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Antimicrobial Activity of Ceftaroline Tested against Contemporary (2012) Bacteria Isolated from Community-Acquired Respiratory Tract Infections, Including Oxacillin-resistant *S. aureus*

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Abstract

Background: Ceftaroline fosamil was approved by the United States (USA) Food and Drug Administration in 2010 for treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections, including those caused by oxacillin-resistant *S. aureus* (MRSA). We evaluated the in vitro potency and spectrum of ceftaroline (CPT) and comparators tested against community-acquired respiratory tract infection (CARTI) pathogens.

Methods: A total of 1,743 unique patient isolates were collected from CARTI in 163 USA medical centers in 2012. Susceptibility (S) was tested by CLSI broth microdilution methods against CPT and antimicrobials used to treat CARTI. *S. aureus* (SA), *Klebsiella* spp. (KSP) and *E. coli* (EC) isolates were obtained from patients with pneumonia ≤48 hrs after hospitalization.

Results: CPT ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) was 8-fold more potent than ceftriaxone (CRO; $MIC_{50/90}$, ≤0.06/1 µg/mL) against *S. pneumoniae* (SPN), and highly active against CRO-non-S SPN strains (MIC_{90}, 0.25 µg/mL). Among SPN, 8.2% of strains were non-S to CRO and resistance (R) rates were high for erythromycin (40.6%), clindamycin (CLI; 18.2%), trimethoprim/sulfamethoxazole (20.4%) and tetracycline (23.6%). CPT was very active against *H. influenzae* (highest MIC, 0.12 µg/mL), including β-lactamase-positive strains (22.7%; CPT MIC_{90}, 0.06 µg/mL), and *M. catarrhalis* (MIC_{90}, 0.12 µg/mL). CPT was 16-fold more active than CRO against methicillin-S SA (MIC_{90}, 0.25 µg/mL) and exhibited potent activity against MRSA ($MIC_{50/90}$, 0.5/1 µg/mL, 97.9% S). R rates were high for levofloxacin (78.0%) and CLI (37.6%) among MRSA. ESBL-phenotype rates were 14.3% and 18.4% for KSP and EC, respectively. CPT exhibited good activity against non-ESBL-phenotype strains ($MIC_{50/90}$, 0.12/0.25-0.5 µg/mL), but limited activity against ESBL-producing strains. Among ESBL-phenotype KSP, 22.2% of strains showed decreased S to meropenem (MIC, ≥4 µg/mL). Overall, 98.9% (1723/1743) of CARTI isolates were CPT-S by CLSI criteria.

Conclusion: CPT exhibited high in vitro activity against bacterial pathogens from CARTI recently (2012) collected from 163 USA medical centers. CPT maintained activity against CRO-non-S SPN and MRSA. These in vitro results are consistent with clinical data that show CPT fosamil to be a valuable agent for treatment of CARTI.

Introduction

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

The prodrug, ceftaroline fosamil, is 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 (ABSSSI). As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study, we evaluated the activity of ceftaroline and comparator agents tested against bacterial isolates collected from patients with CARTI (USA in 2012).

Methods

Organism collection: Unique patient isolates were consecutively collected from patients with CARTI in 163 USA medical centers in 2012. A total of 1,743 organisms were evaluated, including 720 *S. pneumoniae* (8.2% ceftriaxone-non-susceptible), 400 *H. influenzae* (22.7% β-lactamase-producers), 223 *Moraxella catarrhalis*, 299 *S. aureus* (47.2% MRSA); 63 *Klebsiella* spp. and 38 *Escherichia coli*. 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 CARTI. Validated MIC panels were manufactured by ThermoFisher Scientific® (Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), fastidious streptococci 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-S23).

Results

- Ceftaroline was the most potent of all β-lactams tested against *S. pneumoniae* strains ($MIC_{50/90}$, ≤0.015/0.12 µg/mL). The highest ceftaroline MIC value observed was only 0.5 µg/mL (three strains, 0.4%; Table 1), 100.0% susceptible by CLSI breakpoint and USA-FDA criteria (≤0.5 µg/mL; Table 2)
- Against penicillin-non-susceptible *S. pneumoniae* (MIC, ≥4 µg/mL), ceftaroline ($MIC_{50/90}$, 0.25/0.25 µg/mL) was eight- to 16-fold more active than ceftriaxone ($MIC_{50/90}$, 2/4 µg/mL; 26.2% susceptible; data not shown). Ceftaroline was also very active against the five *S. pneumoniae* strains with penicillin MIC values of ≥8 µg/mL (penicillin-resistant by CLSI breakpoint for penicillin parenteral, non-meningitis) with MIC values of 0.25 to 0.5 µg/mL
- The highest ceftaroline MIC value among *H. influenzae* was 0.12 µg/mL (three isolates, 0.7%). All *H. influenzae* isolates were considered susceptible to ceftaroline ($MIC_{50/90}$, ≤0.015/0.03 µg/mL) according to CLSI breakpoints. Most comparator agents exhibited good activity (>98% susceptibility) against *H. influenzae,* except clarithromycin ($MIC_{50/90}$, 8/16 µg/mL; 88.8% susceptibility) and trimethoprim/sulfamethoxazole (TMP/SMX; $MIC_{50/90}$, ≤0.5/>4 µg/mL; 68.3% susceptibility; Table 2)
- Ceftaroline was very active against *S. aureus* overall ($MIC_{50/90}$, 0.5/1 µg/mL; 99.0% susceptible). When tested against oxacillin- (methicillin)-susceptible strains (MSSA), ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 µg/mL) and four-fold more active than linezolid or vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL; Tables 1 and 2)
- Ceftaroline MIC values ranged from 0.25 to 2 µg/mL when tested against MRSA ($MIC_{50/90}$, 0.5/1 µg/mL; 97.9% susceptible). Although ceftaroline MIC values were slightly higher (two- to four-fold) among MRSA compared with MSSA, its activity was considerably greater than other cephalosporins tested against MRSA (data not shown). The overall MRSA rate was 47.2% and MRSA strains exhibited high rates of resistance to erythromycin (90.1%), clindamycin (37.6%) and levofloxacin (78.0%; Table 2)
- Ceftaroline was highly active against *M. catarrhalis* ($MIC_{50/90}$, 0.06/0.12 µg/mL; highest MIC, 0.5 µg/mL; Table 1)
- ESBL-phenotype rates were 14.3 and 18.4% for *Klebsiella* spp. and *E. coli*, respectively. Ceftaroline exhibited good activity against non-ESBL-phenotype strains ($MIC_{50/90}$, 0.12/0.25-0.5 µg/mL; data not shown), but limited activity against ESBL-producing strains (Table 2)
- Resistance rates to "third-generation" cephalosporins were high among ESBL-phenotype *Klebsiella* spp. (88.9 and 77.8% resistance to ceftriaxone and ceftazidime, respectively, according to CLSI breakpoints). Furthermore, 22.2% ESBL-phenotype *Klebsiella* spp. strains showed decreased susceptibility to meropenem (MIC, ≥2 µg/mL; Table 2)
- Overall, 98.9% (1,723/1,743) of CARTI isolates were ceftaroline-susceptible by CLSI criteria (Tables 1 and 2).

Table 1. Summary of ceftaroline activity tested against organisms collected from patients with community-acquired respiratory tract infections in USA hospitals (2012)

	No. of isolates (cumulative %) inhibited at MIC (µg/mL):									
Organism (no. tested)	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
Streptococcus pneumoniae (720)	446 (61.9)	66 (71.1)	72 (81.1)	100 (95.0)	33 (99.6)	3 (100.0)	--	--	--	--
Penicillin-non-susc. (MIC, ≥4 µg/mL; 65)	--	--	1 (1.5)	29 (46.2)	32 (95.4)	3 (100.0)	--	--	--	--
Ceftriaxone-non-susc. (MIC, ≥2 µg/mL; 59)	--	--	--	24 (40.7)	32 (94.9)	3 (100.0)	--	--	--	--
Haemophilus influenzae (400)	201 (85.0)	44 (96.0)	13 (99.3)	3 (100.0)	--	--	--	--	--	--
Staphylococcus aureus (299)	--	--	--	11 (3.7)	138 (49.8)	80 (76.6)	67 (99.0)	3 (100.0)	--	--
MSSA (158)	--	--	--	11 (7.0)	135 (92.4)	12 (100.0)	--	--	--	--
MRSA (141)	--	--	--	--	3 (2.1)	68 (50.4)	67 (97.9)	3 (100.0)	--	--
Moraxella catarrhalis (223)	13 (11.7)	46 (32.3)	75 (65.9)	54 (90.1)	20 (99.1)	2 (100.0)	--	--	--	--
Klebsiella spp. (63)	1 (1.6)	2 (4.8)	21 (38.1)	18 (66.7)	8 (79.4)	4 (85.7)	0 (85.7)	0 (85.7)	1 (87.3)	8 (100.0)
Escherichia coli (38)	--	4 (10.5)	11 (39.5)	5 (52.6)	6 (68.4)	4 (78.9)	0 (78.9)	1 (81.6)	0 (81.6)	7 (100.0)

Table 2. Activity of ceftaroline and comparator antimicrobial agents from CARTI infections (USA)

Organisms (no. tested) / antimicrobial agent	MIC (µg/mL) 50%	MIC (µg/mL) 90%	%S / % I / %R (CLSI)[a]
Streptococcus pneumoniae (720)			
Ceftaroline	≤0.015	0.12	100.0 / - / -
Ceftriaxone	≤0.06	1	91.8 / 6.9 / 1.3
Penicillin[b]	≤0.06	2	91.0 / 8.3 / 0.7
Amoxicillin/clavulanate	≤1	4	87.1 / 3.7 / 9.2
Erythromycin	≤0.12	>16	58.8 / 0.6 / 40.6
Clindamycin	≤0.25	>2	81.1 / 0.7 / 18.2
Levofloxacin	1	1	98.9 / 0.1 / 1.0
Linezolid	1	1	100.0 / - / -
Tetracycline	0.25	32	76.3 / 0.1 / 23.6
Tigecycline[c]	0.03	0.06	100.0 / - / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	66.1 / 13.5 / 20.4
Vancomycin	0.25	0.5	100.0 / - / -
Haemophilus influenzae (400)			
Ceftaroline	≤0.015	0.03	100.0 / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -
Cefuroxime	0.5	2	100.0 / 0.0 / 0.0
Ampicillin[d]	≤0.25	>8	76.5 / 0.7 / 22.8
Amoxicillin/clavulanate	≤1	2	100.0 / 0.0 / 0.0
Azithromycin	1	2	98.5 / - / -
Clarithromycin	8	16	88.8 / 9.2 / 2.0
Levofloxacin	≤0.12	≤0.12	100.0 / - / -
Tetracycline	0.5	1	98.8 / 0.1 / 1.3
Tigecycline[c]	0.25	0.5	71.3 / - / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	68.3 / 3.2 / 28.5
Staphylococcus aureus (299)			
Ceftaroline	0.5	1	99.0 / 1.0 / 0.0
Ceftriaxone	8	>8	52.8 / 0.0 / 47.2
Oxacillin	1	>2	52.8 / 0.0 / 47.2
Amoxicillin/clavulanate	≤1	>8	52.8 / 0.0 / 47.2
Erythromycin	>16	>16	33.8 / 6.0 / 60.2
Clindamycin	≤0.25	>2	77.9 / 0.7 / 21.4
Levofloxacin	0.25	>4	55.9 / 1.0 / 43.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.3 / 0.0 / 0.7
Tigecycline[c]	0.06	0.12	100.0 / - / -
Linezolid	1	1	100.0 / 0.0 / 0.0
Vancomycin	1	1	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -
MSSA (158)			
Ceftaroline	0.25	0.25	100.0 / 0.0 / 0.0
Ceftriaxone	4	4	100.0 / 0.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	100.0 / 0.0 / 0.0
Erythromycin	0.25	>16	58.2 / 8.3 / 33.5
Clindamycin	≤0.25	≤0.25	91.8 / 1.2 / 7.0
Levofloxacin	≤0.12	4	88.0 / 0.0 / 12.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	100.0 / 0.0 / 0.0
Tigecycline[c]	0.06	0.06	100.0 / - / -
Linezolid	1	1	100.0 / 0.0 / 0.0
Vancomycin	1	1	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -
MRSA (141)			
Ceftaroline	0.5	1	97.9 / 2.1 / 0.0
Erythromycin	>16	>16	6.4 / 3.5 / 90.1
Clindamycin	≤0.25	>2	62.4 / 0.0 / 37.6
Levofloxacin	>4	>4	19.9 / 2.1 / 78.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.6 / 0.0 / 1.4
Tigecycline[c]	0.06	0.12	100.0 / - / -
Linezolid	1	1	100.0 / 0.0 / 0.0
Vancomycin	1	1	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	100.0 / - / -
Moraxella catarrhalis (223)			
Ceftaroline	0.06	0.12	- / - / -
Ceftriaxone	0.25	0.5	100.0 / - / -
Penicillin	>2	>2	1.8 / 0.0 / 98.2
Amoxicillin/clavulanate	≤1	≤1	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	≤0.12	100.0 / - / -
Tetracycline	0.25	0.25	100.0 / 0.0 / 0.0
Tigecycline[c]	0.06	0.06	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	96.0 / 4.0 / 0.0
Klebsiella spp.[e] (63)			
Ceftaroline	0.12	>32	85.7 / 0.0 / 14.3
Ceftriaxone	≤0.06	>8	87.3 / 0.0 / 12.7
Ceftazidime	0.12	32	87.3 / 1.7 / 11.1
Piperacillin/tazobactam	4	16	90.5 / 0.0 / 9.5
Meropenem	≤0.06	≤0.06	96.8 / 0.0 / 3.2
Levofloxacin	≤0.12	>4	88.9 / 0.0 / 11.1
Gentamicin	≤1	≤1	95.2 / 3.2 / 1.6
Tigecycline[c]	0.25	0.5	100.0 / 0.0 / 0.0
ESBL-phenotype[f] (9)			
Ceftaroline	>32	-	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	>64	-	33.3 / 0.0 / 66.7
Meropenem	≤0.06	-	77.8 / 0.0 / 22.2
Levofloxacin	>4	-	22.2 / 0.0 / 77.8
Gentamicin	2	-	66.7 / 22.2 / 11.1
Tigecycline[c]	0.5	-	100.0 / 0.0 / 0.0
Escherichia coli (38)			
Ceftaroline	0.12	>32	78.9 / 0.0 / 21.1
Ceftriaxone	≤0.06	>8	84.2 / 0.0 / 15.8
Ceftazidime	0.12	16	86.8 / 2.7 / 10.5
Piperacillin/tazobactam	2	16	92.1 / 0.0 / 7.9
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	65.8 / 0.0 / 34.2
Gentamicin	≤1	>8	83.8 / 0.0 / 16.2
Tigecycline[c]	0.06	0.12	100.0 / 0.0 / 0.0
ESBL-phenotype (7)			
Ceftaroline	>32	-	0.0 / 0.0 / 100.0
Piperacillin/tazobactam	8	-	71.4 / 0.0 / 28.6
Meropenem	≤0.06	-	100.0 / 0.0 / 0.0
Levofloxacin	>4	-	14.3 / 0.0 / 85.7
Gentamicin	2	-	85.7 / 0.0 / 14.3
Tigecycline[c]	0.12	-	100.0 / 0.0 / 0.0

a. Criteria as published by the CLSI [2013].
b. Criteria as published by the CLSI [2012] for 'Penicillin parenteral non-meningitis' (Ss2, I=4, Rz8 µg/mL).
c. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
d. Based on β-lactamase production.
e. Includes: *Klebsiella oxytoca* (13 strains) and *K. pneumoniae* (50 strains).
f. Includes: *Klebsiella oxytoca* (one strain) and *K. pneumoniae* (eight strains).

Conclusions

- Ceftaroline exhibited broad and potent in vitro activity when tested against bacterial pathogens from CARTI collected from 163 USA medical centers
- Ceftaroline retained activity against ceftriaxone-non-susceptible *S. pneumoniae* and MRSA among the isolates sampled in 2012
- These in vitro results are consistent with clinical data that show ceftaroline fosamil to be a valuable agent for treatment of CARTI caused by MDR gram-positive species.

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