

Activities of Ceftaroline, Ceftriaxone and Cefthromycin Against Multi-Drug Resistant (MDR) *Streptococcus pneumoniae* Isolates from Canadian Bacterial Surveillance Network (CBSN)



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ABSTRACT

Background: CBSN has conducted cross-Canada *S. pneumoniae* surveillance since 1987. During the last 5 years we have witnessed not only an increase in the prevalence of MDR (resistance to more than 2 classes of antibiotics) *S. pneumoniae*, but also an increase in the degree of R to the β -lactam antibiotics, including penicillin (PEN), amoxicillin (AMOX) and ceftriaxone.

Methods: In order to evaluate the activity of new antibiotics including ceftazidime, ceftazidime, ceftazidime and cefthromycin against MDR *S. pneumoniae*, we selected a representative sample of 219 isolates between 2003 and 2007. Susceptibility testing by broth-microdilution and breakpoint interpretation was performed as per 2008 CLSI guidelines including the use of the new parenteral PEN non-meningeal breakpoints (S: ≤ 2 $\mu\text{g/ml}$, I: 4 $\mu\text{g/ml}$, R: ≥ 8 $\mu\text{g/ml}$).

Results: Of 219 selected isolates, 25.5% were from blood, 35.6% from sputum, 14.7% from ear and 24.2% from other sites. *In vitro* susceptibility assay demonstrated that ceftazidime and ceftazidime were more potent than ceftriaxone against both PEN S and non-susceptible (NS) isolates. Ceftazidime was the most active against PEN NS with MIC₉₀ values 8-fold lower than ceftriaxone and 4-fold lower than ceftazidime. The MIC₉₀ of cefthromycin was similar to telithromycin (0.03 $\mu\text{g/ml}$) against ERY S isolates and more potent against ERY R isolates with a 4-fold lower MIC₉₀.

MIC ($\mu\text{g/ml}$) (N)	Ceftriaxone		Ceftaroline		Ceftazidime		Telithromycin		Cefthromycin	
	MIC ₅₀	MIC ₉₀								
≤ 2 (42)	1	2	0.12	0.25	0.5	0.5	0.25	2	0.12	0.25
>2 (176)	2	2	0.25	0.25	0.5	1	0.5	0.5	0.12	0.12
AMOX										
<8 (78)	1	2	0.12	0.25	0.5	1	0.25	0.5	0.12	0.25
≥ 8 (140)	2	4	0.25	0.25	0.5	1	0.5	0.5	0.12	0.12
ERY										
<1 (15)	1	4	0.25	0.25	0.5	1	0.01	0.03	0.03	0.03
≥ 1 (203)	2	2	0.12	0.25	0.5	1	0.5	0.5	0.12	0.12

Conclusion: Ceftazidime, ceftazidime, and cefthromycin demonstrate potent *in vitro* activities against MDR *S. pneumoniae* isolates and suggest that these drugs could become important in treating infections due to emerging β -lactam R *S. pneumoniae* isolates.

INTRODUCTION

• The most commonly recommended antimicrobial drugs for treatment of *S. pneumoniae* are β -lactams and macrolides

• Recent trend shows increase in prevalence of MDR pneumococcal isolates in Canada to widely used antimicrobial agents

• A New β -lactam agents ceftazidime and ceftazidime, have wide spectrum of activity against gram-positive and gram-negative organisms including MRSA, *S. pneumoniae* and Enterobacteriaceae

• A newly developed ketolide, cefthromycin, also exhibits potent activity against macrolide resistant gram-positive bacteria

OBJECTIVE

To determine *in vitro* activities of ceftaroline, ceftazidime and cefthromycin against MDR *S. pneumoniae* isolates in Canada

METHODS AND MATERIALS

CBSN is comprised of over 100 volunteer groups of private and hospital-affiliated laboratories from across Canada. Since 1987, laboratories submit *S. pneumoniae* isolates as a part of a nation-wide surveillance program. Susceptibilities to all isolates submitted to a central location are assessed according to CLSI. In addition, isolates are serotyped.

For this study, we selected from our database a representative sample of pneumococci between 2003 and 2007. We selected isolates that were considered multi-drug resistant as defined by resistance to 2 or more classes of drugs. *In vitro* susceptibility testing was performed by broth microdilution according to CLSI guidelines.

RESULTS

Table 1. Characteristics of *S. pneumoniae* isolates.

Year of Isolation	# of isolates (% of total)	Serotypes N (%)	
		19A	19F
2003	35 (16.1)	0(0)	25(71.4)
2004	43 (19.7)	2(4.6)	25(58.1)
2005	54 (24.8)	8(14.8)	28(51.8)
2006	47 (21.6)	14(29.8)	27(57.4)
2007	39 (17.9)	15(38.5)	17(43.6)
Total	219*	39	122

Site Type	# of isolates (% of total)
Non Sterile	157 (71.7)
Sterile	61 (27.9)

Age (yrs)	# of isolates (% of total)
0-15	80(36.5)
16-64	73(33.3)
≥ 65	64 (29.2)

Geographic Area

Western Canada (AB, BC, SK)	13
Manitoba	12
Ontario	145
Quebec	15
Eastern Canada (NF, NS, PEI)	33
*Demographic information on 1 isolate was not known	

• Overall, 96.3% of isolates were R to PEN, 63.9% to AMOX, 68.9% to ceftriaxone and clindamycin, 92.7% to erythromycin (ERY) and trimethoprim, and 72.6% to tetracycline

• The prevalence of serotype 19A among MDR isolates increased from 0% in 2003 to 38.5% in 2007

• Overall, MIC₉₀ of ceftazidime was 8 fold lower, and MIC₉₀ of ceftazidime was 2 fold lower compared with the MIC₉₀ of ceftriaxone (2 $\mu\text{g/ml}$) (Table 2)

• MIC₉₀ of cefthromycin was 4 fold lower than MIC₉₀ of telithromycin (0.50 $\mu\text{g/ml}$) (Table 2)

• Among PEN NS isolates, MIC₉₀ of ceftazidime (0.25 $\mu\text{g/ml}$) was 8-fold lower than ceftriaxone (2 $\mu\text{g/ml}$) and 4-fold lower than ceftazidime (1 $\mu\text{g/ml}$) (table in abstract)

• Among AMOX R isolates, ceftazidime and ceftazidime were more potent with MIC₉₀ 16- and 4-fold lower than MIC₉₀ of ceftriaxone (4 $\mu\text{g/ml}$) (Table in abstract)

• MIC₉₀ of cefthromycin was 4-fold lower than that of telithromycin among ERY R isolates (Table in abstract)

Table 2. *In vitro* activities of new antimicrobial agents against *S. pneumoniae* isolates.

Drugs	Minimal Inhibitory Concentration ($\mu\text{g/ml}$)											N (% of isolates)	Total		
	0.01	0.03	0.06	0.12	0.25	0.50	1	2	4	8	16			32	64
Amoxicillin			6 (2.7)					2 (0.9)	1 (0.5)	69 (31.6)	139 (63.8)	1 (0.5)			218
Ceftriaxone §					7 (3.2)	1 (0.5)	58 (26.6)	134 (61.5)	13 (6.0)	5 (2.3)					218
Ceftaroline §		4 (1.8)		113 (51.6)	44.3 (20.3)	5 (2.3)									219
Ceftazidime §		4 (1.8)			3 (1.4)	170 (77.6)	41 (18.7)	1 (0.5)							219
Erythromycin				14 (6.42)		1 (0.5)		6 (2.7)	7 (3.2)	31 (14.2)	7 (3.2)	26 (11.9)	126 (57.8)		218
Telithromycin	12 (5.5)	7 (3.2)	17 (7.8)	9 (4.1)	64 (29.4)	100 (45.9)	2 (0.9)	6 (2.7)		1 (0.5)					218
Cefthromycin §		40 (18.3)	50 (22.8)	115 (52.5)	8 (3.6)	3 (1.4)		2 (0.9)	1 (0.5)						219

Note:
 Bolded values represent MIC₉₀.
 Yellow shaded boxes correspond to intermediate MIC values according to CLSI.
 § MIC interpretive standards have not been established by CLSI.

SUMMARY AND CONCLUSION

• Prevalence of MDR serotype 19A has increased significantly in last five years

• Ceftazidime and ceftazidime exhibit potent activity against MDR pneumococci than ceftriaxone

• Ceftazidime demonstrated most potent activity among the β -lactam antibiotics tested

• Cefthromycin is significantly more active than telithromycin against MDR *S. pneumoniae*

• These drugs could play a major role in treatment of pneumococcal infection caused by MDR strains.