compared to 4µg/ml and 16µg/ml for ceftriaxone and cefuroxime, respectively.

ACKNOWLEDGEMENTS

Funding for the CANWARD study was provided in part by the University of Manitoba, Health Sciences Center in Winnipeg, National Microbiology Laboratory-Health Canada, Abbott, Affinium Inc., Astellas, Bayer, Janssen Ortho Inc., Oryx, Pfizer Canada, TaiGen, Targanta, and Wyeth Inc. This study was in part supported by the Manitoba Institute of Child Health (MICH). The authors would like to thank the investigators and laboratory site staff at each medical center that participated in the CANWARD 2007 and 2008 study.

RESULTS

Table 1. In vitro activities of BPR vs. comparators against blood and respiratory SPN isolates obtained during CANWARD 2007.

Antimicrobial Agent	MIC (µg/ml) 50%	90%	Range	% of isolates that were Susceptible	Intermediate	Resistant
Blood (n=218)						
Ceftobiprole*	≤0.06	≤0.06	≤0.06-0.25			
Ceftriaxone	≤0.06	≤0.06	≤0.06-1	100.0	0.0	0.0
Cefuroxime	≤0.25	≤0.25	≤0.25-4	96.8	1.8	1.4
Respiratory (n=442)						
Ceftobiprole	≤0.06	≤0.06	≤0.06-0.5			
Ceftriaxone	≤0.06	0.12	≤0.06-4	99.5	0.23	0.23
Cefuroxime	0.25	0.5	≤0.25->16	95.0	2.3	2.7

Ceftobiprole- No breakpoints defined for SPN.

Table 2. In vitro activities of BPR vs. comparators against blood and respiratory SPN isolates obtained during CANWARD 2008.

Antimicrobial Agent	MIC (µg/ml) 50%	90%	Range	% of isolates that were Susceptible	Intermediate	Resistant
Blood (n=117)						
Ceftobiprole	≤0.03	0.06	≤0.03-0.25			
Ceftriaxone	≤0.06	≤0.06	≤0.06-1	100.0	0.0	0.0
Cefuroxime	≤0.25	≤0.25	≤0.25-8	93.9	1.7	4.4
Respiratory (n=405)						
Ceftobiprole	≤0.03	0.12	≤0.03-0.5			
Ceftriaxone	≤0.06	0.12	≤0.06-4	99.0	0.7	0.25
Cefuroxime	≤0.25	1	≤0.25-16	91.3	2.2	6.5

Ceftobiprole- No breakpoints defined for SPN.

Figure 1. In vitro activities of BPR vs. comparators against respiratory SPN obtained during CANWARD 2007 and 2008.

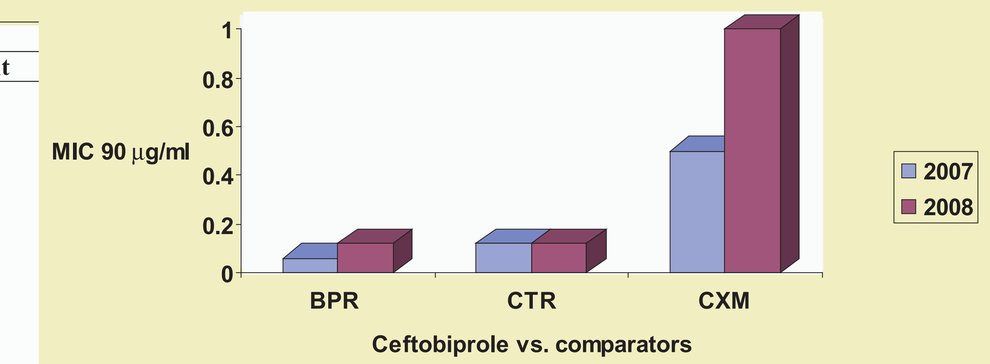


Figure 2. In vitro activities of BPR vs. comparators against blood SPN obtained during CANWARD 2007 and 2008.

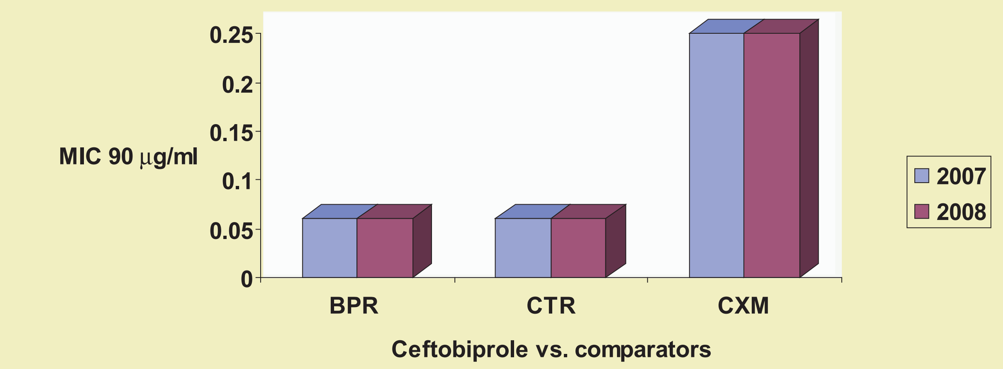


Figure 3. Ceftobiprole MIC distribution for all SPN obtained during CANWARD 2007 and 2008 Study.

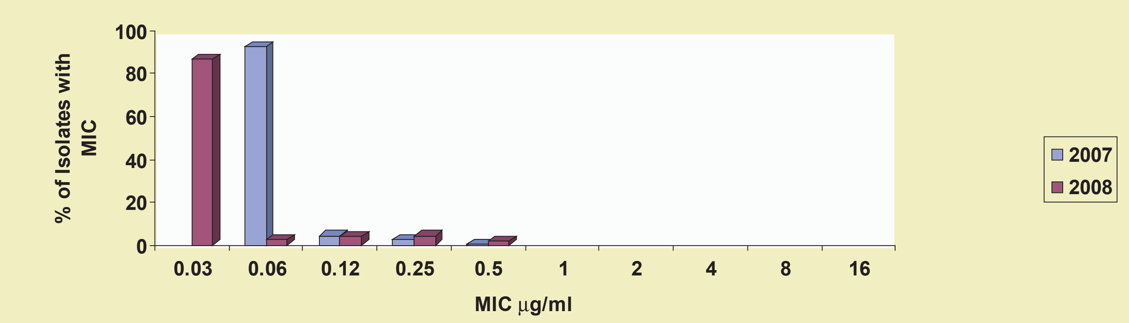


Figure 4. In vitro activity of BPR against SPN with various antibiotic resistance phenotypes.

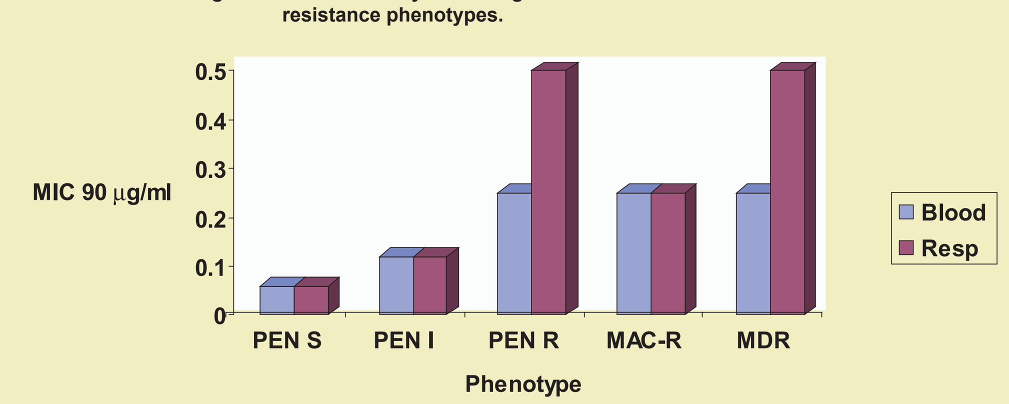


Figure 5. In vitro activity of CTR against SPN with various antibiotic resistance phenotypes.

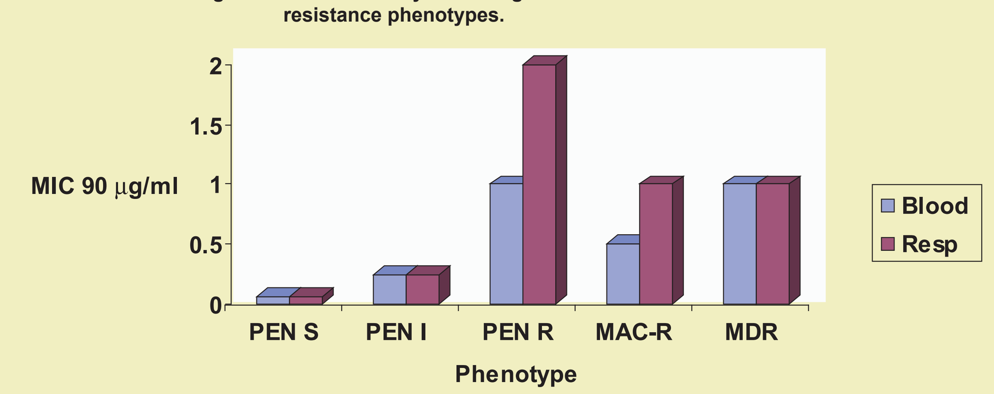


Figure 6. In vitro activity of CXM against SPN with various antibiotic resistance phenotypes.

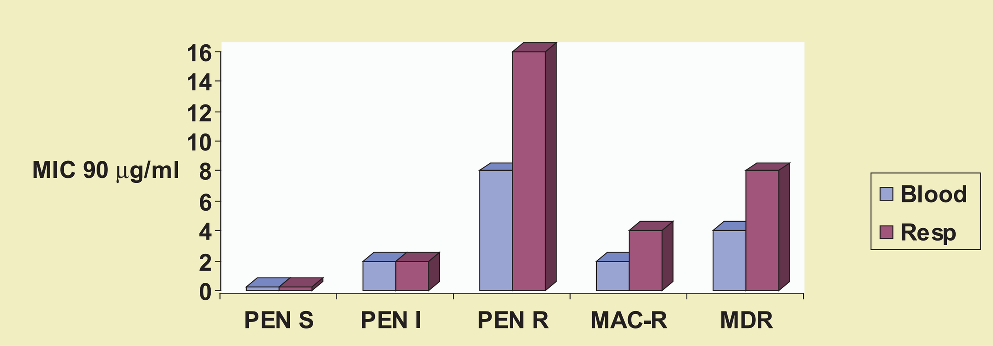


Table 3. In vitro activities of BPR vs. comparators against blood and respiratory SPN isolates with different phenotypes.

Antimicrobial Agent	PEN S MIC (µg/ml) 50%	90%	Range	PEN I MIC (µg/ml) 50%	90%	Range	PEN R MIC (µg/ml) 50%	90%	Range	MACROLIDE R MIC (µg/ml) 50%	90%	Range	MDR MIC (µg/ml) 50%	90%	Range
Blood (n=335)															
Ceftobiprole	≤0.06	≤0.06	≤0.06-0.06	≤0.06	0.12	≤0.06-0.25	025	0.25	0.12-0.25	≤0.06	0.25	≤0.06-0.25	≤0.06	0.25	≤0.06-0.25
Ceftriaxone	≤0.06	≤0.06	≤0.06-0.25	≤0.06	0.25	≤0.06-0.5	0.5	1	≤0.06-1	≤0.06	0.5	≤0.06-1	≤0.06	1	≤0.06-1
Cefuroxime	≤0.25	≤0.25	≤0.25-0.5	≤0.25	2	≤0.25-4	4	8	1-8	≤0.25	2	≤0.25-8	≤0.25	4	≤0.25-8
Respiratory (n=847)															
Ceftobiprole	≤0.06	≤0.06	≤0.06-0.06	≤0.06	0.12	≤0.06-0.5	0.25	0.5	≤0.06-0.5	≤0.06	0.25	≤0.06-0.5	0.06	0.5	≤0.06-0.5
Ceftriaxone	≤0.06	≤0.06	≤0.06-0.12	≤0.06	0.25	≤0.06-2	0.5	2	≤0.06-4	≤0.06	1	≤0.06-4	0.12	1	≤0.06-4
Cefuroxime	≤0.25	≤0.25	≤0.25-1	≤0.25	2	≤0.25-16	4	16	1->16	≤0.25	4	≤0.25->16	0.5	8	≤0.25->16

MDR- Defined as penicillin non-susceptible (MIC≥0.12µg/ml) and clarithromycin non-susceptible (MIC ≥0.5µg/ml).
Macrolide R- Defined as macrolide non-susceptible (MIC ≥0.5µg/ml).

Figure 7. Activities of BPR, CTR, and CXM against penicillin-resistant, macrolide-resistant and multidrug resistant blood SPN.

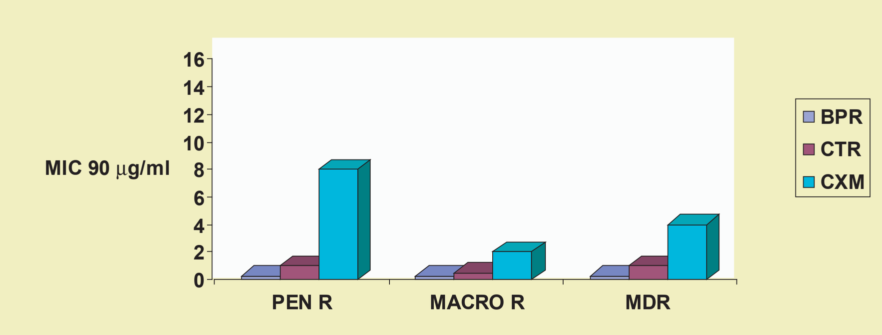
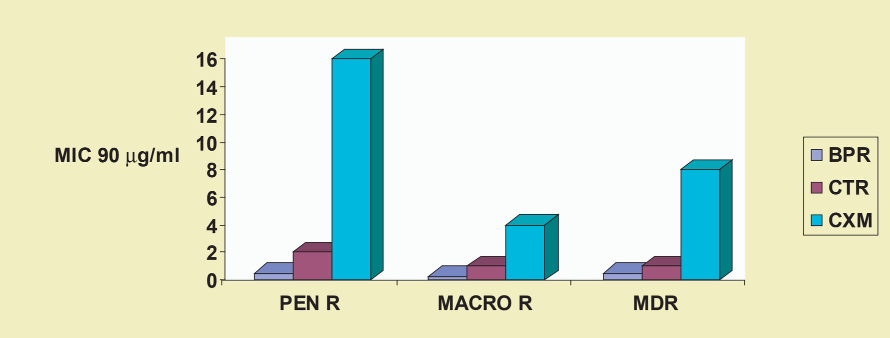


Figure 8. Activities of BPR, CTR, and CXM against penicillin-resistant, macrolide-resistant and multidrug resistant respiratory SPN.



49th ICAAC, San Francisco, CA, September 12-15, 2009