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Antimicrobial Activity of Ceftaroline and Comparator Agents against 6,502 *S. pneumoniae* Isolates from United States Medical Centers over 5 Years (2008-2012)

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Amended Abstract

Rationale: Ceftaroline, the active form of ceftaroline fosamil, is a parenteral, broad-spectrum cephalosporin with potent bactericidal activity against *S. pneumoniae* (SPN). Ceftaroline fosamil was approved by the USA-FDA for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections in late 2010. The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program monitors ceftaroline activity against bacterial organisms from USA medical centers since 2008.

Methods: Susceptibility (S) testing for ceftaroline and commonly used antimicrobials was performed by CLSI broth microdilution methodology on 6,502 SPN isolates collected in 93 USA medical centers from January/2008 to September/2012 (894 to 2,149 isolates/year), as part of the AWARE Program. CLSI breakpoints were applied for ceftaroline and comparators. Multidrug-resistant (MDR) strains were defined as non-S to ≥2 classes of the following antimicrobials: penicillin (≥4 µg/mL), ceftriaxone, erythromycin, levofloxacin, tetracycline and trimethoprim-sulfamethoxazole (TMP/SMX).

Results: All isolates were susceptible to ceftaroline according to the CLSI breakpoint of ≤0.5 µg/mL (99.0% inhibited at the USA-FDA breakpoint of ≤0.25 µg/mL). Susceptibility to ceftriaxone ranged from 90.8% in 2008 to 87.3% in 2009 (89.1% overall). Ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, ≤0.06/2 µg/mL). Ceftriaxone-non-S (≥2 µg/mL), as well as penicillin-non-S (≥4 µg/mL) strains exhibited low susceptibility (<30%) to all tested antimicrobials, except ceftaroline (100.0% S) and levofloxacin (≥98.3% S); see Table. Yearly susceptibility rates to penicillin (≤2 µg/mL), macrolides (erythromycin), clindamycin and TMP/SMX were 84.0-89.9%, 55.2-61.6%, 77.4-83.9% and 65.1-66.7%, respectively.

Conclusions: Ceftaroline was highly active against SPN from USA medical centers, including strains not susceptible to ceftriaxone and other antimicrobials commonly used to treat CABP. Ceftaroline was the most potent parenteral β-lactam tested against SPN isolated in the USA (2008-2012).

Antimicrobial agent	MIC_{50} / % susceptible (no. of isolates)							
	All strains (6502)	CRO-NS (CABP)	PEN-NS (≥4 µg/mL; 915)	A/C-NS (1126)	ERY-NS (2723)	LEV-NS (58)	MDR (2114)	
Ceftaroline	0.12/100.0	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0	
CRO	2/89.1	4/0.0	4/28.5	2/41.2	2/74.7	2/79.3	2/67.3	
PEN	4/85.9	>4/0.0	>4/0.0	4/20.9	4/66.9	4/79.3	4/57.1	
A/C	8/82.7	>8/6.4	>8/2.5	8/0.0	8/61.3	8/74.1	8/50.6	
ERY	>8/58.1	>8/2.0	>8/1.6	>8/6.4	>8/0.0	>8/19.0	>8/2.3	
CLI	>2/79.3	>2/17.4	>2/13.8	>2/26.0	>2/51.1	>2/55.2	>2/39.0	
LEV	1/99.1	1/98.3	1/98.7	1/98.7	1/98.3	>4/0.0	1/97.7	

Abbreviations: CRO = ceftriaxone, A/C = amoxicillin/clavulanate, PEN= penicillin, ERY = erythromycin, LEV = levofloxacin, MDR = multidrug-resistant, CLI = clindamycin, NS = non-susceptible.

Introduction

Ceftaroline, the active form of ceftaroline fosamil, is a parenteral cephalosporin with potent broad-spectrum bactericidal in vitro activity against Gram-positive and common Gram-negative pathogens causing community-acquired respiratory tract infections (CARTI), including multidrug-resistant (MDR) *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and β-lactamase-producing *Haemophilus influenzae*.

Ceftaroline fosamil was approved by the United States Food and Drug Administration (USA-FDA) for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections in late 2010. The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program has monitored ceftaroline activity against bacterial organisms from USA medical centers since 2008. We evaluated the activity of ceftaroline against *S. pneumoniae* isolates collected from patients with CARTI in the USA in 2008 – 2012.

Methods

Organism collection: A total of 6,502 *S. pneumoniae* isolates were collected in 93 USA medical centers from January/2008 to September/2012 (894 to 2,149 isolates/year), as part of the AWARE Program. MDR strains were defined as non-susceptible to ≥2 classes of the following antimicrobials: penicillin (≥4 µg/mL), ceftriaxone, erythromycin, levofloxacin, tetracycline and trimethoprim-sulfamethoxazole (TMP/SMX).

Susceptibility methods: Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) documents were performed to determine antimicrobial susceptibility of ceftaroline and numerous comparator antimicrobials used to treat CARTI. Validated MIC panels were manufactured by ThermoFisher Scientific® (Cleveland, Ohio, USA). *S. pneumoniae* isolates were tested in cation-adjusted Mueller Hinton broth supplemented with 2.5-5% lysed horse blood, according to CLSI document M07-A9 (2012). *S. pneumoniae* ATCC 49619 was tested as quality control (QC). Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S23) and CLSI and USA-FDA breakpoints were applied.

Results

- Ceftaroline was highly active against *S. pneumoniae* ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) and all isolates (100.0%) were categorized as ceftaroline-susceptible according to the CLSI breakpoint of ≤0.5 µg/mL (99.0% inhibited at the USA-FDA breakpoint of ≤0.25 µg/mL; Table 1 and Figure 1)
- Susceptibility to ceftriaxone ranged from 90.8% in 2008 to 87.3% in 2009 (89.1% overall; Table 1 and Figure 2)
- The most active comparator agent was levofloxacin (99.1% susceptible), followed by ceftriaxone (89.1%), penicillin (85.9% at ≤2 µg/mL), amoxicillin/clavulanate (82.7%), clindamycin (79.2%), tetracycline (75.3%), TMP/SMX (65.7%) and erythromycin (58.1%; Table 1)
- Ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, ≤0.06/2 µg/mL) based on the MIC_{90} (Table 1)
- Ceftriaxone-non-susceptible (≥2 µg/mL), as well as penicillin-non-susceptible (≥4 µg/mL) strains exhibited low susceptibility (<30%) to all tested antimicrobials, except ceftaroline ($MIC_{50/90}$, 0.25/0.25 µg/mL; 100.0% susceptible by CLSI criteria) and levofloxacin ($MIC_{50/90}$, 1/1 µg/mL; 98.3-98.7% susceptible; Table 1)
- Ceftaroline also showed good activity (100.0% susceptibility by CLSI criteria) against erythromycin-non-susceptible ($MIC_{50/90}$, 0.06/0.25 µg/mL), levofloxacin-non-susceptible ($MIC_{50/90}$, 0.06/0.25 µg/mL) and MDR ($MIC_{50/90}$, 0.12/0.25 µg/mL) strains (Table 1)
- Yearly susceptibility rates to penicillin (≤2 µg/mL), macrolides (erythromycin), clindamycin and TMP/SMX were 84.0-89.9%, 55.2-61.6%, 77.4-83.9% and 65.1-66.7%, respectively (Figure 2).

Table 1. Activity of ceftaroline and comparator antimicrobial agents when tested against 6,502 isolates of *S. pneumoniae* (USA)

Antimicrobial agent	MIC_{50}	MIC_{90}	%S / I / R [a]
All (6,502)			
Ceftaroline[b]	≤0.015	0.12	100.0 (99.0) / - / -
Ceftriaxone	≤0.06	2	89.1 / 9.4 / 1.6
Penicillin[c]	≤0.06	4	85.9 / 12.6 / 1.5
Penicillin[d]	≤0.06	4	57.3 / 21.0 / 21.7
Amox/clav[e]	≤1	8	82.7 / 3.6 / 13.7
Erythromycin	≤0.25	>2	58.1 / 0.5 / 41.4
Clindamycin	≤0.25	>1	79.2 / 0.5 / 20.3
Levofloxacin	1	1	99.1 / 0.2 / 0.8
Tetracycline	≤2	>8	75.3 / 0.3 / 24.4
TMP/SMX[f]	≤0.5	>2	65.7 / 9.1 / 25.2
Ceftriaxone ≥2 µg/mL (708)			
Ceftaroline[b]	0.25	0.25	100.0 (91.2)/ - / -
Ceftriaxone	2	4	0.0 / 85.2 / 14.8
Penicillin[c]	4	>4	7.6 / 78.7 / 13.7
Amox/clav[e]	8	>8	6.4 / 4.2 / 89.4
Erythromycin	>2	>2	2.7 / 0.0 / 97.3
Clindamycin	>1	>1	17.4 / 0.4 / 82.2
Levofloxacin	1	1	98.3 / 0.4 / 1.3
Tetracycline	>8	>8	12.0 / 0.3 / 87.7
TMP/SMX[f]	>2	>2	2.4 / 1.0 / 96.6
Penicillin MIC ≥4 µg/mL (915)			
Ceftaroline[b]	0.25	0.25	100.0 (93.2) / - / -
Ceftriaxone	2	4	28.5 / 60.8 / 10.7
Amox/clav[e]	8	>8	2.5 / 4.1 / 93.4
Erythromycin	>2	>2	1.6 / 0.0 / 98.4
Clindamycin	>1	>1	13.8 / 0.4 / 85.8
Levofloxacin	1	1	98.7 / 0.2 / 1.1
Tetracycline	>8	>8	9.4 / 0.1 / 90.5
TMP/SMX[f]	>2	>2	1.7 / 0.6 / 97.7
Amoxicillin/clavulanate ≥4 µg/mL (1,126)			
Ceftaroline[b]	0.12	0.25	100.0 (94.5) / - / -
Ceftriaxone	2	2	41.2 / 50.0 / 8.7
Penicillin[c]	4	4	20.9 / 70.2 / 8.9
Amox/clav[e]	8	8	0.0 / 21.0 / 79.0
Erythromycin	>2	>2	6.4 / 0.1 / 93.5
Clindamycin	>1	>1	26.0 / 0.6 / 73.4
Levofloxacin	1	1	98.7 / 0.2 / 1.1
Tetracycline	>8	>8	21.8 / 0.1 / 78.1
TMP/SMX[f]	>2	>2	13.7 / 1.5 / 84.8
Erythromycin ≥0.5 µg/mL (2,723)			
Ceftaroline[b]	0.06	0.25	100.0 (97.8) / - / -
Ceftriaxone	0.5	2	74.7 / 21.7 / 3.7
Penicillin[c]	1	4	66.9 / 29.5 / 3.6
Amox/clav[e]	≤1	8	61.3 / 6.5 / 32.2
Clindamycin	≤0.25	>1	51.1 / 0.7 / 48.2
Levofloxacin	1	1	98.3 / 0.2 / 1.6
Tetracycline	>8	>8	44.0 / 0.3 / 55.7
TMP/SMX[f]	>2	>2	35.7 / 12.5 / 51.8
Levofloxacin ≥4 µg/mL (58)			
Ceftaroline[b]	0.06	0.25	100.0 (100.0) / - / -
Ceftriaxone	≤0.25	2	79.3 / 19.0 / 1.7
Penicillin[c]	0.25	4	79.3 / 19.0 / 1.7
Amox/clav[e]	≤1	8	74.1 / 6.9 / 19.0
Erythromycin	>2	>2	19.0 / 0.0 / 81.0
Clindamycin	≤0.25	>1	55.2 / 1.7 / 43.1
Levofloxacin	>4	>4	0.0 / 8.6 / 91.4
Tetracycline	>8	>8	36.2 / 0.0 / 63.8
TMP/SMX[f]	2	>2	37.9 / 12.1 / 50.0
Multidrug-resistant (2,116)[g]			
Ceftaroline[b]	0.12	0.25	100.0 (97.0) / - / -
Ceftriaxone	1	2	67.5 / 27.7 / 4.7
Penicillin[c]	2	4	57.4 / 37.9 / 4.7
Amox/clav[e]	2	8	50.0 / 8.6 / 41.4
Erythromycin	>2	>2	2.3 / 0.2 / 97.5
Clindamycin	>1	>1	39.9 / 0.5 / 59.6
Levofloxacin	1	1	97.7 / 0.2 / 2.1
Tetracycline	>8	>8	28.8 / 0.2 / 71.0
TMP/SMX[f]	>2	>2	21.4 / 10.6 / 68.0

a. Percentage susceptible / intermediate / resistant according to criteria published by the CLSI [2013].
b. Percentage susceptible based on the USA-FDA package insert breakpoints are shown in parenthesis [Teflaro Product Insert, 2012].
c. Criteria as published by the CLSI [2013] for 'Penicillin parenteral non-meningitis' (S≤2, I=4, R≥8 µg/mL).
d. Criteria as published by the CLSI [2013] for 'Penicillin oral penicillin V' (S ≤0.06, I=0.121, R≥2 µg/mL).
e. Amox/clav = amoxicillin/clavulanate.
f. TMP/SMX = trimethoprim/sulfamethoxazole.
g. Multidrug-resistant (MDR) strains were defined as non-susceptible to ≥2 classes of the following antimicrobials: penicillin (≥4 µg/mL), ceftriaxone, erythromycin, levofloxacin, tetracycline and trimethoprim-sulfamethoxazole (TMP/SMX).

Figure 1. Ceftaroline MIC distributions when testing 6,502 *S. pneumoniae* isolates from USA medical centers (2008-2012)

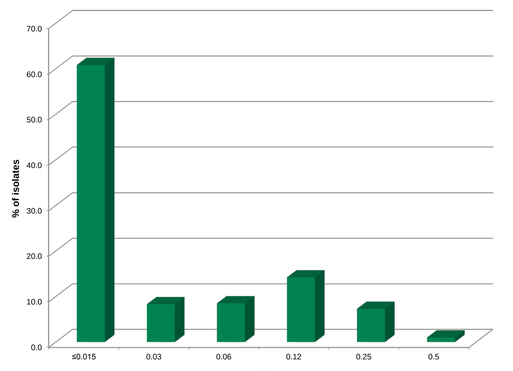
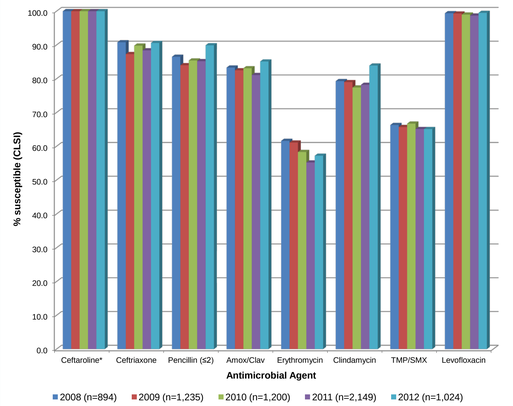


Figure 2. Yearly activity of ceftaroline and comparators tested against 6,502 *S. pneumoniae* isolates



* Based on CLSI breakpoint criteria

Conclusions

- Ceftaroline demonstrated potent in vitro activity against a large collection of *S. pneumoniae* from USA medical centers, including strains not susceptible to ceftriaxone and other antimicrobials commonly used to treat community-acquired bacterial pneumonia
- Ceftaroline was the most potent parenteral β-lactam tested against *S. pneumoniae* isolated in the USA over the last 5 years (2008-2012).

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