

Antimicrobial Activity of Ceftaroline Tested Against Bacteria Collected from Patients with Community-Acquired Respiratory Tract Infections (CARTI) in the USA (2008-2011)

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Abstract

Background: Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against Gram-positive and -negative pathogens causing CARTI, including MRSA, multidrug-resistant *S. pneumoniae* and β -lactamase-producing *H. influenzae*. The prodrug, ceftaroline fosamil, is USA-FDA-approved for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections.

Methods: Isolates were consecutively collected in 72 USA medical centers from patients with CARTI from 2008-2011. Ceftaroline and comparator antimicrobials were evaluated by CLSI broth microdilution methods. 5873 strains were tested, including 3077 *S. pneumoniae* (23.1% penicillin-resistant [MIC, ≥ 2 $\mu\text{g/mL}$]; 11.1% ceftriaxone-non-susceptible), 1540 *H. influenzae* (28.1% β -lactamase-producers), 190 *H. parainfluenzae*, 451 *M. catarrhalis*, and 615 *S. aureus* (45.0% MRSA).

Results: Against penicillin-resistant *S. pneumoniae*, ceftaroline (MIC_{50/90}, 0.12/0.25 $\mu\text{g/mL}$; highest MIC, 0.5 $\mu\text{g/mL}$) was 8- to 32-fold more active than ceftriaxone (MIC_{50/90}, 1/2 $\mu\text{g/mL}$; 52.8% susceptible), cefepime (MIC_{50/90}, 2/2 $\mu\text{g/mL}$; 49.5% susceptible) and amoxicillin/clavulanate (MIC_{50/90}, 8/8 $\mu\text{g/mL}$; 22.5% susceptible). Ceftaroline was also active against ceftriaxone-non-susceptible *S. pneumoniae* (MIC_{50/90}, 0.25/0.5 $\mu\text{g/mL}$). The highest ceftaroline MIC among *H. influenzae* was 0.5 $\mu\text{g/mL}$ (1 isolate) and activity against *H. influenzae* was not adversely affected by β -lactamase production. *H. parainfluenzae* (MIC_{50/90}, $\leq 0.015/0.03$ $\mu\text{g/mL}$) and *M. catarrhalis* (MIC_{50/90}, 0.06/0.12 $\mu\text{g/mL}$) were very ceftaroline-susceptible. Ceftaroline was highly active against MRSA (MIC_{50/90}, 0.5/1 $\mu\text{g/mL}$) and 16-fold more active than ceftriaxone (MIC_{50/90}, 4/4 $\mu\text{g/mL}$) when tested against MSSA (MIC_{50/90}, 0.25/0.25 $\mu\text{g/mL}$).

Conclusion: Ceftaroline exhibited potent *in vitro* activity against pathogens collected from CARTI patients in USA centers, including multidrug-resistant *S. pneumoniae* and MRSA. Ceftaroline fosamil appears to be a valuable agent for contemporary treatment of CARTI. Clinical studies of resistant pathogens are needed.

Introduction

Ceftaroline is a broad-spectrum cephalosporin with *in vitro* bactericidal activity against Gram-positive and common Gram-negative pathogens causing community-acquired respiratory tract infections (CARTI), including 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 against bacterial isolates collected from patients with CARTI in the USA in 2008–2011.

Methods

Organism collection: Isolates were consecutively collected in 72 USA medical centers from patients with CARTI in the 2008-2011 time period. A total of 5,873 organisms were evaluated, including 3,077 *S. pneumoniae* (23.1% penicillin-resistant [MIC, ≥ 2 $\mu\text{g/mL}$] and 11.1% ceftriaxone-non-susceptible), 1,540 *H. influenzae* (28.1% β -lactamase-producers), 190 *H. parainfluenzae*, 451 *M. catarrhalis*, and 615 *S. aureus* (45.0% MRSA).

Susceptibility testing 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® (formerly TREK Diagnostics®, Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), β -hemolytic 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 M7-A09 (2012).

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-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). USA-FDA interpretive criteria for ceftaroline susceptibility were used when available.

Results

Ceftaroline was the most potent of all β -lactams tested against *S. pneumoniae* strains (MIC_{50/90}, $\leq 0.015/0.12$ $\mu\text{g/mL}$). The highest ceftaroline MIC value observed was only 0.5 $\mu\text{g/mL}$ (1.2%; Tables 1 and 2), 98.8% susceptible by USA-FDA breakpoint criteria (≤ 0.25 $\mu\text{g/mL}$) and 100.0% susceptible by CLSI (June 2012) breakpoint criteria (≤ 0.5 $\mu\text{g/mL}$)

Against *S. pneumoniae* with penicillin MIC of ≥ 2 $\mu\text{g/mL}$ (penicillin-resistant by CLSI breakpoint for oral penicillin), ceftaroline (MIC_{50/90}, 0.12/0.25 $\mu\text{g/mL}$) was 8- to 64-fold more active than ceftriaxone (MIC_{50/90}, 1/2 $\mu\text{g/mL}$; 52.8% susceptible), cefepime (MIC_{50/90}, 2/2 $\mu\text{g/mL}$; 49.5% susceptible) and amoxicillin/clavulanate (MIC_{50/90}, 8/8 $\mu\text{g/mL}$; 22.5% susceptible; Table 2)

Ceftaroline was also very active against *S. pneumoniae* strains with penicillin MIC of ≥ 8 $\mu\text{g/mL}$ (penicillin-resistant by CLSI breakpoint for penicillin parenteral, nonmeningitis). Ceftaroline MIC values ranged from 0.25 to 0.5 $\mu\text{g/mL}$ (MIC₅₀, 0.25 $\mu\text{g/mL}$) and 55.0% were inhibited at ceftaroline MIC of ≤ 0.25 $\mu\text{g/mL}$. Ceftaroline was eight- and 32-fold more active than ceftriaxone (MIC₅₀, 4 $\mu\text{g/mL}$) and amoxicillin/clavulanate (MIC₅₀, 8 $\mu\text{g/mL}$), respectively, against this group of MDR organisms (Table 2). Furthermore, ceftaroline was highly active against ceftriaxone-non-susceptible *S. pneumoniae* (MIC_{50/90}, 0.25/0.5 $\mu\text{g/mL}$; 89.7% susceptible by USA-FDA breakpoint criteria (≤ 0.25 $\mu\text{g/ml}$) and 100.0% susceptible by CLSI (June 2012) breakpoint criteria (≤ 0.5 $\mu\text{g/mL}$; Tables 1 and 2)

H. parainfluenzae (MIC_{50/90}, $\leq 0.015/0.03$ $\mu\text{g/mL}$) and *M. catarrhalis* (MIC_{50/90}, 0.06/0.12 $\mu\text{g/mL}$) were also very susceptible to ceftaroline (Tables 1 and 2)

The highest ceftaroline MIC value among *H. influenzae* was 0.5 $\mu\text{g/mL}$ (one isolate) and ceftaroline activity against *H. influenzae* was not adversely affected by β -lactamase production (Tables 1 and 2). Most comparator agents exhibited good activity (>98% susceptibility) against *H. influenzae*, except clarithromycin (MIC_{50/90}, 8/16 $\mu\text{g/mL}$; 77.5% susceptibility) and trimethoprim/ sulfamethoxazole (TMP/SMX; MIC_{50/90}, $\leq 0.5/ > 2$ $\mu\text{g/mL}$; 76.6% susceptibility; Table 2)

Ceftaroline was very active against *S. aureus* overall (MIC_{50/90}, 0.25/1 $\mu\text{g/mL}$; 97.9% susceptible by CLSI [June 2012] and USA-FDA breakpoint criteria). When tested against oxacillin- (methicillin)-susceptible strains (MSSA), ceftaroline (MIC₅₀ and MIC₉₀, 0.25 $\mu\text{g/mL}$) was 16-fold more active than ceftriaxone (MIC₅₀ and MIC₉₀, 4 $\mu\text{g/mL}$) and four- to eight-fold more active than linezolid (MIC_{50/90}, 1/2 $\mu\text{g/mL}$). The highest ceftaroline MIC value among MSSA strains was only 0.5 $\mu\text{g/mL}$ (Tables 1 and 2)

Ceftaroline MIC values ranged from 0.25 to 2 $\mu\text{g/mL}$ (MIC_{50/90}, 0.5/1 $\mu\text{g/mL}$) when tested against MRSA. Although ceftaroline MIC values were slightly higher (two- to four-fold) among MRSA compared to MSSA, its activity was considerably greater than other cephalosporins tested against MRSA. Furthermore, ceftaroline was slightly more potent than linezolid (MIC_{50/90}, 1/2 $\mu\text{g/mL}$) and vancomycin (MIC_{50/90}, 1/1 $\mu\text{g/mL}$) when tested against MRSA (Table 2)

The overall MRSA rate was 45.0% and MRSA strains exhibited high rates of resistance to erythromycin (93.5 and 94.6% according to CLSI and EUCAST breakpoint criteria, respectively), clindamycin (43.3%) and levofloxacin (79.8%; Table 2).

Table 1. Summary of ceftaroline activity tested against organisms collected from patients with respiratory tract infections in USA hospitals (2008-2011).

Organism/subset (no. tested)	Cumulative % inhibited at ceftaroline MIC ($\mu\text{g/mL}$) of:							
	≤ 0.015	0.03	0.06	0.12	0.25	0.5	1	2
<i>S. pneumoniae</i> (3,077)	53.5	66.7	76.1	91.2	98.8	100.0	-	-
Penicillin-resistant at ≥ 2 $\mu\text{g/mL}$ (712)	-	0.4	3.9	61.9	94.9	100.0	-	-
Penicillin-resistant at ≥ 8 $\mu\text{g/mL}$ (40)	-	-	-	-	55.0	100.0	-	-
Ceftaroline-non-susceptible (341)	0.3	0.3	0.6	29.9	89.7	100.0	-	-
<i>H. influenzae</i> (1540)	88.5	96.7	99.1	99.7	99.9	100.0	-	-
β -lactamase-positive (433)	73.9	90.3	97.0	99.1	99.8	100.0	-	-
<i>H. parainfluenzae</i> (190)	83.7	92.6	94.7	96.8	97.9	99.0	99.5	100.0
<i>M. catarrhalis</i> (451)	15.1	42.3	74.9	96.9	99.3	100.0	-	-
<i>S. aureus</i> (615)	-	-	0.2	5.4	53.0	79.8	97.9	100.0
MSSA (338)	-	-	0.3	9.8	94.4	100.0	-	-
MRSA (277)	-	-	-	-	2.5	55.2	95.3	100.0

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against 5,873 bacterial isolates collected from patients with CARTI in USA medical centers (2008-2011).

Organism/antimicrobial agent (no. tested)	MIC ($\mu\text{g/mL}$)			CLSI ^a %S / %R	EUCAST ^a %S / %R	Organism/antimicrobial agent (no. tested)	MIC ($\mu\text{g/mL}$)			CLSI ^a %S / %R	EUCAST ^a %S / %R
	MIC ₅₀	MIC ₉₀	Range				MIC ₅₀	MIC ₉₀	Range		
<i>Streptococcus pneumoniae</i> (3,077)						β -lactamase positive (433)					
Ceftaroline ^b	≤ 0.015	0.12	$\leq 0.015 - 0.5$	98.8 / - (100.0 / -) ^b	- / -	Ceftaroline ^b	≤ 0.015	0.03	$\leq 0.015 - 0.5$	99.1 / - (100.0 / -) ^b	- / -
Ceftriaxone	≤ 0.25	2	$\leq 0.25 - 8$	88.9 / 1.8	76.4 / 1.8	Ceftriaxone	≤ 0.25	≤ 0.25	$\leq 0.25 - 0.5$	100.0 / -	99.8 / 0.2
Cefepime	≤ 0.5	2	$\leq 0.5 - 4$	88.2 / 1.0	88.2 / 1.0	Penicillin	>4	>4	0.25 - >4	- / -	- / -
Amoxicillin/clavulanate	≤ 0.06	4	$\leq 0.06 - 4$	85.2 / 1.3	- / -	Amoxicillin/clavulanate	≤ 1	2	$\leq 1 - 8$	99.8 / 0.2	88.2 / 11.8
Penicillin ^d	≤ 0.06	4	$\leq 0.06 - 4$	55.1 / 23.1	55.1 / 14.8	Cefuroxime	≤ 1	2	$\leq 1 - 8$	99.3 / 0.0	81.8 / 2.5
Amoxicillin/clavulanate	≤ 1	8	$\leq 1 - 8$	81.9 / 14.2	- / -	Meropenem	≤ 0.12	≤ 0.12	$\leq 0.12 - 0.25$	100.0 / -	100.0 / 0.0
Cefuroxime	≤ 1	8	$\leq 1 - 8$	70.9 / 25.2	69.6 / 29.1	Clarithromycin	8	16	$\leq 0.25 - >32$	6.4 / 3.9	1.4 / 0.5
Erythromycin	≤ 0.12	>8	$\leq 0.12 - >8$	57.2 / 42.4	57.2 / 42.4	Azithromycin	1	2	$\leq 0.03 - >4$	98.6 / -	0.5 - 1.4
Clindamycin	≤ 0.25	>1	$\leq 0.25 - >1$	78.1 / 21.4	78.6 / 21.4	Levofloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - 1$	100.0 / -	100.0 / 0.0
Levofloxacin	1	1	$\leq 0.5 - >4$	98.9 / 1.1	98.9 / 1.1	Moxifloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - 1$	100.0 / -	99.8 / 0.2
Moxifloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - 4$	99.1 / 0.6	98.9 / 1.1	Tetracycline	≤ 2	≤ 2	$\leq 2 - >8$	96.1 / 3.2	96.1 / 3.9
Tetracycline	≤ 2	>8	$\leq 2 - >8$	74.4 / 25.3	74.2 / 25.6	TMP/SMX ^e	≤ 0.5	>2	$\leq 0.5 - >2$	77.6 / 21.0	77.6 / 21.9
TMP/SMX ^e	≤ 0.5	>2	$\leq 0.5 - >2$	64.3 / 26.9	69.2 / 26.9	<i>Haemophilus parainfluenzae</i> (190)					
Penicillin-resistant (≥ 2 $\mu\text{g/mL}$; 712)						Ceftaroline ^b	≤ 0.015	0.03	$\leq 0.015 - 2$	- / - (99.0 / -) ^b	- / -
Ceftaroline ^b	0.12	0.25	0.03 - 0.5	94.9 / - (100.0 / -) ^b	- / -	Ceftriaxone	≤ 0.6	≤ 0.6	$\leq 0.6 - 0.5$	100.0 / -	- / -
Ceftriaxone	1	2	$\leq 0.25 - 8$	52.8 / 7.3	4.9 / 7.3	Amoxicillin/clavulanate	≤ 1	≤ 1	$\leq 1 - 4$	100.0 / 0.0	- / -
Cefepime	2	2	$\leq 0.5 - 4$	49.5 / 4.3	49.5 / 4.3	Cefuroxime	≤ 0.5	1	$\leq 0.5 - 16$	99.5 / 0.5	- / -
Amoxicillin/clavulanate	8	8	$\leq 1 - 8$	22.5 / 61.1	- / -	Meropenem	≤ 0.12	≤ 0.12	$\leq 0.12 - 0.25$	100.0 / -	- / -
Cefuroxime	8	>8	$\leq 1 - >8$	0.7 / 97.6	0.6 / 99.3	Clarithromycin	8	16	$\leq 0.25 - >32$	75.3 / 3.2	- / -
Erythromycin	>8	>8	$\leq 0.12 - >8$	11.2 / 88.5	11.2 / 88.5	Azithromycin	1	2	$\leq 0.06 - >4$	98.9 / -	- / -
Clindamycin	>1	>1	$\leq 0.25 - >1$	37.4 / 62.2	37.8 / 62.2	Levofloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - >4$	97.4 / -	- / -
Levofloxacin	1	1	$\leq 0.5 - >4$	98.6 / 1.1	98.6 / 1.4	Moxifloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - >4$	93.2 / -	- / -
Moxifloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - 4$	99.0 / 1.0	98.9 / 1.1	Tetracycline	0.5	1	$\leq 0.25 - >8$	92.1 / 5.8	- / -
Tetracycline	>8	>8	$\leq 2 - >8$	34.6 / 65.4	34.4 / 65.4	TMP/SMX ^e	≤ 0.5	>4	$\leq 0.5 - >4$	78.9 / 18.9	- / -
TMP/SMX ^e	>2	>2	$\leq 0.5 - >2$	20.9 / 76.0	22.8 / 76.0	<i>Moraxella catarrhalis</i> (451)					
Penicillin-resistant (≥ 8 $\mu\text{g/mL}$; 40)						Ceftaroline ^b	0.06	0.12	$\leq 0.015 - 0.5$	- / - (- / -) ^b	- / -
Ceftaroline ^b	0.25	0.5	0.25 - 0.5	55.0 / - (100.0 / -) ^b	- / -	Amoxicillin/clavulanate	≤ 1	≤ 1	≤ 1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	4	8	1 - 8	2.5 / 42.1	0.0 / 42.1	Cefuroxime	≤ 0.25	0.5	$\leq 0.25 - 2$	100.0 / -	99.6 / 0.0
Cefepime	2	4	2 - 4	0.0 / 32.4	0.0 / 32.4	Meropenem	≤ 0.12	≤ 0.12	$\leq 0.12 - 0.12$	99.8 / 0.2	77.2 / 1.3
Amoxicillin/clavulanate	8	>8	8 - >8	0.0 / 100.0	- / -	Levofloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - 1$	100.0 / -	100.0 / 0.0
Cefuroxime	>8	>8	8 - >8	0.0 / 100.0	0.0 / 100.0	Moxifloxacin	≤ 0.5	≤ 0.5	≤ 0.5	- / -	100.0 / 0.0
Erythromycin	>16	>16	$\leq 0.06 - >16$	2.5 / 97.5	2.5 / 97.5	Tetracycline	≤ 2	≤ 2	$\leq 2 - 8$	99.8 / 0.2	99.8 / 0.2
Clindamycin	>1	>1	$\leq 0.25 - >1$	17.5 / 80.0	20.0 / 80.0	TMP/SMX ^e	≤ 0.5	≤ 0.5	$\leq 0.5 - >2$	95.3 / 2.2	95.3 / 2.9
Levofloxacin	1	1	$\leq 0.5 - >4$	97.5 / 2.5	97.5 / 2.5	<i>Staphylococcus aureus</i> (615)					
Moxifloxacin	≤ 0.5	≤ 0.5	$\leq 0.5 - 4$	97.5 / 2.5	97.5 / 2.5	Ceftaroline ^b	0.25	1	0.06 - 2	97.9 / - (97.9 / 0.0) ^b	- / -
Tetracycline	>8	>8	$\leq 2 - >8$	12.5 / 87.5	12.5 / 87.5	Ceftriaxone	4	>8	1 - 8	93.3 / 45.0	55.0 / 45.0
TMP/SMX ^e	>2	>2	2 - >4	0.0 / 97.5	0.0 / 97.5	Oxacillin	0.5	>2	$\leq 0.25 - >2$	55.0 / 45.0	55.0 / 45.0
Ceftaroline-non-susceptible (341)						Erythromycin	>2	>2	$\leq 0.25 - >2$		