Ceftaroline Activity Against Clinical Isolates from United States Hospitals: Results from the 2011 Assessing Worldwide Antimicrobial Resistance Evaluation Programme (AWARE)

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Abstract

Objective: To evaluate the activity of ceftaroline (CPT) tested against prevalent Gram-positive and -negative species isolated in USA hospitals (2011). CPT, the active form of CPT fosamil, is a new, parenteral, broad-spectrum cephalosporin exhibiting *in vitro* bactericidal activity against Gram-positive organisms, including MRSA and multidrug-resistant (R) *Streptococcus pneumoniae* (SPN), as well as common Gram-negative pathogens. CPT is approved in the USA for treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP).

Methods: 5635 consecutive, nonduplicate isolates from bloodstream, ABSSSI, and respiratory tract infections were collected from 52 medical centres and tested for susceptibility (S) to CPT and comparator agents at a central laboratory using the reference CLSI broth microdilution method. CLSI and EUCAST breakpoint criteria were used to determine S/R rates for comparator agents. USA-FDA interpretive criteria were used for CPT.

Results: CPT inhibited all *S. aureus* strains (49.3% MRSA) at ≤2 mg/L and 98.8% of MRSA were S to CPT (Table 1). CPT was 8- to 16-fold more active than ceftriaxone (CRO; $MIC_{50/90}$, 4/4 mg/L) against MSSA. CPT inhibited all tested SPN at ≤0.5 mg/L and remained active against penicillin-R and CRO-non-S SPN (MIC_{90}, 0.25 mg/L for both subsets; Table 1). The highest CPT MIC value among β-haemolytic streptococci was only 0.03 mg/L. CPT activity against coagulase-negative staphylococci (CoNS; 61.6% methicillin-R) was similar to that against *S. aureus*. CPT showed only moderate activity against *E. faecalis* ($MIC_{50/90}$, 2/8 mg/L). *Haemophilus influenzae* (MIC_{90}, 0.03 mg/L; 27.2% β-lactamase [BL] producers), *H. parainfluenzae* (MIC_{90}, 0.12 mg/L) and *Moraxella catarrhalis* (MIC_{90}, 0.12 mg/L) were highly CPT-S. CPT activity against the most frequently isolated Enterobacteriaceae species (MIC_{50}, 0.12-0.25 mg/L) was similar to that of CRO (MIC_{50}, ≤0.06-0.25 mg/L) and ceftazidime (MIC_{50}, 0.12-0.25 mg/L). Extended-spectrum BL (ESBL) phenotype was observed in 9.9% of *E. coli* and 12.4% of *Klebsiella* spp., and all cephalosporins tested showed limited activity against ESBL-producing strains.

Conclusions: CPT demonstrated enhanced activity against staphylococci, including MRSA, various streptococcal groups, and *H. influenzae* strains recently isolated from USA hospitals. CPT activity against Enterobacteriaceae was similar to that of currently marketed broad-spectrum cephalosporins.

Introduction

β-lactam antibiotics are among the most commonly prescribed antimicrobial agents in the community and hospital settings. They have a long history of use demonstrating both safety and efficacy over a broad range of infections and organisms. Ceftaroline, the active form of ceftaroline fosamil, is a broad-spectrum cephalosporin exhibiting *in vitro* bactericidal activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Streptococcus pneumoniae*, as well as common Gram-negative pathogens.

Ceftaroline fosamil is approved by the United States Food and Drug Administration (USA-FDA) for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP). As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Programme, a global ceftaroline surveillance study, we evaluated the activity of ceftaroline against prevalent Gram-positive and -negative species isolated in USA hospitals in 2011.

Methods

Organism collection: A total of 5635 nonduplicate isolates were collected from 52 medical centres in 2011. The isolates were collected primarily from respiratory tract infections, ABSSSI, 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 minimum inhibitory concentration (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: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. 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

- The strains were isolated from respiratory tract infections (30.7%), ABSSSI (27.9%), bloodstream infections (14.6%), urinary tract infections (7.6%), and other infection sites (19.2%)
- Ceftaroline exhibited potent activity against methicillin-susceptible *S. aureus* (MSSA) isolates (MIC_{50} and MIC_{90}, 0.25 mg/L) and MRSA isolates ($MIC_{50/90}$, 0.5/1 mg/L). Against MSSA, ceftaroline was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 mg/L). The highest ceftaroline MIC results observed were 0.5 and 2 mg/L for MSSA and MRSA, respectively (Tables 1 and 2)
- The most active agents against MRSA were ceftaroline (MIC_{90}, 1 mg/L; 98.8% susceptible (S) and 100% inhibited at ≤2 mg/L), linezolid (MIC_{90}, 1 mg/L; 100% S), vancomycin (MIC_{90}, 1 mg/L; 100% S), daptomycin (MIC_{90}, 0.5 mg/L; 100% S), and tigecycline (MIC_{90}, 0.12 mg/L; 100% S); see Table 2
- Ceftaroline and ceftriaxone had similar in vitro activities against *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. and *Proteus mirabilis* (data not shown)

Table 2. Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Selected Organisms from USA Medical Centres (2011)

Antimicrobial agent (no. tested)	MIC (mg/L)			CLSI[a]	EUCAST[a]
	MIC_{50}	MIC_{90}	Range	%S / %R	%S / %R
S. aureus (1496)					
Ceftaroline[b]	0.25	1	0.06 – 2	99.4 / -	- / -
Ceftriaxone	8	>8	1 – >8	49.7 / 49.3	50.7 / 49.3
Oxacillin	2	>2	≤0.25 – >2	50.7 / 49.3	50.7 / 49.3
Erythromycin	>16	>16	≤0.12 – >16	37.7 / 60.4	37.9 / 61.7
Clindamycin	≤0.25	>2	≤0.25 – >2	84.4 / 15.6	84.2 / 15.6
Levofloxacin	0.25	>4	≤0.12 – >4	61.1 / 37.0	61.1 / 37.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline	0.06	0.12	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MSSA (758)					
Ceftaroline[b]	0.25	0.25	0.06 – 0.5	100.0 / -	- / -
Ceftriaxone	4	4	1 – 8	97.8 / 0.0	100.0 / 0.0
Erythromycin	0.25	>16	≤0.12 – >16	64.6 / 32.8	64.8 / 34.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.3 / 4.6	94.9 / 4.7
Levofloxacin	≤0.12	4	≤0.12 – >4	88.9 / 10.3	88.9 / 10.3
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.06	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MRSA (738)					
Ceftaroline[b]	0.5	1	0.12 – 2	98.8 / -	- / -
Ceftriaxone	>8	>8	4 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>16	>16	≤0.12 – >16	10.0 / 88.6	10.3 / 89.7
Clindamycin	≤0.25	>2	≤0.25 – >2	73.2 / 26.8	73.2 / 26.8
Levofloxacin	4	>4	≤0.12 – >4	32.5 / 64.5	32.5 / 64.5
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline	0.06	0.12	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (360)					
Ceftaroline[c]	≤0.015	0.03	≤0.015 – 0.03	- / -	- / -
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Erythromycin	≤0.12	>16	≤0.12 – >16	66.1 / 33.3	66.1 / 33.3
Clindamycin	≤0.25	>2	≤0.25 – >2	82.5 / 17.5	82.5 / 17.5
Levofloxacin	0.5	1	≤0.12 – >4	99.7 / 0.3	93.6 / 0.3
Linezolid	1	1	0.25 – 1	100.0 / -	100.0 / 0.0
Tetracycline	4	>8	≤0.25 – >8	49.7 / 49.7	48.9 / 50.3
Tigecycline	≤0.03	≤0.03	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
S. pneumoniae (956)					
Ceftaroline[b]	≤0.015	0.12	≤0.015 – 0.5	99.4 / -	- / -
Ceftriaxone	≤0.06	2	≤0.06 – 8	87.0 / 0.7	77.3 / 0.7
Penicillin[c]	≤0.06	4	≤0.06 – 8	85.4 / 1.9	- / -
Penicillin[d]	≤0.06	4	≤0.06 – 8	57.9 / 23.2	57.9 / 14.6
Amoxicillin/clavulanate	≤1	8	≤1 – >8	81.7 / 14.1	- / -
Cefuroxime	≤0.5	8	≤0.5 – >16	72.9 / 23.8	70.4 / 27.1
Erythromycin	≤0.12	>16	≤0.12 – >16	54.5 / 45.3	54.5 / 45.3
Clindamycin	≤0.25	>2	≤0.25 – >2	78.1 / 21.4	78.6 / 21.4
Levofloxacin	1	1	≤0.12 – >4	98.8 / 1.2	98.8 / 1.2
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Penicillin-resistant *S. pneumoniae*[d] (222)					
Ceftaroline[b]	0.12	0.25	0.06 – 0.5	97.3 / -	- / -
Ceftriaxone	2	2	0.25 – 8	45.0 / 3.2	5.0 / 3.2
Penicillin[c]	4	4	2 – 8	36.9 / 8.1	- / -
Penicillin[d]	4	4	2 – 8	0.0 / 100.0	0.0 / 63.1
Amoxicillin/clavulanate	8	8	≤1 – >8	21.6 / 60.8	- / -
Cefuroxime	8	16	2 – >16	0.0 / 96.8	0.0 / 100.0
Erythromycin	>16	>16	≤0.12 – >16	9.9 / 90.1	9.9 / 90.1
Clindamycin	>2	>2	≤0.25 – >2	37.4 / 62.6	37.4 / 62.6
Levofloxacin	1	1	0.5 – >4	97.7 / 2.3	97.7 / 2.3
Linezolid	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
H. influenzae (389)					
Ceftaroline[b]	≤0.015	0.03	≤0.015 – 0.5	99.5 / -	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Ampicillin	0.25	>8	≤0.12 – >8	72.5 / 26.7	72.5 / 27.5
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	90.7 / 9.3
Cefuroxime	1	2	≤0.5 – 8	99.5 / 0.0	79.9 / 1.8
Azithromycin	1	2	≤0.03 – >4	99.5 / -	1.5 / 0.5
Levofloxacin	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	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. US-FDA breakpoints were applied [Teflaro® Package Insert, 2010].
c. Criteria as published by the CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2012] for 'Penicillin (oral penicillin V)'.

- Against β-haemolytic streptococci, ceftaroline demonstrated potent activity ($MIC_{50/90}$, ≤0.015/0.03 mg/L) comparable to that of penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L). All group A (*S. pyogenes*) and 80.5% of group B streptococci (*S. agalactiae*) were inhibited at ≤0.015 mg/L and the highest ceftaroline MIC value among β-haemolytic streptococci was only 0.03 mg/L (Tables 1 and 2). Decreased susceptibility was observed only with erythromycin (MIC_{90}, >16 mg/L; 66.1% S) and clindamycin (MIC_{90}, >2 mg/L; 82.5% S by CLSI and EUCAST criteria)
- Ceftaroline activity against coagulase-negative staphylococci (CoNS; $MIC_{50/90}$, 0.25/0.5 mg/L) was slightly greater (2-fold) than that observed against *S. aureus* ($MIC_{50/90}$, 0.25/1 mg/L; Table 1). Oxacillin (methicillin) resistance was observed in 61.6% of CoNS strains (data not shown)
- Ceftaroline was highly active against *Haemophilus influenzae* ($MIC_{50/90}$, ≤0.015/0.03 mg/L). Comparators with the highest susceptibility rates were ceftriaxone, cefuroxime, amoxicillin/clavulanate, azithromycin, and levofloxacin (≥99.5% S; Table 2)
- Ceftaroline exhibited modest in vitro activity against *E. faecalis* ($MIC_{50/90}$, 2/8 mg/L; Table 1). Other cephalosporins tested showed very limited activity against these organisms (data not shown)
- Depending on the penicillin breakpoints used, the collection of *S. pneumoniae* contained up to 23.2% penicillin-resistant strains (using CLSI criteria for meningitis [penicillin parenteral; ≥2 mg/L]; CLSI 2012). When the CLSI (≥8 mg/L) and EUCAST (≥4 mg/L) resistant breakpoints for nonmeningitis were applied, penicillin resistance rates were 1.9% and 14.6%, respectively. Susceptibility rates to ceftriaxone were 87.0% and 77.3% according to CLSI (nonmeningitis; ≤1 mg/L) and EUCAST (≤0.5 mg/L) breakpoint criteria, respectively (Table 2)
- Ceftaroline was highly active against *S. pneumoniae* ($MIC_{50/90}$ at ≤0.015/0.12 mg/L) with 99.4% of isolates inhibited at ≤0.25 mg/L. Against penicillin-resistant (MIC, ≥2 mg/L) strains, ceftaroline ($MIC_{50/90}$, 0.12/0.25 mg/L) was 8- to 16-fold more active than ceftriaxone ($MIC_{50/90}$, 2/2 mg/L) and 32- to 64-fold more active than amoxicillin/clavulanate ($MIC_{50/90}$, 8/8 mg/L; Table 2). Among 124 ceftriaxone-non-susceptible (MIC, ≥2 mg/L) strains of *S. pneumoniae*, all were inhibited by 0.5 mg/L or less of ceftaroline (MIC_{90}, 0.25 mg/L; Table 1)
- ESBL phenotypes were observed in 9.9% of *E. coli* and 12.4% of *Klebsiella* spp., and all cephalosporins showed limited activity against ESBL-producing strains (data not shown).

Conclusions

- Ceftaroline demonstrated enhanced activity against staphylococci, including MRSA (MIC_{90}, 1 mg/L), various streptococcal groups, and *H. influenzae* strains recently isolated from USA hospitals
- Ceftaroline activity against Enterobacteriaceae was similar to that of currently marketed broad-spectrum cephalosporins, such as ceftriaxone
- Surveillance monitoring of ceftaroline, a new broad-spectrum, anti-MRSA β-lactam, in the AWARE USA Programme has demonstrated the excellent activity of ceftaroline against bacteria from across the USA. The continuation of the AWARE Surveillance Programme will provide both current and longitudinal information on the activity of ceftaroline and comparator agents.

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Table 1. Summary of Ceftaroline Activity Tested Against Organisms Collected in USA Medical Centres in 2011

Organisms (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline MIC (mg/L) of:									
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8
S. aureus (1496)	-	-	4(0.3)	124(8.6)	629(50.6)	500(84.0)	230(99.4)	9(100.0)	-	-
MSSA (758)	-	-	4(0.5)	121(16.5)	611(97.1)	22(100.0)	-	-	-	-
MRSA (738)	-	-	-	3(0.4)	18(2.9)	478(67.6)	230(98.8)	9(100.0)	-	-
β-haemolytic strep. (360)	317(88.1)	43(100.0)	-	-	-	-	-	-	-	-
Group A (154)	154(100.0)	-	-	-	-	-	-	-	-	-
Group B (179)	144(80.5)	35(100.0)	-	-	-	-	-	-	-	-
Group C (27)	19(70.4)	8(100.0)	-	-	-	-	-	-	-	-
CoNS (172)	-	1(0.6)	49(29.1)	26(44.2)	56(76.7)	36(96.7)	3(99.4)	1(100.0)	-	-
E. faecalis (132)	-	-	-	-	2(1.5)	5(5.3)	26(25.0)	65(74.2)	17(87.1)	16(99.2)
Viridans group strep. (63)	30(47.6)	27(90.5)	5(98.4)	1(100.0)	-	-	-	-	-	-
S. pneumoniae (956)	568(59.4)	101(70.0)	69(77.2)	131(90.9)	81(99.4)	6(100.0)	-	-	-	-
Penicillin-susceptible[a] (554)	528(95.3)	24(99.6)	2(100.0)	-	-	-	-	-	-	-
Penicillin-intermediate[a] (180)	40(22.2)	77(65.0)	55(95.6)	8(100.0)	-	-	-	-	-	-
Penicillin-resistant[a] (222)	-	-	12(5.4)	123(60.8)	81(97.3)	6(100.0)	-	-	-	-
Ceftriaxone-non-susc[a] (124)	-	2(1.6)	0(1.6)	38(32.3)	118(95.1)	6(100.0)	-	-	-	-
H. influenzae (389)	315(81.0)	52(94.3)	16(98.5)	4(99.5)	1(99.7)	1(100.0)	-	-	-	-
β-lactamase-negative (283)	254(89.8)	27(99.3)	2(100.0)	-	-	-	-	-	-	-
β-lactamase-positive (106)	61(57.6)	25(81.1)	14(94.3)	4(98.1)	1(99.1)	1(100.0)	-	-	-	-
H. parainfluenzae (56)	43(76.8)	7(89.3)	0(89.3)	3(94.6)	1(96.4)	0(96.4)	2(100.0)	-	-	-
M. catarrhalis (63)	8(12.7)	15(36.5)	18(65.1)	16(90.5)	5(98.4)	1(100.0)	-	-	-	-
Klebsiella spp. (539)	3(0.6)	19(4.1)	193(39.9)	122(62.5)	84(78.1)	40(85.5)	13(87.9)	3(88.5)	4(89.2)	2(89.6)
Non-ESBL-phenotype[b] (472)	3(0.6)	19(4.7)	192(45.3)	122(71.2)	84(89.0)	38(97.0)	11(99.4)	2(99.8)	1(100.0)	-
ESBL-phenotype[b] (67)	-	-	1(1.5)	0(1.5)	0(1.5)	2(4.5)	2(7.5)	1(9.0)	3(13.4)	2(16.4)
E. coli (435)	5(1.2)	34(9.0)	156(44.8)	100(67.8)	58(81.2)	13(84.1)	13(87.1)	8(89.0)	4(89.9)	4(90.8)
Non-ESBL-phenotype[b] (392)	5(1.3)	34(10.0)	155(49.5)	98(74.5)	57(89.0)	13(92.4)	13(95.7)	7(97.5)	4(98.5)	3(99.2)
ESBL-phenotype[b] (43)	0(0.0)	0(0.0)	1(2.3)	2(7.0)	1(9.3)	0(9.3)	0(9.3)	1(11.6)	0(11.6)	1(14.0)
Enterobacter spp. (337)	5(1.5)	5(3.0)	53(18.7)	87(44.5)	69(65.0)	38(76.3)	11(79.5)	6(81.3)	2(81.9)	3(82.8)
Ceftazidime-susc.[c] (277)	5(1.8)	5(3.6)	53(22.7)	87(54.2)	69(79.1)	38(92.8)	9(96.0)	5(97.8)	2(98.6)	1(98.9)
Ceftazidime-non-susc.[c] (60)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(3.3)	1(5.0)	0(5.0)	2(8.3)
P. mirabilis (150)	-	9(6.0)	74(55.3)	45(85.3)	8(90.7)	2(92.0)	4(94.7)	1(95.3)	1(96.0)	0(96.0)
S. marcescens (148)	-	-	-	-	10(6.7)	55(43.9)	60(84.5)	9(90.5)	5(93.9)	6(98.0)
Citrobacter spp. (100)	1(1.0)	0(1.0)	14(15.0)	33(48.0)	27(75.0)	11(86.0)	2(88.0)	1(89.0)	0(89.0)	0(89.0)
Indole-positive Proteae (91)	1(1.1)	5(6.6)	25(34.1)	22(58.2)	8(67.0)	4(71.4)	3(74.7)	2(76.9)	2(79.1)	1(80.2)
P. aeruginosa (148)	-	-	-	-	-	-	1(0.7)	2(2.0)	7(6.7)	31(27.7)

a. Criteria as published by the CLSI [2012] for 'Penicillin (oral penicillin V), ie. penicillin-susceptible at MIC of ≤0.06 mg/L and penicillin-resistant at MIC of ≥2 mg/L.
b. ESBL phenotype defined as an MIC ≥2 mg/L for ceftazidime or ceftriaxone [CLSI, 2012].
c. Ceftazidime susceptible at ≤4 mg/L and non-susceptible at ≥8 mg/L, defined according to the CLSI breakpoint criteria for Enterobacteriaceae [CLSI, 2012].
Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; ESBL = extended-spectrum β-lactamase.