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Antimicrobial Activity of Ceftaroline Tested Against Respiratory Tract Infection Pathogens Isolated from USA Medical Centers in 2013

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Amended Abstract

Background: Ceftaroline fosamil (CPT) is a broad-spectrum cephalosporin prodrug with potent in vitro activity against pathogens causing community-acquired (CA) respiratory tract infections (RTI), including ceftriaxone (CRO)-resistant (R) *Streptococcus pneumoniae* (SPN) and methicillin-R *Staphylococcus aureus* (MRSA). We evaluated the potency and spectrum of CPT and several comparators tested against CA-RTI pathogens.

Methods: 4,533 unique patient isolates were collected from 149 USA medical centers during 2013. The collection includes 3,099 *S. pneumoniae* (SPN; 6.5% CRO-non-S), 931 *Haemophilus influenzae* (HI; 23.8% β-lactamase-positive [BL+]), 99 *H. parainfluenzae* (HPAR) and 404 *Moraxella catarrhalis* (MCAT). Susceptibility (S) was tested by CLSI broth microdilution methods against CPT and other antimicrobials used to treat CA-RTI.

Results: CPT ($MIC_{50/90}$, ≤0.015/0.12 µg/mL was eight-fold more potent than CRO ($MIC_{50/90}$, ≤0.06/1 µg/mL) against SPN, and highly active against CRO-non-S SPN strains (n=201; MIC_{90}, 0.25 µg/mL). S rates for SPN were 92.8% for penicillin (MIC, ≤2 µg/mL), 88.5% for amoxicillin/clavulanate, 56.0% for erythromycin, 77.0% for tetracycline and 98.8% for levofloxacin (LEV). CPT was very active against HI ($MIC_{50/90}$, 0.008/0.015 µg/mL), including BL+ strains (CPT $MIC_{50/90}$, 0.015/0.03 µg/mL). S rates for clarithromycin, azithromycin and LEV among HI were 90.3, 99.1 and 99.8%, respectively. CPT was also active against HPAR ($MIC_{50/90}$, 0.008/0.03 µg/mL) and MCAT ($MIC_{50/90}$, 0.06/0.12 µg/mL; see Table 1).

Conclusion: CPT exhibited high activity against bacterial pathogens from CA-RTI recently (2013) collected from 149 USA medical centers; all organisms (100.0%) were CPT-S. CPT was particularly active against CRO-non-S SPN. Based on these results, CPT represents a valuable agent for treatment of CA-RTI, including multidrug-R isolates.

Introduction

Community-acquired (CA) respiratory tract infections (RTI) may be caused by bacteria resistant to some or many available therapies and the choice of the appropriate initial empiric therapy is important to minimize morbidity and mortality. In spite of the increasing concern over the emergence of antimicrobial resistance, there have been relatively few new antibacterial agents licensed for the treatment of RTI in the United States (USA) and/or Europe.

Ceftaroline is a cephalosporin with broad-spectrum in vitro bactericidal activity against gram-positive and common gram-negative pathogens causing CA-RTI, including oxacillin (methicillin)-susceptible (MSSA) and -resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) *Streptococcus pneumoniae* and β-lactamase-producing *Haemophilus influenzae*. The prodrug, ceftaroline fosamil, was approved by the USA Food and Drug Administration (FDA) for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in 2010.

The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program monitors the activity of ceftaroline and comparator agents tested against pathogens causing either community-acquired or health-care associated infections worldwide. As part of the USA AWARE Program, we evaluated the potency and spectrum ceftaroline and several comparators tested against CA-RTI pathogens collected from USA medical centers in 2013.

Methods

Organism collection: A total of 4,533 unique patient isolates were collected from patients with CA-RTI in 149 USA medical centers in 2013. The collection included 3,099 *S. pneumoniae* (6.5% ceftriaxone-non-susceptible), 931 *Haemophilus influenzae* (23.8% β-lactamase-positive), 99 *H. parainfluenzae* and 404 *Moraxella catarrhalis*. All medical centers collected the strains following a common protocol and only isolates determined to be significant by local criteria as the reported probable cause of the infection were included in this investigation. Species identification was performed at the participant medical center and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using the Vitek 2 System (bioMerieux, Hazelwood, Missouri, USA) or MALDI-TOF (Bruker Daltonics, Bremen, Germany), when necessary.

Susceptibility methods: Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) documents determined antimicrobial susceptibility of ceftaroline and numerous comparator antimicrobials used to treat CA-RTI. Validated MIC panels were manufactured by ThermoFisher Scientific® (Cleveland, Ohio, USA). *Moraxella catarrhalis* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), *S. pneumoniae* isolates were tested in CA-MHB supplemented with 2.5-5% lysed horse blood, and *Haemophilus* spp. strains were tested in Haemophilus Test Medium (HTM) according to CLSI document M07-A9 (2012). Quality control (QC) strains included: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *H. influenzae* 49247. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S24).

Results

- Ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 µg/mL; 100.0% susceptible) was eight-fold more potent than ceftriaxone ($MIC_{50/90}$, ≤0.06/1 µg/mL; 93.5% susceptible; Tables 1 and 2 and Figure 1) against *S. pneumoniae*, and highly active against ceftriaxone-non-susceptible *S. pneumoniae* strains (n=201; $MIC_{50/90}$, 0.12/0.25 µg/mL; highest MIC, 0.5 µg/mL; Table 1).
- Ceftaroline was also very active against penicillin-non-susceptible *S. pneumoniae* (penicillin MIC of >2 µg/mL) strains (n=222), with MIC_{50} of 0.12 µg/mL and MIC_{90} of 0.25 µg/mL (100.0% susceptible); whereas only 22.5% (50/222) of these strains were susceptible to ceftriaxone (Table 1 and Figure 2).
- Susceptibility rates (CLSI criteria) for *S. pneumoniae* were 92.8% for penicillin (MIC, ≤2 µg/mL), 88.5% for amoxicillin/clavulanate, 81.6% for meropenem, 56.0% for erythromycin, 77.0% for tetracycline and 98.8% for levofloxacin (Table 2).
- Ceftaroline exhibited potent activity against *H. influenzae* ($MIC_{50/90}$, 0.008/0.015 µg/mL; 100.0% susceptible). The highest ceftaroline MIC value among *H. influenzae* was 0.25 µg/mL (one isolate, 0.1%), and 99.7% of isolates were inhibited at ≤0.06 µg/mL of ceftaroline (Table 1 and Figure 3).
- Among *H. influenzae,* 23.8% of isolates were β-lactamase producers and ceftaroline was very active against these strains ($MIC_{50/90}$, 0.015/0.03 µg/mL; Table 1 and Figure 3). Susceptibility rates for clarithromycin (MIC_{50} and MIC_{90}, 8 µg/mL), azithromycin ($MIC_{50/90}$, 1/2 µg/mL) and levofloxacin (MIC_{50} and MIC_{90}, ≤0.12 µg/mL) among *H. influenzae* were 90.3, 99.1 and 99.8%, respectively (Table 2).
- Ceftaroline was also highly active against *H. parainfluenzae* ($MIC_{50/90}$, 0.008/0.03 µg/mL) and *M. catarrhalis* ($MIC_{50/90}$, 0.06/0.12 µg/mL; Tables 1 and 2).

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against isolates of *S. pneumoniae* and *H. influenzae* from CA-RTI (USA, 2013)

Organism (no. tested) / Antimicrobial agent	MIC (µg/mL) MIC_{50}	MIC_{90}	Range	%S / I / R[a] CLSI[a] %S / %I / %R	EUCAST[a] %S / %I / %R
S. pneumoniae (3,099)					
Ceftaroline[b]	≤0.015	0.12	≤0.015 – 0.5	100.0 / - / -	99.6 / 0.0 / 0.4
Ceftriaxone	≤0.06	1	≤0.06 – 8	93.5 / 6.0 / 0.5	81.9 / 17.6 / 0.5
Penicillin[c]	≤0.06	2	≤0.06 – 8	92.8 / 6.8 / 0.4	- / -
Penicillin[d]	≤0.06	2	≤0.06 – 8	60.7 / 24.9 / 14.5	60.7 / 32.0 / 7.2
Amoxicillin/clavulanate	≤1	4	≤1 – >8	88.5 / 3.7 / 7.8	- / - / -
Meropenem	≤0.06	0.5	≤0.06 – 2	81.6 / 11.2 / 7.2	100.0 / 0.0 / 0.0
Erythromycin	≤0.12	>16	≤0.12 – >16	56.0 / 0.8 / 43.2	56.0 / 0.8 / 43.2
Clindamycin	≤0.25	>2	≤0.25 – >2	83.6 / 0.5 / 15.9	84.1 / 0.0 / 15.9
Levofloxacin	1	1	≤0.12 – >4	98.8 / 0.3 / 0.9	98.8 / 0.0 / 1.2
Linezolid	1	1	≤0.12 – 2	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	0.25	32	≤0.03 – >32	77.0 / 0.2 / 22.8	77.0 / 0.2 / 22.8
TMP/SMX[e]	≤0.5	>4	≤0.5 – >4	70.1 / 12.5 / 17.4	77.3 / 5.3 / 17.4
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / - / -	100.0 / 0.0 / 0.0
H. influenzae (931)					
Ceftaroline[b]	0.008	0.015	≤0.001 – 0.25	100.0 / - / -	98.3 / 0.0 / 1.7
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Ampicillin	≤0.25	>8	≤0.25 – >8	75.8 / 1.1 / 23.1	75.8 / 0.0 / 24.2
Amoxicillin/clavulanate	≤1	2	≤1 – 4	100.0 / 0.0 / 0.0	99.8 / 0.0 / 0.2
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5	100.0 / 0.0 / 0.0	- / - / -
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	0.5	0.5	≤0.12 – >16	99.1 / 0.2 / 0.8	99.1 / 0.0 / 0.9
TMP/SMX[e]	≤0.5	>4	≤0.5 – >4	67.7 / 4.1 / 28.2	67.7 / 1.8 / 30.5
Azithromycin	1	2	≤0.03 – >4	99.1 / - / -	1.6 / 97.5 / 0.9
Clarithromycin	8	8	≤0.12 – >16	90.3 / 8.4 / 1.3	1.7 / 98.3 / 0.0
Levofloxacin	≤0.12	≤0.12	≤0.12 – >4	99.8 / - / -	99.8 / 0.0 / 0.2

a. Criteria as published by the CLSI [2014] and EUCAST [2014].
b. US-FDA breakpoints were applied when available [Teflaro Product Insert, 2012].
c. Criteria as published by the CLSI [2012] for 'Penicillin parenteral non-meningitis' (S ≤2, I= 4, R ≥8 µg/mL).
d. Criteria as published by the CLSI [2012] for 'Penicillin oral penicillin V' (S ≤0.06, I =0.12-1, R ≥2 µg/mL).
e. TMP/SMX = trimethoprim/sulfamethoxazole.

Table 1. Summary of ceftaroline activity when tested against bacterial isolates from CA-RTI (USA, 2013)

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of: ≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC (µg/mL) 50%	90%
S. pneumoniae (3,099)			1,938 (62.5%)[a]	303 (72.3)	303 (82.1)	443 (96.4)	100 (99.6)	12 (100.0)	≤0.015	0.12
Ceftriaxone-non-S[b] (201)				1 (0.5)	1 (1)	101 (51.2)	86 (94.0)	12 (100.0)	0.12	0.25
Penicillin-non-S[c] (222)					2 (0.9)	124 (56.8)	84 (94.6)	12 (100.0)	0.12	0.25
H. influenzae (931)	116 (12.5)	465 (62.4)	259 (90.2)	75 (98.3)	13 (99.7)	2 (99.9)	1 (100.0)		0.008	0.015
β-lactamase-positive (222)	10 (4.5)	82 (41.4)	80 (77.5)	38 (94.6)	9 (98.6)	2 (99.5)	1 (100.0)		0.15	0.03
H. parainfluenzae (99)	19 (22.2)	36 (58.6)	19 (87.9)	7 (94.9)	2 (97.0)	2 (99.0)	0 (99.0)	1 (100.0)	0.008	0.03
M. catarrhalis (404)		17 (4.2)	24 (10.1)	95 (33.7)	132 (66.3)	101 (91.3)	32 (99.3)	3 (100.0)	0.06	0.12

a. Lowest dilution tested for *S. pneumoniae*.
b. Ceftriaxone MIC values of >1 µg/mL (CLSI, 2014).
c. Penicillin MIC values of >2 µg/mL (CLSI, 2014)

Figure 1. Ceftaroline MIC distributions when tested against *S. pneumoniae* (n=3,099), including penicillin-susceptible (PEN-S [MIC, ≤2 µg/mL], n=2,877) and –non-susceptible (PEN-NS [MIC, >2 µg/mL], n=222)

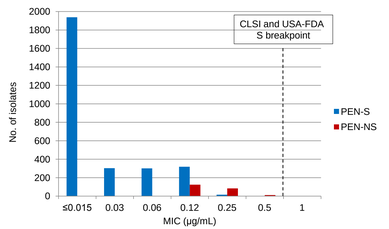


Figure 2. Ceftaroline and ceftriaxone MIC distributions when tested against penicillin-non-susceptible (MIC, >2 µg/mL) *S. pneumoniae* (n=222)

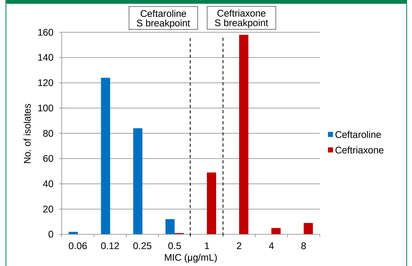
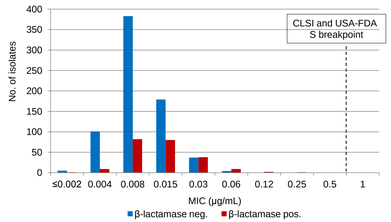


Figure 3. Ceftaroline MIC distributions when tested against *H. influenzae* (n=931, 709 β-lactamase-negative and 222 β-lactamase-positive strains)



Conclusions

- Ceftaroline exhibited potent activity against bacterial pathogens from CA-RTI recently (2013) collected from 149 USA medical centers. All organisms (100.0%) were susceptible to ceftaroline.
- Ceftaroline was particularly active against ceftriaxone-non-susceptible *S. pneumoniae*.
- Based on these results, ceftaroline represents a valuable agent for treatment of CA-RTI, including MDR strains.

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Acknowledgments

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