P20

Antimicrobial Activity and Spectrum of the Novel Cephalosporin Ceftaroline Tested Against Bacterial Isolates Causing Skin and Skin Structure Infections in USA Medical Centers

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Amended Abstract

Introduction: Ceftaroline fosamil is the prodrug of ceftaroline (CPT), a novel, broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive organisms, including methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* (MDRSP) and common Gram-negative pathogens, including non-ESBL-producing Enterobacteriaceae (ENT). Ceftaroline fosamil is in late-stage development for treatment of complicated skin and skin structure infections (cSSSI) and community-acquired pneumonia (CAP). We evaluated the activity of CPT and comparator agents tested against cSSSI pathogens.

Methods: Unique (1 per patient) clinically significant isolates were consecutively collected from cSSSI in 25 USA medical centers in 2008-2009. Each medical center contributed approximately 50 strains each year and the most frequently isolated organisms were analyzed. Susceptibility (S) testing was performed by reference CLSI broth microdilution method (M07-A8; M100-S20) against CPT and numerous antimicrobials currently available for cSSSI treatment.

Results: More than 2,000 strains were tested and the 8 most common organisms are shown in the Table. The most frequently isolated organisms were MRSA (31.9%), methicillin-S *S. aureus* (MSSA; 27.8%) and *E. coli* (9.3%). 53.5% of *S. aureus* were MRSA. CPT was very active against MSSA and MRSA with highest MIC being 0.5 and 2 μg/mL, respectively. CPT (MIC_{90}, 1 μg/mL; 100% inhibited at ≤2 μg/mL), linezolid (MIC_{90}, 2 μg/mL; 100% S) and vancomycin (MIC_{90}, 2 μg/mL; 100% S) were the most active compounds tested against MRSA. Levofloxacin (LEV; 44% S) and clindamycin (80% S) showed limited activity against MRSA. CPT was 8-fold more potent than ceftriaxone (CRO) against MSSA. Against Enterobacteriaceae, CPT and CRO showed similar spectrum with 80-90% S and 79-92% S rates, respectively (see Table). LEV showed variable activity against ENT species; only 69% of *E. coli* was LEV-S. *P. aeruginosa* (PSA) showed high resistance (R) rates to most antimicrobials; the most active agents were piperacillin/tazobactam (88% S) and imipenem (IMI; 89% S). PSA and CRO-R ENT generally exhibited elevated CPT MIC values.

Organism (no. tested)	MIC_{90} (μg/mL)/% Susceptible			
	CPT	CRO	IMI	LEV
MRSA (656)	1/100[a]	>32/0	8/0	>4/44
MSSA (571)	0.5/100[a]	4/>99	≤0.12/100	≤0.5/91
βHS (72)	0.015/100[a]	≤0.25/100	≤0.12/100	1/100
EF (99)	4/80[a]	>32/NA	2/99	>4/78
E. coli (190)	2/90[a]	≤0.25/92	0.25/100	>4/69
KSP (93)	>16/85[a]	32/86	1/94	>4/88
ESP (94)	>16/80[a]	32/79	1/100	≤0.5/99
PSA (118)	>16/3[a]	>32/2	>8/86	>4/73

a. % inhibited at ≤2 μg/mL for CPT.
NA = not applicable, βHS = beta-haemolytic streptococci, EF = *E. faecalis*; KSP = *Klebsiella* spp., ESP = *Enterobacter* spp., PSA = *P. aeruginosa*

Conclusions: CPT was highly active against Gram-positive and ENT pathogens recently isolated from cSSSI in USA medical centers, including MRSA. CPT spectrum against Gram-positive pathogens was similar to those of LZD and vancomycin; while against Gram-negative organisms CPT showed spectrum comparable to CRO. Ceftaroline fosamil appears to be a promising agent for the treatment of cSSSI, including those caused by MRSA.

Introduction

Ceftaroline, the active form of the prodrug ceftaroline fosamil, is a broad-spectrum cephalosporin that has bactericidal activity against resistant Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, and commonly occurring Gram-negative pathogens. Ceftaroline fosamil is currently in late-stage development for the treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia.

S. aureus and *Streptococcus pyogenes* are considered the most important pathogens associated with cSSSI. Ceftaroline has demonstrated excellent in vitro activity against both of these species as well as against coagulase-negative staphylococci (CoNS), enterococci, and viridans group streptococci, which are occasionally associated with cSSSI. Ceftaroline provides additional in vitro activity against these Gram-positive pathogens and commonly isolated Enterobacteriaceae species, excluding those that produce extended-spectrum β-lactamase (ESBL).

The objective of this study was to evaluate the spectrum of antimicrobial activity of ceftaroline and several comparator agents when tested against clinical isolates recovered from cSSSI collected in medical institutions throughout the USA.

Methods

Clinically significant, nonduplicate isolates were consecutively collected from hospitalized patients with cSSSI from USA medical centers in 2008-2009. There were 25 participating medical centers that contributed isolates for testing and analysis. Each site submitted approximately 50 strains each year and the most frequently isolated organisms were analyzed. A total of 2054 isolates were received. The most prevalent pathogens included: *S. aureus* (1227 strains; 53.5% MRSA), *Escherichia coli* (190), *Pseudomonas aeruginosa* (118), *Enterococcus faecalis* (99), *Enterobacter* spp. (94), *Klebsiella* spp. (93), and β-haemolytic streptococci (72).

Broth microdilution methods used according to the Clinical and Laboratory Standards Institute (CLSI) documents were performed to determine antimicrobial susceptibility against ceftaroline and up to 20 comparison agents. Validated MIC panels were manufactured by TREK Diagnostics (Cleveland, Ohio, USA). *S. aureus, E. faecalis*, and Gram-negative strains were tested in Mueller-Hinton (MH) broth and *Streptococcus* spp. were tested in MH broth supplemented with 3-5% lysed horse blood (M07-A8, 2009).

Concurrent quality control (QC) testing was performed to determine proper test conditions and procedures. QC strains included: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *S. pneumoniae* ATCC 49619. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S20) and susceptibility breakpoints were used to determine susceptibility/resistance percentages; however, no criteria for ceftaroline susceptibility have been established.

Results

- *S. aureus* was the most frequently recovered cSSSI pathogen (59.7%) from the consecutively collected isolates within monitored USA medical centers, and 53.5% of the *S. aureus* were MRSA. The next most common pathogens were *E. coli* (9.3%), *P. aeruginosa* (5.7%), *E. faecalis* (4.8%), *Enterobacter* spp. (4.6%), *Klebsiella* spp. (4.5%), and β-haemolytic streptococci (3.5%; Table 1)
- Methicillin-susceptible *S. aureus* (MSSA) isolates had slightly lower ceftaroline MIC values ($MIC_{50/90}$, 0.25/0.5 μg/mL) compared with MRSA isolates ($MIC_{50/90}$, 1/1 μg/mL; Tables 1 and 2). Against MSSA and MRSA, the highest MIC results observed were 0.5 and 2 μg/mL, respectively
- The most active agents tested against MRSA isolates were: ceftaroline (MIC_{90}, 1 μg/mL; 100% inhibited at ≤2 μg/mL), linezolid (MIC_{90}, 2 μg/mL; 100% susceptible [S]), vancomycin (MIC_{90}, 1 μg/mL; 100% S), daptomycin (MIC_{90}, 0.5 μg/mL; 100% S), and tigecycline (MIC_{90}, 0.25 μg/mL; 100% S). In contrast, the highest resistance rate was observed for erythromycin (91.5%), followed by levofloxacin (55.0%) and clindamycin (19.7%; Table 2)
- Ceftaroline was 8-fold more active than ceftriaxone against MSSA based on MIC_{50} (Table 2); 100.0% of MSSA were inhibited at ≤0.5 μg/mL of ceftaroline (Table 1)
- Elevated MIC values were observed for ceftaroline ($MIC_{50/90}$, 2/4 μg/mL) against *E. faecalis* isolates compared with other Gram-positive species tested
- Ceftaroline demonstrated excellent activity against the β-haemolytic streptococci (MIC_{90}, 0.015 μg/mL) and viridans group streptococci (MIC_{90}, 0.12 μg/mL; Tables 1 and 2). Penicillin (MIC_{90}, 0.06 μg/mL) was 4-fold less active than ceftaroline against the β-haemolytic streptococci
- Ceftaroline and ceftriaxone exhibited similar in vitro activities when tested against *E. coli*, *Enterobacter* spp., and *Klebsiella* spp. Isolates susceptible to ceftriaxone generally had low ceftaroline MICs. The lowest susceptibility was observed for levofloxacin among *E. coli* (69.5%) and for cefuroxime among *Enterobacter* spp. (53.2%; Table 3)
- Against *P. aeruginosa* isolates, ceftaroline and other β-lactam agents generally showed elevated MIC values (MIC_{50}, >16 μg/mL; Table 3)

Table 1. Frequency of Occurrence of Ceftaroline MIC Values for Bacterial Strains Collected from cSSSI in the USA

Organism (no. tested)	No. of strains (cumulative %) inhibited at ceftaroline MIC (μg/mL)											
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
S. aureus												
All strains (1227)	-	-	-	2 (0.2)	37 (3.2)	476 (42.0)	326 (68.5)	371 (98.8)	15 (100.0)	-		
MSSA (571)	-	-	-	2 (0.4)	37 (6.8)	467 (88.6)	65 (100.0)	-	-	-		
MRSA (656)	-	-	-	-	-	9 (1.4)	261 (41.2)	371 (97.7)	15 (100.0)	-		
E. faecalis (99)	-	-	-	-	-	-	1 (1.0)	32 (33.3)	46 (79.8)	16 (96.0)	3 (99.0)	1 (100.0)
βHS (72)[a]	54 (75.0)	15 (95.8)	3 (100.0)	-	-	-	-	-	-	-	-	-
VGS (10)[a]	1 (10.0)	0 (10.0)	7 (80.0)	0 (80.0)	1 (90.0)	1 (100.0)	-	-	-	-		
E. coli (190)	-	-	19 (10.0)	62 (32.6)	43 (65.3)	31 (81.6)	7 (85.3)	5 (87.9)	4 (90.0)	2 (91.1)	1 (91.6)	16 (100.0)
Enterobacter spp. (94)			2 (2.1)	8 (10.6)	19 (30.9)	25 (57.5)	15 (73.4)	5 (78.7)	1 (79.8)	1 (80.9)	1 (81.9)	17 (100.0)
Klebsiella spp. (93)	1 (1.1)	2 (3.2)	2 (5.4)	19 (25.8)	31 (59.1)	16 (76.3)	6 (82.8)	2 (85.0)	0 (85.0)	1 (86.0)	1 (87.1)	12 (100.0)
P. aeruginosa (118)	-	-	-	-	-	1 (0.9)	0 (0.9)	0 (0.9)	3 (3.4)	4 (6.8)	13 (17.8)	97 (100.0)

βHS = β-haemolytic streptococci; cSSSI = complicated skin and skin structure infection; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; VGS = viridans group streptococci

Table 2. Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Gram-positive cSSSI Bacterial Isolates from 2008-2009

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% Susceptible/ % Resistant[a]
S. aureus (1227)				
Ceftaroline	0.5	1	0.06 – 2	- / -[b]
Oxacillin	>2	>2	≤0.25 – >2	46.5 / 53.5
Erythromycin	>2	>2	≤0.25 – >2	33.7 / 65.9
Clindamycin	≤0.25	>2	≤0.25 – >2	87.2 / 12.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	66.1 / 33.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	99.2 / 0.8
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -
Methicillin-susceptible *S. aureus* (MSSA; 571)				
Ceftaroline	0.25	0.5	0.06 – 0.5	- / -
Ceftriaxone	4	4	0.5 – 16	99.5 / 0.0
Cefepime	2	4	0.5 – 8	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0
Erythromycin	0.5	>2	≤0.25 – >2	63.0 / 36.6
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.3 / 4.6
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	91.1 / 8.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.9 / 1.1
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -
Methicillin-resistant *S. aureus* (MRSA; 656)				
Ceftaroline	1	1	0.25 – 2	- / -
Erythromycin	>2	>2	≤0.25 – >2	8.1 / 91.5
Clindamycin	≤0.25	>2	≤0.25 – >2	80.2 / 19.7
Levofloxacin	4	>4	≤0.5 – >4	44.4 / 55.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	99.4 / 0.6
Linezolid	2	2	0.5 – 2	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0
Daptomycin	0.5	0.5	0.12 – 1	100.0 / -
Tigecycline[c]	0.12	0.25	0.06 – 0.5	100.0 / -
E. faecalis (99)				
Ceftaroline	2	4	0.5 – 16	- / -
Ampicillin	≤1	2	≤1 – 8	100.0 / 0.0
Imipenem	2	2	0.25 – 4	99.0 / -
Piperacillin/tazobactam	4	8	2 – 32	99.0 / -
Erythromycin	>2	>2	≤0.25 – >2	13.1 / 54.5
Levofloxacin	1	>4	≤0.5 – >4	77.8 / 22.2
Linezolid	2	2	0.5 – 2	100.0 / 0.0
Vancomycin	1	2	1 – >16	97.0 / 3.0
Daptomycin	1	2	0.5 – 8	99.0 / -
Tigecycline[c]	0.12	0.25	≤0.03 – 0.25	100.0 / -
βHS (72)[d]				
Ceftaroline	≤0.008	0.015	≤0.008 – 0.03	- / -
Penicillin	≤0.015	0.06	≤0.015 – 0.06	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -
Imipenem	≤0.12	≤0.12	≤0.12	100.0 / -
Erythromycin	≤0.25	>2	≤0.25 – >2	83.3 / 13.9
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.7 / 8.3
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0
Linezolid	1	1	0.12 – 1	100.0 / -
Vancomycin	0.25	0.5	0.25 – 1	100.0 / -
Daptomycin	≤0.06	0.25	≤0.06 – 0.5	100.0 / -
Tigecycline[c]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -
VGS (10)[d]				
Ceftaroline	0.03	0.12	≤0.008 – 0.25	- / -
Penicillin	0.06	0.12	0.03 – 2	90.0 / 0.0
Ceftriaxone	≤0.25	0.5	≤0.25 – 2	90.0 / 0.0
Cefepime	0.5	1	≤0.12 – 4	90.0 / 10.0
Erythromycin	≤0.25	>2	≤0.25 – >2	60.0 / 30.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.0 / 10.0
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -
Vancomycin	0.5	0.5	0.5	100.0 / -
Daptomycin	0.25	1	≤0.06 – 1	100.0 / -
Tigecycline[c]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -

a. According to CLSI breakpoints [CLSI, 2010].
b. - = No breakpoint has been established by CLSI or US FDA.
c. US FDA breakpoints were applied [Tygacil Product Insert, 2005].
d. βHS = β-haemolytic streptococci; CLSI = Clinical and Laboratory Standards Institute; cSSSI = complicated skin and skin structure infection; FDA = Food and Drug Administration; VGS = viridans group streptococci.

Table 3. Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Gram-negative cSSSI Bacterial Isolates from 2008-2009

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% Susceptible/ % Resistant[a]
E. coli (190)				
Ceftaroline	0.12	2	0.03 – >16	- / -[b]
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >32	92.1 / 7.9
Ceftazidime	≤1	≤1	≤1 – >16	94.2 / 5.3
Cefepime	≤0.12	0.25	≤0.12 – >16	94.7 / 4.7
Cefuroxime	4	16	≤2 – >16	83.2 / 10.0
Imipenem	0.25	0.25	≤0.12 – 2	100.0 / 0.0
Ertapenem	≤0.06	≤0.06	≤0.06 – 2	100.0 / 0.0
Piperacillin/tazobactam	2	16	≤0.5 – >64	90.5 / 5.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	69.5 / 30.5
Amikacin	2	4	0.5 – 32	99.5 / 0.0
Tigecycline[c]	0.12	0.25	0.06 – 1	100.0 / 0.0
Enterobacter spp. (94)				
Ceftaroline	0.25	>16	0.03 – >16	- / -
Ceftriaxone	≤0.25	32	≤0.25 – >32	78.7 / 19.1
Ceftazidime	≤1	>16	≤1 – >16	83.0 / 16.0
Cefepime	≤0.12	1	≤0.12 – >16	96.8 / 2.1
Cefuroxime	8	>16	≤2 – >16	53.2 / 33.0
Imipenem	0.5	1	0.25 – 2	100.0 / 0.0
Ertapenem	≤0.06	0.25	≤0.06 – 8	97.9 / 1.1
Piperacillin/tazobactam	2	32	1 – >64	86.2 / 5.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	98.9 / 1.1
Amikacin	1	2	0.5 – 8	100.0 / 0.0
Tigecycline[c]	0.25	0.5	0.12 – 4	98.9 / 0.0
Klebsiella spp. (93)				
Ceftaroline	0.12	>16	≤0.008 – >16	- / -
Ceftriaxone	≤0.25	32	≤0.25 – >32	86.0 / 14.0
Ceftazidime	≤1	>16	≤1 – >16	87.1 / 12.9
Cefepime	≤0.12	2	≤0.12 – >16	94.6 / 3.2
Cefuroxime	≤2	>16	≤2 – >16	82.8 / 12.9
Imipenem	0.25	1	≤0.12 – >8	93.5 / 3.2
Ertapenem	≤0.06	≤0.06	≤0.06 – >8	93.5 / 6.5
Piperacillin/tazobactam	2	>64	≤0.5 – >64	87.1 / 10.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	88.2 / 11.8
Amikacin	1	16	0.5 – >32	93.5 / 1.1
Tigecycline[c]	0.25	0.5	0.12 – 2	100.0 / 0.0
P. aeruginosa (118)				
Ceftaroline	>16	>16	0.25 – >16	- / -
Ceftazidime	32	>16	≤1 – >16	83.9 / 11.0
Cefepime	2	16	≤0.12 – >16	86.4 / 4.2
Imipenem	2	>8	≤0.12 – >8	85.6 / 11.9
Piperacillin/tazobactam	8	>64	≤0.5 – >64	88.1 / 11.9
Levofloxacin	≤0.5	>4	≤0.5 – >4	72.9 / 22.9
Amikacin	2	8	≤0.25 – >32	96.6 / 2.5
Tigecycline[c]	4	>4	0.12 – >4	- / -

a. According to CLSI breakpoints [CLSI, 2010].
b. - = No breakpoint has been established by CLSI or US FDA.
c. US FDA breakpoints were applied [Tygacil Product Insert, 2005].

Conclusions

- Ceftaroline was highly active against the most common cSSSI pathogens isolated in USA medical centers, including Gram-positive pathogens (such as MRSA) and non-ESBL-producing Enterobacteriaceae
- Ceftaroline activity against staphylococci that caused cSSSI was similar to that of vancomycin, daptomycin and inezolid; streptococcal activity was similar to that of ceftriaxone
- Based on the broad-spectrum coverage and excellent activity of ceftaroline, ceftaroline fosamil appears to be a promissing agent for the treatment of cSSSIs, including those caused by MRSA

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