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Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Contemporary (2010) *Staphylococcus aureus*, Including MRSA Isolates, from Latin America

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Amended Abstract

- **Background:** Ceftaroline (CPT) is the active component of the prodrug CPT fosamil, a novel parenteral cephalosporin, exhibiting broad-spectrum *in vitro* bactericidal activity against Gram-positive organisms including methicillin-susceptible (MS) and resistant (MR) *S. aureus* (SA). The aim of this study was to determine the activity of CPT and comparators tested against SA isolated in Latin America (LA) in 2010.
- **Methods:** Susceptibility (S) testing for CPT and commonly used antimicrobials was performed by CLSI broth microdilution methodology on a total of 1,259 isolates from the 2010 Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program. Isolates were collected consecutively from clinical infections in 15 medical centers in Argentina (2 centers), Brazil (6), Chile (2), Colombia (1) and Mexico (4). In the absence of CLSI breakpoints, United States (USA)-FDA breakpoints were applied; susceptible (S) ≤1 µg/ml, with isolates >1 µg/ml classified as non-susceptible (NS) due to limited clinical information about strains having CPT MICs at 2 µg/ml.
- **Results:** CPT was very active ($MIC_{50/90}$, 0.25/2 µg/ml) and inhibited all 1,259 isolates (100.0%) at a MIC of ≤2 µg/ml (see Table). CPT was active against both MSSA (n=692, 55.0%; $MIC_{50/90}$, 0.25/0.25 µg/ml) and MRSA (n=567, 45.0%; $MIC_{50/90}$ 1/2 µg/ml). When tested against MSSA, CPT was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/ml). Overall, 85.7% of isolates were S (USA-FDA) to CPT with 100.0 and 68.3% of MSSA and MRSA, respectively, classified as S. Overall/MSSA/MRSA resistance rates to several commonly used antimicrobial agents were: levofloxacin (38.4/2.3/82.5%), erythromycin (47.8/16.0/86.6%), clindamycin (38.1/2.7/81.3%), tetracycline (7.2/9.1/4.9%), and trimethoprim-sulfamethoxazole (3.3/1.2/5.8%). All (100.0%) isolates were S to vancomycin and linezolid.
- **Conclusions:** This study demonstrates the potent *in vitro* activity of CPT tested against recent (2010) SA isolates, including against MRSA strains in LA. Resistance to many commonly selected antimicrobial agents was high. These data suggest that CPT fosamil could emerge as an important therapy for infections caused by SA, including MRSA, in LA with all strains inhibited at ≤2 µg/ml.

Organism/Group (n)	No. of isolates (%) inhibited at ceftaroline MIC value (µg/ml) of: ≤0.06	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}
S. aureus (1259)	2 (0.2)	73 (5.8)	610 (48.5)	132 (10.5)	262 (20.8)	180 (14.3)	0.25	2
MSSA (692)	2 (0.3)	73 (10.5)	610 (86.8)	16 (2.3)	-	-	0.25	0.25
MRSA (567)	-	-	10 (1.8)	116 (20.5)	261 (46.0)	180 (31.7)	1	2

Introduction

- β-lactam antibiotics are among the most commonly prescribed antimicrobial agents in the community and hospital settings. These agents bind to penicillin-binding proteins (PBPs) in the cell wall and inhibit transpeptidase activity with resulting cell death. The β-lactam agents, particularly the cephalosporins, have a long history of use demonstrating both safety and efficacy over a broad range of infections and organisms.
- Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil, an N-phosphonoamino water-soluble cephalosporin, which, in contrast to other β-lactams, has been shown to have a high affinity for PBP2a in MRSA. In two large, randomized Phase 3 trials, ceftaroline was found to be non-inferior to vancomycin plus aztreonam for the treatment of adult hospitalized patients with acute bacterial skin and skin structure infection (ABSSSI). Ceftaroline fosamil was approved in 2010 by the United States Food and Drug Administration (USA-FDA) for the treatment of ABSSSI and community-acquired bacterial pneumonia (CABP). In this study, we evaluated the *in vitro* activities of ceftaroline and comparator antimicrobial agents tested against *Staphylococcus aureus* isolated in Latin American medical centers in 2010.

Materials and Methods

- Organism collection: A total of 1,259 *S. aureus* isolates from the 2010 Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) Surveillance Program were evaluated. Isolates were collected consecutively from clinical infections in 15 medical centers in Argentina (2 centers), Brazil (6), Chile (2), Colombia (1) and Mexico (4). The isolates were collected primarily from ABSSSI, respiratory tract infections and bloodstream infections in hospitalized patients according to a common surveillance design. The isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmation of species identification, when necessary, and reference antimicrobial susceptibility testing.
- 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. aureus* ATCC 29213 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). USA-FDA interpretive criteria for ceftaroline susceptibility were used (susceptible at ≤1 µg/ml). Isolates with ceftaroline MIC >1 µg/ml were classified as non-susceptible (NS) due to limited clinical information about strains having CPT MICs at ≥2 µg/ml.

Results

- Ceftaroline was active ($MIC_{50//90}$, 0.25/2 µg/ml) and inhibited all 1,259 isolates of *S. aureus* (100.0%) at a MIC of ≤2 µg/ml. Ceftaroline was active against both MSSA ($MIC_{50/90}$, 0.25/0.25 µg/ml) and MRSA ($MIC_{50/90}$, 1/2 µg/ml; Tables 1 and 2).
- Overall, 85.7% of isolates were susceptible to ceftaroline when the USA-FDA breakpoint criterion was applied (Table 2). The percentages of strains inhibited at ceftaroline MIC of ≤1 µg/ml varied widely from as high as 95.5% in Mexico, 90.2% in Brazil and 90.0% in Colombia, to 82.1% in Argentina and 59.9% in Chile (Tables 1 and 3).
- When tested against MSSA ($MIC_{50/90}$, 0.25/0.25 µg/ml; 100.0% susceptible), ceftaroline was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/ml; 98.6% susceptible; Table 2). The highest ceftaroline MIC value among MSSA strains was only 0.5 µg/ml and 97.7% of strains were inhibited at a ceftaroline MIC of ≤0.25 µg/ml (Table 1).
- Although ceftaroline MIC values were slightly higher (approximately four-fold) among MRSA compared to MSSA, its activity was considerably greater than other cephalosporins and carbapenems tested against MRSA (data not shown). Furthermore, ceftaroline activity was comparable to those of linezolid (MIC_{50} and MIC_{90}, 1 µg/ml) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/ml; Table 2).
- MRSA strains exhibited high rates of resistance to erythromycin (86.6 and 87.1% according to CLSI and EUCAST breakpoint criteria, respectively), clindamycin (81.3 and 81.5% according to CLSI and EUCAST breakpoint criteria, respectively) and levofloxacin (82.5%; Table 2).
- MRSA rate was highest in Mexico (58.8%), followed by Argentina (51.7%), Chile (51.6%), Brazil (30.5%) and Colombia (26.7%; Table 3).

Table 1. *Summary of Ceftaroline Activity Tested Against Organisms Collected in Latin American Medical Centers in 2010.*

Country/subset (no. tested)	No. of isolates (cumulative %) inhibited at CPT MIC (µg/ml) of: ≤0.12	0.25	0.5	1	2
Argentina (207)	7 (3.4)	94 (48.8)	52 (73.9)	17 (82.1)	37 (100.0)
MSSA (100)	7 (7.0)	93 (100.0)	-	-	-
MRSA (107)	-	1 (0.9)	52 (49.5)	17 (65.4)	37 (100.0)
Brazil (478)	43 (9.0)	286 (68.8)	48 (78.9)	54 (90.2)	47 (100.0)
MSSA (332)	43 (13.0)	282 (97.9)	7 (100.0)	-	-
MRSA (146)	-	4 (2.7)	41 (30.8)	54 (67.8)	47 (100.0)
Chile (192)	12 (6.3)	80 (47.9)	15 (55.7)	8 (59.9)	77 (100.0)
MSSA (93)	12 (12.9)	78 (96.8)	3 (100.0)	-	-
MRSA (99)	-	2 (2.0)	12 (14.1)	8 (22.2)	77 (100.0)
Colombia (30)	-	21 (70.0)	5 (86.7)	1 (90.0)	3 (100.0)
MSSA (22)	-	21 (95.5)	1 (100.0)	-	-
MRSA (8)	-	-	4 (50.0)	1 (62.5)	3 (100.0)
Mexico (352)	13 (3.7)	130 (40.6)	12 (44.0)	181 (95.5)	16 (100.0)
MSSA (145)	13 (9.0)	127 (96.6)	5 (100.0)	-	-
MRSA (207)	-	3(1.5)	7 (4.8)	181 (92.3)	16 (100.0)
All countries (1,259)	75 (6.0)	611 (54.5)	132 (65.0)	261 (85.7)	180 (100.0)
MSSA (692)	75 (10.8)	601 (97.7)	16 (100.0)	-	-
MRSA (567)	-	10 (1.8)	116 (22.2)	261 (68.3)	180 (100.0)

Table 2. *Activity of Ceftaroline and Comparator Antimicrobial Agents When Tested against Isolates of S. aureus from Latin America (2010; All Countries Combined).*

Antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% Susc. / % Resistant CLSI[a]	EUCAST[a]
All strains (1,259)					
Ceftaroline	0.25	2	0.06 – 2	85.7[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	55.0 / 45.0	55.0 / 45.0
Ceftriaxone	4	>8	≤0.06 – >8	54.5[c] / 45.0	55.0 / 45.0
Erythromycin	0.5	>4	≤0.25 – >4	50.3 / 47.8	50.3 / 48.8
Clindamycin	≤0.25	>2	≤0.25 – >2	61.7 / 38.1	61.4 / 38.3
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	1	≤0.25 – >8	91.9 / 7.2	90.2 / 8.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	60.8 / 38.4	60.8 / 38.4
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	96.7 / 3.3	96.7 / 2.9
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (692)					
Ceftaroline	0.25	0.25	0.06 – 0.5	100.0[b] / -	- / -
Ceftriaxone	4	4	≤0.06 – 8	98.6[c] / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	81.1 / 16.0	81.1 / 17.5
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.1 / 2.7	96.5 / 2.9
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	8	≤0.25 – >8	89.3 / 9.1	88.7 / 11.1
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	97.0 / 2.3	97.0 / 2.3
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	98.8 / 1.2	98.8 / 1.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (567)					
Ceftaroline	1	2	0.25 – 2	68.3[b] / -	- / -
Ceftriaxone	>8	>8	4 – >8	0.0[c] / 100.0	0.0 / 100.0
Erythromycin	>4	>4	≤0.25 – >4	12.7 / 86.6	12.7 / 87.1
Clindamycin	>2	>2	≤0.25 – >2	18.5 / 81.3	18.5 / 81.5
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	1	≤0.25 – >8	95.1 / 4.9	92.1 / 5.1
Levofloxacin	>4	>4	≤0.5 – >4	16.8 / 82.5	16.8 / 82.5
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	94.2 / 5.8	94.2 / 5.3
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-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. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Rocephin Product Insert, 2010].
d. TMP/SMX = Trimethoprim/sulfamethoxazole.

Table 3. *Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against S. aureus Isolates from Latin American Medical Centers Stratified by Country (2010).*

Antimicrobial agent (no. tested)	MIC in µg/ml 50%	90%	Range	% Susc. / % Resistant CLSI[a]	EUCAST[a]
Argentina (207)					
Ceftaroline	0.5	2	0.06 – 2	82.1[b] / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	48.3 / 51.7	48.3 / 51.7
Ceftriaxone	>8	>8	≤0.06 – >8	48.3[c] / 51.7	48.3 / 51.7
Erythromycin	≤0.25	>4	≤0.25 – >4	65.2 / 33.3	65.2 / 33.8
Clindamycin	≤0.25	>2	≤0.25 – >2	78.3 / 21.3	77.8 / 21.7
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	≤0.25	≤0.25 – >8	99.5 / 0.5	99.5 / 0.5
Levofloxacin	≤0.5	4	≤0.5 – >4	73.4 / 25.6	73.4 / 25.6
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	99.5 / 0.5	99.5 / 0.5
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Brazil (478)					
Ceftaroline	0.25	1	0.12 – 2	90.2[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	69.5 / 30.5	69.5 / 30.5
Ceftriaxone	4	>8	0.5 – >8	68.3[c] / 30.5	69.5 / 30.5
Erythromycin	≤0.25	>4	≤0.25 – >4	56.3 / 40.2	56.3 / 42.3
Clindamycin	≤0.25	>2	≤0.25 – >2	73.0 / 27.0	72.4 / 27.0
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	83.2 / 14.9	79.2 / 17.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	72.8 / 25.9	72.8 / 25.9
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	93.5 / 6.5	93.5 / 6.1
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Chile (192)					
Ceftaroline	0.5	2	0.12 – 2	59.9[b] / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	48.4 / 51.6	48.4 / 51.6
Ceftriaxone	>8	>8	2 – >8	48.4[c] / 51.6	48.4 / 51.6
Erythromycin	>4	>4	≤0.25 – >4	41.7 / 56.3	41.7 / 57.3
Clindamycin	≤0.25	>2	≤0.25 – >2	50.5 / 49.5	50.5 / 49.5
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	≤0.25	≤0.25 – >8	99.0 / 1.0	98.4 / 1.0
Levofloxacin	2	>4	≤0.5 – >4	49.5 / 50.0	49.5 / 50.0
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	99.0 / 1.0	99.0 / 1.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Colombia (30)					
Ceftaroline	0.25	1	0.25 – 2	90.0[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	73.3 / 26.7	73.3 / 26.7
Ceftriaxone	4	>8	2 – >8	73.3[c] / 26.7	73.3 / 26.7
Erythromycin	0.5	>4	≤0.25 – >4	60.0 / 40.0	60.0 / 40.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.0 / 10.0	90.0 / 10.0
Linezolid	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	8	≤0.25 – >8	83.3 / 10.0	80.0 / 20.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	90.0 / 10.0	90.0 / 10.0
TMP/SMX[d]	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
Mexico (352)					
Ceftaroline	1	1	0.06 – 2	95.5[b] / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	41.2 / 58.8	41.2 / 58.8
Ceftriaxone	>8	>8	1 – >8	41.2[c] / 58.8	41.2 / 58.8
Erythromycin	>4	>4	≤0.25 – >4	37.2 / 62.8	37.2 / 62.8
Clindamycin	>2	>2	≤0.25 – >2	40.3 / 59.4	40.3 / 59.7
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	96.0 / 4.0	96.0 / 4.0
Levofloxacin	>4	>4	≤0.5 – >4	40.9 / 59.1	40.9 / 59.1
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	98.0 / 2.0	98.0 / 1.4
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-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. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Rocephin Product Insert, 2010].
d. TMP/SMX = Trimethoprim/sulfame.

Conclusions

- This study demonstrates the potent *in vitro* activity of ceftaroline tested against recent (2010) *S. aureus* isolates from Latin America, including against MRSA strains. All strains were inhibited at ≤2 µg/ml.
- Resistance to many commonly selected antimicrobial agents was generally high, particularly among MRSA.

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