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Ceftaroline Activity against MDR *Streptococcus pneumoniae* Subsets from United States Medical Centers (2014)

DJ FARRELL, RE MENDES, RK FLAMM, HS SADER, RN JONES

JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, M.D., Ph.D.
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Rationale: Ceftaroline, the active form of ceftaroline fosamil, is a parenteral, broad-spectrum cephalosporin with potent bactericidal activity against *Streptococcus pneumoniae* (SPN). Ceftaroline fosamil was approved by the United States (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. The aim of this report is to describe the activity of ceftaroline and comparator agents against SPN, including multidrug-resistant (MDR)-SPN, collected from USA medical centers in 2014.

Methods: Susceptibility (S) testing for ceftaroline and commonly used antimicrobials was performed by CLSI broth microdilution methods on 2,614 SPN isolates collected in 135 USA medical centers from January to December 2014, as part of the AWARE Program. CLSI breakpoints were applied for ceftaroline and comparators. 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.

Results: All but one isolate were susceptible (>99.9%) to ceftaroline according to the CLSI breakpoint of ≤0.5 µg/mL. Susceptibility to ceftriaxone was 94.7% and ceftaroline (MIC_{90}, 0.12 µg/mL) was eight-fold more potent than ceftriaxone (MIC_{90}, 1 µg/mL). The overall erythromycin non-S rate was high at 45.9%. The overall MDR-SPN rate was 28.8% and ceftaroline was the most active agent (S=99.9%) tested against these strains with S for other agents ranging from 2.3% for erythromycin to 96.3% for levofloxacin (Table). Ceftriaxone-non-S (≥2 µg/mL) strains exhibited low susceptibility (<30%) to all tested antimicrobials, except ceftaroline (99.3% S) and levofloxacin (96.4% S); see Table.

Conclusions: Ceftaroline was very active against SPN from USA medical centers, including MDR strains and strains not susceptible to ceftriaxone and other antimicrobials commonly used to treat CABP. Ceftaroline was the most potent β-lactam tested against SPN isolated in the USA (2014).

Antimicrobial agent	MIC_{50} (µg/mL) / % susceptible (no. of isolates)						
	All strains (2614)	CRO-NS (139)	PEN-R (≥8 µg/mL; 10)	A/C-NS (274)	ERY-NS (1198)	LEV-NS (43)	MDR (753)
Ceftaroline	0.12/>99.9	0.25/99.3	0.5/90.0	0.25/99.6	0.12/99.9	0.12/100.0	0.25/99.9
CRO	1/94.7	4/0.0	8/0.0	2/55.1	2/88.6	2/88.4	2/81.5
PEN	2/93.7	4/18.0	8/0.0	4/42.0	4/86.5	4/86.0	4/78.5
A/C	4/89.5	8/11.5	>8/0.0	8/0.0	8/78.5	8/74.4	8/70.9
ERY	>16/54.1	>16/2.2	>16/0.0	>16/5.8	>16/0.0	>16/46.5	>16/2.3
CLI	>2/84.2	>2/25.2	>2/20.0	>2/36.5	>2/65.5	>2/69.8	>2/48.3
LEV	1/98.4	1/96.4	1/90.0	1/96.0	1/98.1	>4/0.0	1/96.3

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

Introduction

Ceftaroline, the active metabolite 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 in 2010 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. The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program has monitored ceftaroline activity against bacterial organisms from USA medical centers since 2008. The aim of this report is to describe the activity of ceftaroline and comparator agents against *S. pneumoniae*, including MDR isolates, collected from USA medical centers in 2014.

Methods

Organism collection: A total of 2,614 *S. pneumoniae* isolates were collected in 135 USA medical centers from January to December 2014, as part of the AWARE Program. MDR strains were defined as non-susceptible to ≥2 classes of the following antimicrobials: penicillin (MIC, ≥4 µg/mL), ceftriaxone (MIC, ≥2 µg/mL), 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 M7-A10 (2015). *S. pneumoniae* ATCC 49619 was tested for quality control (QC). Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S26) and CLSI and USA-FDA breakpoints were applied.

Results

- All but one isolate (>99.9%) were susceptible to ceftaroline (MIC_{50}, ≤0.015 µg/mL and MIC_{90}, 0.12 µg/mL) according to the CLSI susceptible breakpoint of ≤0.5 µg/mL (Table 1).
- Ceftaroline was also very active against all resistant subsets evaluated, including ceftriaxone-non-susceptible (MIC_{50} and MIC_{90}, 0.25 µg/mL), penicillin-resistant (penicillin MIC, ≥8 µg/mL; ceftaroline MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL) and amoxicillin-clavulanate-non-susceptible isolates (MIC_{50}, 0.12 µg/mL and MIC_{90}, 0.25 µg/mL; Table 1).
- Resistance to erythromycin and levofloxacin did not adversely affect ceftaroline activity; ceftaroline $MIC_{50/90}$ values were 0.06/0.12 µg/mL for erythromycin-resistant and ≤0.015/0.12 µg/mL for levofloxacin-non-susceptible isolates (Table 1).
- Susceptibility to ceftriaxone was 94.7% and ceftaroline (MIC_{90}, 0.12 µg/mL) was eight-fold more potent than ceftriaxone (MIC_{90}, 1 µg/mL; Table 2).
- The overall erythromycin-non-susceptibility rate (MIC, ≥0.5 µg/mL [CLSI]) was high at 45.9%. Moreover, 15.8% of isolates were clindamycin-non-susceptible (Table 2).
- Linezolid (MIC_{50} and MIC_{90}, 1 µg/mL), tigecycline (MIC_{50} and MIC_{90}, 0.03 µg/mL) and vancomycin (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL) were active against 100.0% of isolates at the respective CLSI/USA-FDA susceptible breakpoints (Table 2).
- Ceftriaxone-non-susceptible (≥2 µg/mL) isolates exhibited low susceptibility (<30%) to most tested antimicrobials, but remained susceptible to ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL; 99.3% susceptible) and levofloxacin (MIC_{50} and MIC_{90}, 1 µg/mL; 96.4% susceptible; Table 2).
- Ceftaroline was the only β-lactam agent that retained *in vitro* activity against isolates with penicillin MICs of ≥8 µg/mL, with $MIC_{50/90}$ values of 0.25/0.5 µg/mL (Tables 1 and 2).
- The overall MDR rate was 28.8% and ceftaroline was the most active agent (MIC_{50}, 0.06 µg/mL and MIC_{90}, 0.25 µg/mL; 99.9% susceptible) tested against these strains. Susceptibility rates of MDR isolates to other agents ranged from 2.3% for erythromycin to 96.3% for levofloxacin (Table 2).

Table 1. Summary of ceftaroline *in vitro* activity against *S. pneumoniae* from USA medical centers (2014)

Organism/subset	No. of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of:									
	Total	≤0.015	0.03	0.06	0.12	0.25	0.5	1	MIC_{50}	MIC_{90}
All Strains	2614	1604 (61.4)	276 (71.9)	277 (82.5)	371 (96.7)	77 (99.7)	8 (>99.9)	1 (100.0)	≤0.015	0.12
Ceftriaxone-non-susceptible (MIC, ≥2 µg/mL)	139		1 (0.7)	3 (2.9)	58 (44.6)	68 (93.5)	8 (99.3)	1 (100.0)	0.25	0.25
Penicillin-resistant (MIC, ≥8 µg/mL)	10					5 (50.0)	4 (90.0)	1 (100.0)	0.25	0.5
Amoxicillin-clavulanate-non-susceptible (MIC, ≥4 µg/mL)	274			13 (4.7)	185 (72.3)	67 (96.7)	8 (99.6)	1 (100.0)	0.12	0.25
Erythromycin-non-susceptible (MIC, ≥0.5 µg/mL)	1198	431 (36.0)	138 (47.5)	221 (65.9)	324 (93.0)	75 (99.2)	8 (99.9)	1 (100.0)	0.06	0.12
Levofloxacin-non-susceptible (MIC, ≥4 µg/mL)	43	22 (51.2)	3 (58.1)	5 (69.8)	12 (97.7)	0 (97.7)	1 (100.0)		≤0.015	0.12
MDR[a]	753	196 (26.0)	110 (40.6)	157 (61.5)	207 (89.0)	74 (98.8)	8 (99.9)	1 (100.0)	0.06	0.25

MDR = multidrug-resistant, defined as non-susceptible to ≥2 classes of the following antimicrobials: penicillin (≥4 µg/mL), ceftriaxone, erythromycin, levofloxacin, tetracycline and trimethoprim-sulfamethoxazole.

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against S. pneumoniae isolates from USA medical centers (2014)

Antimicrobial Agent (no. tested)	MIC_{50}	MIC_{90}	Range	%S[a]	%R[a]
All Strains (2,614)					
Ceftaroline	≤0.015	0.12	≤0.015 — 1	>99.9	-[b]
Ceftriaxone	≤0.06	1	≤0.06 — 8	82.6 94.7	5.3[c] 0.7[b]
Penicillin	≤0.06	2	≤0.06 — 8	60.4 93.7	13.0[d] 0.4[e]
Amoxicillin-clavulanate	≤1	4	≤1 — >8	89.5	6.3[b]
Meropenem	≤0.06	0.5	≤0.06 — 2	82.2	5.3
Clindamycin	≤0.25	>2	≤0.25 — >2	84.2	15.4
Erythromycin	≤0.12	>16	≤0.12 — >16	54.1	45.1
Levofloxacin	1	1	≤0.12 — >4	98.4	1.1
Linezolid	1	1	≤0.12 — 2	100.0	-
Tetracycline	≤0.5	>8	≤0.5 — >8	78.5	21.2
Tigecycline[f]	0.03	0.03	≤0.015 — 0.06	100.0[f]	-
TMP/SMX	≤0.5	>4	≤0.5 — >4	72.4	16.4
Vancomycin	0.25	0.5	≤0.12 — 1	100.0	-
Ceftriaxone-non-susceptible (MIC, ≥ 2 µg/mL) (139)					
Ceftaroline	0.25	0.25	0.03 — 1	99.3	-[b]
Penicillin	4	4	0.25 — 8	0.0 18.0	95.7[d] 7.2[e]
Amoxicillin-clavulanate	8	8	≤1 — >8	11.5	80.6[b]
Meropenem	1	1	0.06 — 2	4.3	65.5
Clindamycin	>2	>2	≤0.25 — >2	25.2	74.8
Erythromycin	>16	>16	≤0.12 — >16	2.2	97.8
Levofloxacin	1	1	0.5 — >4	96.4	3.6
Tetracycline	>8	>8	≤0.5 — >8	15.8	84.2
TMP/SMX	>4	>4	≤0.5 — >4	4.3	93.5
Penicillin-Resistant (MIC, ≥ 8 µg/mL) (10)					
Ceftaroline	0.25	0.5	0.25 — 1	90.0	-[b]
Ceftriaxone	4	8	2 — 8	0.0 0.0	100.0[c] 80.0[b]
Amoxicillin-clavulanate	>8	>8	4 — >8	0.0	90.0[b]
Meropenem	1	1	0.5 — 2	0.0	90.0
Clindamycin	>2	>2	≤0.25 — >2	20.0	80.0
Erythromycin	>16	>16	2 — >16	0.0	100.0
Levofloxacin	1	1	0.5 — >4	90.0	10.0
Tetracycline	>8	>8	≤0.5 — >8	10.0	90.0
TMP/SMX	>4	>4	4 — >4	0.0	100.0
Amoxicillin-clavulanate-non-susceptible (MIC, ≥4 µg/mL) (274)					
Ceftaroline	0.12	0.25	0.06 — 1	99.6	-[b]
Ceftriaxone	1	2	0.5 — 8	2.9 55.1	44.9[c] 6.9[b]
Penicillin	4	4	0.5 — 8	0.0 42.0	96.0[d] 3.6[e]
Meropenem	1	1	0.25 — 2	1.5	50.4
Clindamycin	>2	>2	≤0.25 — >2	36.5	62.8
Erythromycin	>16	>16	≤0.12 — >16	5.8	94.2
Levofloxacin	1	1	0.5 — >4	96.0	2.9
Tetracycline	>8	>8	≤0.5 — >8	31.8	68.2
TMP/SMX	4	>4	≤0.5 — >4	23.4	74.1
Erythromycin-non-susceptible (MIC, ≥0.5 µg/mL) (1,198)					
Ceftaroline	0.06	0.12	≤0.015 — 1	99.9	-[b]
Ceftriaxone	0.25	2	≤0.06 — 8	65.9 88.6	11.4[c] 1.6[b]
Penicillin	0.25	4	≤0.06 — 8	34.1 86.5	26.0[d] 0.8[e]
Amoxicillin-clavulanate	≤1	8	≤1 — >8	78.5	13.6[b]
Meropenem	0.12	1	≤0.06 — 2	65.5	11.3
Clindamycin	≤0.25	>2	≤0.25 — >2	65.5	33.5
Erythromycin	8	>16	0.5 — >16	0.0	98.2
Levofloxacin	1	1	0.25 — >4	98.1	1.6
Tetracycline	≤0.5	>8	≤0.5 — >8	56.5	43.2
TMP/SMX	≤0.5	>4	≤0.5 — >4	54.1	30.1
Levofloxacin-non-susceptible (MIC, ≥ 4 µg/mL) (43)					
Ceftaroline	≤0.015	0.12	≤0.015 — 0.5	100.0	-[b]
Ceftriaxone	0.12	2	≤0.06 — 8	69.8 88.4	11.6[c] 4.7[b]
Penicillin	≤0.06	4	≤0.06 — 8	51.2 86.0	25.6[d] 2.3[e]
Amoxicillin-clavulanate	≤1	8	≤1 — 8	74.4	11.6[b]
Meropenem	≤0.06	1	≤0.06 — 1	72.1	11.6
Clindamycin	≤0.25	>2	≤0.25 — >2	69.8	27.9
Erythromycin	2	>16	≤0.12 — >16	46.5	53.5
Tetracycline	≤0.5	>8	≤0.5 — >8	58.1	41.9
TMP/SMX	≤0.5	>4	≤0.5 — >4	65.1	30.2
MDR (753)					
Ceftaroline	0.06	0.25	≤0.015 — 1	99.9	-[b]
Ceftriaxone	0.25	2	≤0.06 — 8	61.6 81.5	18.5[c] 2.5[b]
Penicillin	0.25	4	≤0.06 — 8	23.4 78.5	33.6[d] 1.3[e]
Amoxicillin-clavulanate	≤1	8	≤1 — >8	70.9	21.6[b]
Meropenem	0.12	1	≤0.06 — 2	62.2	16.6
Clindamycin	1	>2	≤0.25 — >2	48.3	50.7
Erythromycin	>16	>16	≤0.12 — >16	2.3	96.0
Levofloxacin	1	1	0.25 — >4	96.3	2.9
Tetracycline	>8	>8	≤0.5 — >8	29.1	70.1
TMP/SMX	2	>4	≤0.5 — >4	25.0	49.3

a. %S = % susceptible and %R = % resistant according to CLSI criteria [CLSI, 2016]
b. Using non-meningitis breakpoints [CLSI, 2016]
c. Using meningitis breakpoints [CLSI, 2016]
d. Using oral breakpoints [CLSI, 2016]
e. Using parenteral, non-meningitis breakpoints [CLSI, 2016]
f. Breakpoints from USA-FDA Package Insert [Tygacil 2014]

Conclusions

- Ceftaroline was very active against *S. pneumoniae* from USA medical centers, including MDR isolates and isolates not susceptible to ceftriaxone and other antimicrobials commonly used to treat CABP.
- Ceftaroline was the most potent β-lactam tested against *S. pneumoniae* isolated in the USA (2014).
- The *in vitro* data presented here support the use of ceftaroline fosamil for the treatment of *S. pneumoniae* infections, including those caused by ceftriaxone-non-susceptible and MDR isolates.

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