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Antimicrobial Activity of Ceftaroline Tested against Multidrug Resistant (MDR) *Streptococcus pneumoniae* in the USA (2009-2012)

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Amended Abstract

Background: The increase in MDR *S. pneumoniae* (SPN) strains has led to reduced therapeutic choices and poor patient outcomes. Ceftaroline (CPT) fosamil is an intravenous prodrug and its active component, CPT, is active in vitro against SPN including ceftriaxone (CRO)- and penicillin (PEN)-resistant (R) strains due to its high affinity for PBP2X and MRSA due to its high affinity for PBP2a.

Methods: Isolates were consecutively collected from patients from 163 USA medical centers with community and hospitalized respiratory tract infections (RTI). A total of 6,958 were recovered during 2009-2012. Susceptibility (S) was determined by CLSI broth microdilution methods tested against CPT and selected comparators.

Results: SPN were evaluated for MDR status against PEN, CRO, erythromycin (ERY), tetracycline (TET), trimethoprim/sulfamethoxazole (TMP/SMX), and levofloxacin (LEV). MDR were defined as non-susceptible (NS) to at least 2 of the above agents. CPT ($MIC_{50/90}$, ≤0.015/0.12 µg/mL;100.0% S by USA-FDA/CLSI criteria) was 16-fold more potent than CRO ($MIC_{50/90}$, ≤0.25/2 µg/mL) and 64-fold more potent than cefuroxime ($MIC_{50/90}$, ≤2/8 µg/mL) against 6,958 SPN. PEN-NS was high among SPN; only 57.3 and 86.5% of strains were inhibited at ≤0.06 and ≤2 µg/mL, respectively, while amoxicillin/clavulanate inhibited 83.3% at ≤2 µg/mL. SPN NS was also high for erythromycin (43.2%), clindamycin (20.8%), TMP/SMX (34.1%) and TET (25.0%). 66.0/100.0% of PEN-R (MIC ≥8 µg/mL) isolates were inhibited by CPT at ≤0.25/ ≤0.5 µg/mL. For MDR SPN (2,449), CPT ($MIC_{50/90}$, 0.06/0.25 µg/mL) was the most active agent tested, 8-fold more potent than CRO ($MIC_{50/90}$, 0.5/2 µg/mL) and 16-fold more potent than PEN ($MIC_{50/90}$, 1/4 µg/mL). Only 61.8 and 16.5% of MDR were inhibited at ≤0.06 and ≤2 µg/mL of PEN, respectively, while for CPT, 100.0% of MDR isolates were inhibited at ≤0.25/≤0.5 µg/mL.

Conclusion: CPT was active against the major phenotypic groups of MDR SPN including those that were CRO-, LEV-, TET-, TMP/SMX-, PEN- and ERY-NS. All SPN recovered including strains NS to ≥6 drugs were CPT-S based on USA-FDA and CLSI interpretive criteria.

Introduction

Multidrug-resistant *Streptococcus pneumoniae* are a growing therapeutic problem in the community and hospital setting. *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia, and its resistance to currently available therapies leads to increased morbidity and mortality. As *S. pneumoniae* may have resistance to β-lactams, and/or macrolides and/or fluoroquinolones, the choice of appropriate therapies may be limited.

Ceftaroline fosamil is a parenteral agent which has been recently approved (2010 and 2012, respectively) in the United States (USA) and Europe, and has been shown to be effective for patients with community-acquired pneumonia caused by *S. pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible [MSSA] isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *K. oxytoca* and *Escherichia coli*. Further, ceftaroline has been demonstrated to be active in vitro against drug-resistant *S. pneumoniae* (DRSP) and *S. aureus* including MRSA. Reported ceftaroline MIC_{90} values against *S. pneumoniae* are generally at 0.12-0.25 µg/mL and for *S .aureus* at 1 µg/mL.

In this study, the activity of ceftaroline was evaluated against *S. pneumoniae* isolates collected during 2009-2012 in USA hospitals.

Methods

Organism collection: Isolates were collected from patients in 163 USA medical centers with community and hospitalized respiratory tract infections (RTI).These isolates were sent to a central laboratory (JMI laboratories, North Liberty, Iowa, USA) for confirmatory identification and susceptibility testing. A total of 6,958 *S. pneumoniae* were recovered during 2009-2012.

Susceptibility methods: Broth microdilution tests were conducted at the central monitoring laboratory according to Clinical and Laboratory Standards Institute (CLSI) methods in order to determine the antimicrobial susceptibility of ceftaroline and comparator antimicrobials. Validated MIC panels were manufactured by ThermoFisher Scientific (Cleveland, Ohio, USA). *S. pneumoniae* were tested in cation-adjusted Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood according to CLSI document M7-A09 (2012). The quality control strain, *S. pneumoniae* ATCC 49619, was tested concurrently. Susceptibility and quality control validation of results were based on the CLSI guidelines (M100-S23). The original abstract was submitted before the USA-FDA susceptibility breakpoint for ceftaroline was harmonized to CLSI (susceptible, 0.5 µg/mL). The abstract for this poster and the results and conclusions presented herein are based on the most current susceptible breakpoint (0.5 µg/mL).

Multidrug-resistance (MDR) status was determined based on non-susceptibility to the antimicrobial agents penicillin (PEN), ceftriaxone (CRO), levofloxacin (LEV), tetracycline (TET), trimethoprim/sulfamethoxazole and erythromycin (ERY). MDR were defined as non-susceptible to at least two of the above agents.

Results

- Ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) was 16-fold more potent than ceftriaxone ($MIC_{50/90}$, ≤0.25/2 µg/mL) and 64-fold more potent than cefuroxime ($MIC_{50/90}$, ≤2/8 µg/mL) when tested against 6,958 *S. pneumoniae* isolates collected in the USA during 2009-2012 (Table 1)
- Ceftaroline and levofloxacin exhibited high rates of susceptibility at 100.0 and 98.9%, respectively (Table 2). Ceftriaxone, cefuroxime and amoxicillin/clavulanate susceptibilities were at 89.2, 71.8 and 83.3%, respectively (Table 2). There was a high rate of resistance to erythromycin at 42.7%, and resistance to tetracycline, trimethoprim/sulfamethoxazole and clindamycin ranged from 20.3-24.6% (Table 2)
- Only 86.5% of *S. pneumoniae* strains were inhibited at a penicillin MIC of ≤2 µg/mL (penicillin parenteral non-meningitis susceptible breakpoint) and 57.3% at ≤0.06 µg/mL (Table 2)
- All of the highly penicillin-resistant isolates (MIC, ≥8 µg/mL) were susceptible to ceftaroline. A total of 66.0 and 100.0% of isolates were inhibited by ceftaroline at ≤0.25 and ≤0.5 µg/mL, respectively (Tables 1 and 2)
- For *S. pneumoniae* isolates that were non-susceptible to two or more drugs (MDR), the ceftaroline MIC_{50} and MIC_{90} were 0.06 and 0.25 µg/mL, respectively (Table 1). Ceftaroline was eight-fold more potent than ceftriaxone against this group of organism (ceftriaxone $MIC_{50/90}$, 0.5/2 µg/mL) and 16-fold more potent than penicillin (penicillin $MIC_{50/90}$, 1/4 µg/mL; Table 2)
- Only 61.8 and 16.5% of MDR were inhibited at ≤0.06 and ≤2 µg/mL of penicillin, respectively while for ceftaroline, 97.3 and 100.0% of MDR isolates were inhibited at ≤0.25 and ≤0.5 µg/mL, respectively (Table 1)
- In this *S. pneumoniae* collection, the most common non-susceptible phenotype for two antimicrobials that occurred together among the six antimicrobials that were evaluated was erythromycin and trimethoprim/sulfamethoxazole followed by erythromycin and tetracycline, and tetracycline and trimethoprim/sulfamethoxazole (Table 3)
- The most common non-susceptible phenotype for three antimicrobials that occurred together was erythromycin, tetracycline, and trimethoprim/sulfamethoxazole (Table 3), and the four most common non-susceptible phenotype pattern occurring together was penicillin, erythromycin, tetracycline, and trimethoprim/ sulfamethoxazole (Table 3).

Table 1. Cumulative frequency MIC distribution for ceftaroline tested against 6,958 *S. pneumoniae* isolates (2009-2012)

Organism (no.)[a]	Cumulative % inhibited at ceftaroline MIC (µg/mL) of:							
	≤0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
S. pneumoniae (6,958)	4,224 (60.7)	591 (69.2)	612 (78.0)	992 (92.3)	473 (99.1)	66 (100.0)	≤0.015	0.12
Penicillin MIC, ≥8 µg/mL (106)	--	--	1 (0.9)	3 (3.8)	66 (66.0)	36 (100.0)	0.25	0.5
Penicillin MIC at 4 µg/mL (831)	--	--	6 (0.7)	407 (49.7)	390 (96.6)	28 (100.0)	0.25	0.25
Ceftriaxone MIC, ≥2 µg/mL (750)	0 (0.0)	2(0.3)	4 (0.8)	264 (36.0)	415 (91.3)	65 (100.0)	0.25	0.25
MDR, NS ≥2 drugs (2,449)	548 (22.4)	274 (33.6)	431 (51.2)	661 (78.2)	469 (97.3)	66 (100.0)	0.06	0.25
MDR, NS ≥3 drugs (1,509)	132 (8.7)	130 (17.4)	201 (30.7)	513 (64.7)	468 (95.7)	65 (100.0)	0.12	0.25
MDR, NS ≥4 drugs (948)	6 (0.6)	3 (0.9)	17 (2.7)	397 (44.6)	461 (93.2)	64 (100.0)	0.25	0.25
MDR, NS ≥5 drugs (646)	--	--	1 (0.2)	209 (32.5)	385 (92.1)	51 (100.0)	0.25	0.25

a. MDR = multidrug-resistant; NS = non-susceptible (includes isolates that test as intermediate or resistant).

Table 2. In vitro activity of ceftaroline and comparator agents against *S. pneumoniae* (2009-2012)

Organism/antimicrobial agent (no. tested)	MIC (µg/mL)		%S / %I / %R
	MIC_{50}	MIC_{90}	CLSI[a]
S. pneumoniae (6,958)			
Ceftaroline	≤0.015	0.12	100.0 / - / -
Penicillin[b]	≤0.06	4	86.5 / 12.0 / 1.5
Penicillin[c]	≤0.06	4	57.3 / 22.0 / 20.7
Ceftriaxone	≤0.25	2	89.2 / 9.2 / 1.6
Cefuroxime	≤2	8	71.8 / 3.9 / 24.3
Amoxicillin/clavulanate	≤1	8	83.3 / 3.5 / 13.2
Erythromycin	≤0.25	>2	56.8 / 0.5 / 42.7
Clindamycin	≤0.25	>1	79.2 / 0.5 / 20.3
Tetracycline	≤2	>8	75.0 / 0.4 / 24.6
Trimethoprim/sulfamethoxazole	≤0.5	>2	65.9 / 9.5 / 24.6
Levofloxacin	1	1	98.9 / 0.1 / 1.0
S. pneumoniae (Penicillin MIC, ≥8 µg/mL; 106)			
Ceftaroline	0.25	0.5	100.0 / - / -
Penicillin[b]	>4	>4	0.0 / 0.0 / 100.0
Penicillin[c]	>4	>4	0.0 / 0.0 / 100.0
Ceftriaxone	2	8	3.8 / 51.9 / 44.3
Cefuroxime	>8	>8	0.0 / 0.0 / 100.0
Amoxicillin/clavulanate	>8	>8	0.0 / 0.9 / 99.1
Erythromycin	>2	>2	0.0 / 0.0 / 100.0
Clindamycin	>1	>1	15.1 / 0.9 / 84.0
Tetracycline	>8	>8	10.4 / 0.0 / 89.6
Trimethoprim/sulfamethoxazole	>2	>2	0.0 / 0.9 / 99.1
Levofloxacin	1	1	99.1 / 0.0 / 0.9
S. pneumoniae (MDR NS≥2; 2,449)			
Ceftaroline	0.06	0.25	100.0 / - / -
Penicillin[b]	1	4	16.5 / 35.8 / 47.7
Penicillin[c]	1	4	61.8 / 33.9 / 4.3
Ceftriaxone	0.5	2	69.6 / 26.0 / 4.4
Cefuroxime	4	>8	37.9 / 7.9 / 54.2
Amoxicillin/clavulanate	≤1	8	58.0 / 4.7 / 37.3
Erythromycin	>2	>2	4.9 / 1.0 / 94.1
Clindamycin	>1	>1	43.2 / 0.5 / 56.3
Tetracycline	>8	>8	31.8 / 0.7 / 67.5
Trimethoprim/sulfamethoxazole	>2	>2	18.9 / 18.6 / 62.5
Levofloxacin	1	1	97.3 / 0.2 / 2.5

Organism/antimicrobial agent (no. tested)	MIC (µg/mL)		%S / %I / %R
	MIC_{50}	MIC_{90}	CLSI[a]
S. pneumoniae (MDR NS≥3; 1,509)			
Ceftaroline	0.12	0.25	100.0 / - / -
Penicillin[b]	4	4	38.6 / 54.4 / 7.0
Penicillin[c]	4	4	3.8 / 27.4 / 68.9
Ceftriaxone	1	2	51.4 / 41.6 / 7.0
Cefuroxime	8	>8	22.5 / 3.9 / 73.6
Amoxicillin/clavulanate	8	8	35.3 / 5.0 / 59.7
Erythromycin	>2	>2	0.8 / 0.5 / 98.7
Clindamycin	>1	>1	26.9 / 0.4 / 72.7
Tetracycline	>8	>8	12.2 / 0.4 / 87.4
Trimethoprim/sulfamethoxazole	>2	>2	1.7 / 17.3 / 81.0
Levofloxacin	1	1	96.1 / 0.4 / 3.6
S. pneumoniae (MDR NS≥4; 948)			
Ceftaroline	0.25	0.25	100.0 / - / -
Penicillin[b]	4	>4	4.9 / 84.0 / 11.1
Penicillin[c]	4	>4	0.4 / 1.7 / 97.9
Ceftriaxone	2	4	24.5 / 64.5 / 11.0
Cefuroxime	8	>8	1.4 / 0.3 / 98.3
Amoxicillin/clavulanate	8	>8	5.3 / 3.5 / 91.2
Erythromycin	>2	>2	0.3 / 0.1 / 99.6
Clindamycin	>1	>1	12.3 / 0.5 / 87.2
Tetracycline	>8	>8	6.5 / 0.4 / 93.1
Trimethoprim/sulfamethoxazole	>2	>2	0.4 / 1.7 / 97.9
Levofloxacin	1	1	96.3 / 0.3 / 3.4
S. pneumoniae (MDR NS≥5; 646)			
Ceftaroline	0.25	0.25	100.0 / - / -
Penicillin[b]	4	>4	0.2 / 85.1 / 14.7
Penicillin[c]	4	>4	0.0 / 0.0 / 100.0
Ceftriaxone	2	4	0.0 / 87.2 / 12.8
Cefuroxime	>8	>8	0.5 / 0.0 / 99.5
Amoxicillin/clavulanate	8	>8	1.1 / 2.2 / 96.7
Erythromycin	>2	>2	0.0 / 0.0 / 100.0
Clindamycin	>1	>1	8.5 / 0.3 / 91.2
Tetracycline	>8	>8	2.2 / 0.0 / 97.8
Trimethoprim/sulfamethoxazole	>2	>2	0.0 / 0.2 / 99.8

a. Criteria as published by the CLSI [2013].
b. Criteria as published by the CLSI [2013] for 'Penicillin parenteral non-meningitis' (S ≤2, I=4, R ≥8 µg/mL).
c. Criteria as published by the CLSI [2013] for 'Penicillin oral penicillin V' (S ≤0.06, I=0.12-1, R ≥2 µg/mL).

Table 3. Most frequent occurrences of non-susceptible (NS) drug phenotypes linked together:

Number of NS drugs linked	Three most common occurrences in descending order:		
Two	ERY, TMP/SMX	ERY, TET	TET, TMP/SMX
Three	ERY, TET, TMP/SMX	PEN, ERY, TMP/SMX	PEN, ERY, TET
Four	PEN, ERY, TET, TMP/SMX	PEN, CRO, ERY, TMP/SMX	CRO, ERY, TET, TMP/SMX
Five	PEN, CRO, ERY, TET, TMP/SMX	CRO, ERY, TET, TMP/SMX, LEV	PEN, CRO, ERY, TET, LEV

a. Penicillin (PEN), ceftriaxone (CRO), levofloxacin (LEV), tetracycline (TET), trimethoprim/sulfamethoxazole (TMP/SMX), and erythromycin (ERY) were used to categorize multidrug- resistance.

Conclusions

- The ceftaroline USA-FDA susceptibility interpretive criteria (USA prescribing information) for *S. pneumoniae* have recently been modified, and now are harmonized with the CLSI interpretive criteria (susceptible, ≤0.5 µg/mL; no intermediate or resistant category)
- Ceftaroline was very active against USA isolates of *S. pneumoniae* collected from 2009-2012. All *S. pneumoniae* isolates were susceptible to ceftaroline according to the USA-FDA/CLSI susceptible breakpoint of 0.5 µg/mL
- Included in this collection were isolates that were non-susceptible to ceftriaxone (10.8% of all isolates), penicillin (MIC ≥4 µg/mL,13.5%; MIC ≥0.12 µg/mL, 42.7%), levofloxacin (only 1.1%), tetracycline (25.0%), trimethoprim/sulfamethoxazole (34.1%), and erythromycin (43.2%).

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