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Antimicrobial Activity of Ceftaroline and Comparator Agents Against Contemporary (2010) *Streptococcus pneumoniae* Isolates from Latin America

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Abstract

- **Background:** Ceftaroline (CPT) is the active component of the prodrug CPT fosamil, a novel cephalosporin exhibiting broad-spectrum bactericidal activity *in vitro* against Gram-positive organisms including *S. pneumoniae* (SPN) and multidrug-resistant (MDR)-SPN. This study determined activity of CPT against recent (2010) SPN isolated in Latin America (LA).

- **Methods:** Susceptibility testing for CPT and commonly used antimicrobials was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology on a total of 212 isolates from the 2010 Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program. Isolates were collected consecutively from clinical infections (mostly community-acquired bacterial pneumonia) in 14 medical centers in Argentina (2 centers), Brazil (5), Chile (2), Colombia (1) and Mexico (4). MDR-SPN status was determined by resistance to ≥2 classes of the following antimicrobials: penicillin (PEN), erythromycin (ERY), levofloxacin (LEV), tetracycline (TET) and trimethoprim-sulfamethoxazole (SXT). In absence of CLSI breakpoints, USA-FDA breakpoints were applied; susceptible (S) ≤0.25 µg/ml, with isolates >0.25 µg/ml classified as non-S (NS) due to limited clinical outcomes information about strains having CPT MICs at ≥0.5 µg/ml.

- **Results:** CPT MIC distribution and MIC_{50} and MIC_{90} against all isolates and by MDR status are found in the Table. CPT was very active against all isolates with the highest CPT MIC being only 0.5 µg/ml (1 isolate). The CPT MIC_{90} was 8-fold higher in MDR (28.3% of isolates) compared to non-MDR isolates. Overall, 99.5% of isolates were S (USA-FDA) to CPT. CPT was 8-fold more active than ceftriaxone ($MIC_{50/90}$, ≤0.06/1 µg/ml). Using CLSI oral breakpoints for PEN (S, ≤0.06 µg/ml), 45.8% of isolates were NS (20.8% resistant [R]). R to other commonly used antimicrobial agents were ERY (25.9%), TET (21.7%), SXT (28.8%), and LEV (0.0%).

- **Conclusions:** This study demonstrated the potent *in vitro* activity of CPT against recent (2010) SPN isolates including MDR strains in LA. Although clinical data are currently limited, these *in vitro* results suggest that CPT fosamil may emerge as an important treatment regimen for infections caused by MDR strains and SPN resistant to other beta-lactams and commonly used antimicrobials.

Group	No. (cum.%) of isolates inhibited at Ceftaroline MIC (µg/ml) ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
All isolates (212)	105 (49.5)	28 (62.7)	21 (72.6)	12 (78.3)	39 (96.7)	6 (99.5)	1 (100.0)	0.015	0.12
non-MDR (152)	103 (67.8)	22 (82.2)	18 (94.1)	9 (100.0)	-	-	-	≤0.008	0.03
MDR (60)	2 (3.3)	6 (13.3)	3 (18.3)	3 (23.3)	39 (88.3)	6 (98.3)	1 (100.0)	0.12	0.25

Introduction

- Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil. Ceftaroline fosamil was approved in 2010 by the United States Food and Drug Administration (USA-FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Ceftaroline has demonstrated broad-spectrum *in vitro* activity against pathogens frequently encountered in CABP, including penicillin-resistant and ceftriaxone-non-susceptible *Streptococcus pneumoniae*.

- As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study, we evaluated the spectrum and antimicrobial activity of ceftaroline and comparator agents tested against *S. pneumoniae* isolates recovered from respiratory tract infections, including CABP, in Latin American medical centers.

Materials and Methods

- Organism collection: A total of 212 *S. pneumoniae* isolates from the 2010 AWARE Surveillance Program were evaluated. Isolates were collected consecutively from clinical infections in 14 medical centers in Argentina (two centers), Brazil (five centers), Chile (two centers), Colombia (one center) and Mexico (four centers). Multidrug-resistant (MDR) *S. pneumoniae* status was determined by resistance to ≥2 classes of the following antimicrobials: penicillin, erythromycin, levofloxacin, tetracycline and trimethoprim-sulfamethoxazole (TMP-SMX).

- Susceptibility methods: Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine antimicrobial susceptibility of ceftaroline and comparator agents. Validated MIC panels were manufactured by ThermoFisher Scientific Inc. (formerly TREK Diagnostics; Cleveland, Ohio, USA). Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included *S. pneumoniae* ATCC 49619, among others. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012 for comparators). In absence of CLSI breakpoints, USA-FDA breakpoints were applied for ceftaroline; susceptible ≤0.25 µg/ml, with isolates >0.25 µg/ml classified as non-susceptible due to limited clinical outcome information about strains having ceftaroline MIC values at ≥0.5 µg/ml.

Results

- Ceftaroline was active ($MIC_{50/90}$, 0.015/0.12 µg/ml) against all isolates with the highest MIC being 0.5 µg/ml (one isolate from Brazil; 0.5% of total; Tables 1 and 2). Overall, 96.7% of strains were inhibited at ≤0.12 µg/ml of ceftaroline, and 99.5% of isolates were categorized as ceftaroline susceptible when the USA-FDA susceptible breakpoint was applied (Table 2).

Table 1. *Antimicrobial Activity of Ceftaroline Against S. pneumoniae from Latin American Medical Centers (2010).*

Subset/country (no. tested)	no. of isolates (cumulative %) inhibited at CPT MIC (µg/ml) of: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All strains (212)	105 (49.5)	28 (62.7)	21 (72.6)	12 (78.3)	39 (96.7)	6 (99.5)	1 (100.0)
Penicillin-susceptible (≤0.06 µg/ml)	102 (88.7)	10 (97.4)	3 (100.0)	-	-	-	-
Penicillin-intermediate (0.12-1 µg/ml)	3 (5.7)	18 (39.6)	18 (73.6)	12 (96.2)	2 (100.0)	-	-
Penicillin-resistant (≥2 µg/ml)	-	-	-	-	37 (84.1)	6 (97.7)	1 (100.0)
MDR[a] (60)	2 (3.3)	6 (13.3)	3 (18.3)	3 (23.3)	39 (88.3)	6 (98.3)	1 (100.0)
Argentina (33)	19 (57.6)	4 (69.7)	3 (78.8)	4 (90.9)	3 (100.0)	-	-
Brazil (74)	43 (58.1)	8 (68.9)	10 (82.4)	3 (86.5)	9 (98.7)	0 (98.5)	1 (100.0)
Chile (60)	26 (43.3)	5 (51.7)	6 (61.7)	2 (65.0)	16 (91.7)	5 (100.0)	-
Colombia (9)	6 (66.7)	2 (88.9)	0 (88.9)	0 (88.9)	1 (100.0)	-	-
Mexico (36)	11 (30.6)	9 (55.6)	2 (61.1)	3 (69.4)	10 (97.2)	1 (100.0)	-

a. Multidrug-resistant (MDR) *S. pneumoniae* status was determined by resistance to ≥2 classes of the following antimicrobials: penicillin, erythromycin, levofloxacin, tetracycline and trimethoprim/sulfamethoxazole.

Table 2. *Activity of Ceftaroline and Comparator Antimicrobial Agents When Tested Against Isolates of S. pneumoniae from Latin America.*

Antimicrobial agent (no. tested)	MIC in µg/ml 50%	90%	Range	% Susc. / % Resistant CLSI[a]	EUCAST[a]
All strains (212)					
Ceftaroline	0.015	0.12	≤0.008 – 0.5	99.5[b] / -	- / -
Penicillin (parenteral)[c]	≤0.03	2	≤0.03 – 4	92.9[c] / 0.0[c]	- / -
Penicillin (oral)[d]	≤0.03	2	≤0.03 – 4	54.2[d] / 20.8[d]	54.2 / 7.1
Amoxicillin/clavulanate	≤1	2	≤1 – 8	92.0 / 4.7	- / -
Ceftriaxone	≤0.06	1	≤0.06 – 8	94.3 / 0.5	79.2 / 0.5
Cefuroxime	≤0.12	8	≤0.12 – >16	76.9 / 22.2	73.6 / 23.1
Erythromycin	≤0.06	>8	≤0.06 – >8	73.1 / 25.9	73.1 / 25.9
Clindamycin	≤0.25	>1	≤0.25 – >1	89.6 / 10.4	89.6 / 10.4
Levofloxacin	1	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	76.4 / 21.7	75.9 / 23.6
TMP/SMX[e]	≤0.5	>4	≤0.5 – >4	56.1 / 28.8	65.6 / 28.8
Penicillin-susceptible (MIC, ≤0.06 µg/ml; 115)					
Ceftaroline	≤0.008	0.015	≤0.008 – 0.03	100.0[b] / -	- / -
Amoxicillin/clavulanate	≤1	≤1	≤1	100.0 / 0.0	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Cefuroxime	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.06	≤0.06	≤0.06 – >8	91.3 / 7.8	91.3 / 7.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >16	98.3 / 1.7	98.3 / 1.7
Levofloxacin	1	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	8	≤0.25 – >8	86.1 / 10.4	85.2 / 13.9
TMP/SMX[e]	≤0.5	2	≤0.5 – >4	82.6 / 6.1	88.7 / 6.1
Penicillin-intermediate (MIC, 0.12 - 1 µg/ml; 53)					
Ceftaroline	0.03	0.06	≤0.008 – 0.12	100.0[b] / -	- / -
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Ceftriaxone	0.12	0.5	≤0.06 – 1	100.0 / 0.0	94.3 / 0.0
Cefuroxime	0.25	1	≤0.12 – 4	90.6 / 7.5	77.4 / 9.4
Erythromycin	≤0.06	>8	≤0.06 – >8	60.4 / 37.7	60.4 / 37.7
Clindamycin	≤0.25	>16	≤0.25 – >16	83.0 / 17.0	83.0 / 17.0
Levofloxacin	1	1	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	73.6 / 26.4	73.6 / 26.4
TMP/SMX[e]	1	4	≤0.5 – >4	45.3 / 26.4	67.9 / 26.4
Penicillin-resistant (MIC, ≥2 µg/ml; 44)					
Ceftaroline	0.12	0.25	0.12 – 0.5	97.7[b] / -	- / -
Penicillin (parenteral)	2	4	2 – 4	65.9[c] / 0.0[c]	0.0 / 34.1
Amoxicillin/clavulanate	2	8	≤1 – 8	61.4 / 22.7	- / -
Ceftriaxone	1	2	0.5 – 8	72.7 / 2.3	6.8 / 2.3
Cefuroxime	8	8	2 – >16	0.0 / 97.7	0.0 / 100.0
Erythromycin	4	>8	≤0.06 – >8	40.9 / 59.1	40.9 / 59.1
Clindamycin	≤0.25	>1	≤0.25 – >1	75.0 / 25.0	75.0 / 25.0
Levofloxacin	1	1	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.5	>8	≤0.25 – >8	54.5 / 45.5	54.5 / 45.5
TMP/SMX[e]	>4	>4	1 – >4	0.0 / 90.9	2.3 / 90.9

a. Criteria as published by the CLSI [2011] and EUCAST [2011], ß-lactam susceptibility should be directed by the oxacillin test results.
b. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Teflaro Product Insert, 2010].
c. Criteria as published by the CLSI [2011] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2011] for 'Penicillin (oral penicillin V)'.
e. TMP/SMX = Trimethoprim/sulfamethoxazole.

- Ceftaroline was eight-fold more potent than ceftriaxone based on MIC_{90} ($MIC_{50/90}$, ≤0.06/1 µg/ml). Using CLSI oral breakpoints for penicillin (≤0.06 µg/ml), 45.8% of isolates were penicillin-non-susceptible (20.8% penicillin-resistant). Resistance rates to other commonly used antimicrobial agents were 25.9% for erythromycin, 21.7% for tetracycline, 28.8% for trimethoprim/sulfamethoxazole, and 0.0% for levofloxacin (Table 2).

- Ceftaroline MIC_{50} varied from ≤0.008 µg/ml for the penicillin-susceptible (MIC, ≤0.06 µg/ml) to 0.12 µg/ml for the penicillin-resistant (MIC, ≥2 µg/ml) strains (Tables 1 and 2).

- Against penicillin-resistant (MIC, ≥2 µg/ml) pneumococci, ceftaroline (MIC_{50}, 0.12 µg/ml and MIC_{90}, 0.25 µg/ml) was eight-fold more potent than ceftriaxone (MIC_{50}, 1 µg/ml and MIC_{90}, 2 µg/ml; 72.7 and 6.8% susceptible according to CLSI and EUCAST criteria, respectively) and 16- and 64-fold more potent than amoxicillin/clavulanic acid based on MIC_{50} and MIC_{90} respectively (MIC_{50}, 2 µg/ml and MIC_{90}, 8 µg/ml; 61.4% susceptible according to CLSI criteria; Table 2).

- Penicillin resistance (MIC, ≥2 µg/ml) was highest among isolates from Chile (35.0%; 60 strains tested), followed by Mexico (25.0%; 36 strains tested), Brazil (13.5%; 74 strains tested), Colombia (11.1%; nine strains tested) and Argentina (9.1%; 33 strains tested; Table 3).

- Highest rates of resistance to erythromycin, tetracycline and trimethoprim/sulfamethoxazole were observed in Mexico (36.1, 36.1 and 50.0% respectively) and Chile (36.7, 21.7 and 36.7%; respectively; Table 3).

Table 3. *Antimicrobial Susceptibility of S. pneumoniae Stratified by Country (2010).*

Antimicrobial agent	%Susceptible[a] / % Resistant[a] (no. tested) Argentina (33)	Brazil (74)	Chile (60)	Colombia (9)	Mexico (36)
Ceftaroline[b]	100.0 / -	98.6 / -	100.0 / -	100.0 / -	100.0 / -
Penicillin[c]	66.7 / 9.1	59.5 / 13.5	48.3 / 35.0	88.9 / 11.1	33.3 / 25.0
Amoxicillin/Clavulanate	93.9 / 0.0	94.6 / 4.1	81.7 / 11.7	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	100.0 / 0.0	98.6 / 1.4	85.0 / 0.0	100.0 / 0.0	94.4 / 0.0
Erythromycin	69.7 / 30.3	86.5 / 13.5	61.7 / 36.7	100.0 / 0.0	61.1 / 36.1
Tetracycline	90.9 / 9.1	74.3 / 21.6	76.7 / 21.7	88.9 / 11.1	63.9 / 36.1
TMP/SMX[d]	75.8 / 9.1	55.4 / 21.6	56.7 / 36.7	66.7 / 22.2	36.1 / 50.0
Levofloxacin	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI (2012) unless noted.
b. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Teflaro Product Insert, 2010].
c. Criteria as published by CLSI for "oral penicillin V" as follows: susceptible at ≤0.06 µg/ml and resistant at ≥2 µg/ml (CLSI, 2012).
d. TMP/SMX=trimethoprim/sulfamethoxazole.

Conclusions

- This study demonstrated the potent *in vitro* activity of ceftaroline tested against recent (2010) *S. pneumoniae* isolates from the Latin America region, including multidrug-resistant strains.

- Overall, ceftaroline was the most potent β-lactam agent tested with eight-fold greater potency than the next most potent β-lactam (ceftriaxone) tested.

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