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Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against Bacterial Organisms Causing Bacteremia in Patients With Skin and Skin Structure Infections in United States Medical Centers (2008-2014)

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Abstract

Background: Ceftaroline (CPT), the active metabolite of the prodrug CPT fosamil, is a cephalosporin with potent in vitro activity against methicillin-resistant *S. aureus* (MRSA). CPT fosamil was approved by the USA-FDA in 2010 for treatment of acute bacterial SSSI, including those caused by MRSA, and of community-acquired bacterial pneumonia.

Methods: Among 16,413 organisms consecutively collected from patients with bacteremia in the AWARE CPT surveillance program (2008-2014), 1,380 (8.4%) were from cases where SSSI was reported as the primary site of infection. These organisms were collected in 24 medical centers in the USA and tested for susceptibility (S) against CPT and comparators by the broth microdilution method.

Results: The most common organisms isolated from bacteremia associated with SSSI were *S. aureus* (670; 48.6%), *E. coli* (200; 14.5%), β-hemolytic streptococci (BHS; 138; 10.0%) and *K. pneumoniae* (KPN; 109; 7.9%). MIC_{90} and %S are summarized in the Table. Among *S. aureus*, 50.6% of isolates were MRSA, and CPT was very active against both methicillin-S *S. aureus* (MSSA; $MIC_{50/90}$, 0.25/0.25 μg/mL; highest MIC, 0.5 μg/mL; 100.0% S) and MRSA ($MIC_{50/90}$, 1/1 μg/mL; 95.9% S; highest MIC, 2 μg/mL). Against MSSA, CPT was 16-, 4- and 4- to 8-fold more active than ceftriaxone, vancomycin and linezolid, respectively. Among MSSA, S rates to clindamycin (CLI) and levofloxacin (LEV), were 94.9 and 87.6%, respectively. For MRSA, 95.9% and 100.0% of strains were inhibited at ≤1 and ≤2 μg/mL of CPT, respectively; all other β-lactams exhibited very limited activity against these organisms. 29.5 and 67.8% of MRSA were resistant to CLI and LEV, respectively. ESBL phenotype was observed among 13.0 and 10.1% of EC and KPN, respectively.

Conclusions: CPT and tigecycline provided the best in vitro overall coverage against organisms causing bacteremia in patients with SSSI.

Organism (no. tested)	MIC_{90} in μg/mL (%S)					
	Ceftaroline	Ceftriaxone	Meropenem	Levofloxacin	Tigecycline	Linezolid
S. aureus (670)	1 (97.9)	>8 (49.4)	8 (49.4)	>4 (59.0)	0.25 (100.0)	2 (99.9)
MSSA (331)	0.25 (100.0.0)	4 (100.0)	≤0.12 (100.0)	4 (87.6)	0.25(100.0)	2 (100.0)
MRSA (339)	1 (95.9)	>8 (0.0)	>8 (0.0)	>4 (31.0)	0.25 (100.0)	2 (99.7)
BHS (138)	≤0.015 (100.0)	≤0.25 (100.0)	≤0.12 (100.0)	1 (99.3)	0.06 (100.0)	1 (100.0)
E. coli (200)	16 (85.0)	>8 (89.0)	≤0.12 (100.0)	>4 (67.0)	0.25 (100.0)	--
KPN (109)	8 (86.2)	0.5 (90.8)	≤0.12 (99.1)	1 (90.8)	1 (100.0)	--
Other enterics (132)	1 (68.2)	8 (83.3)	≤0.12 (100.0)	≤0.5 (80.3)	1 (93.2)	--

Introduction

Bloodstream infections (BSIs) constitute one of the most severe forms of bacterial infection. Despite impressive achievements reached both in the field of microbiological diagnosis and antimicrobial therapy, bacteremia still accounts for significant morbidity and mortality. The etiology of BSI may vary significantly according to the type of patient and source of infection, and studies evaluating large series of BSI with nonselected types of patients or specific pathogens are scarce. It has been documented, however, that skin and skin structure infection represents an important source of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

Ceftaroline is a cephalosporin with anti-MRSA activity that was approved for clinical use in the United States (US; in 2010; Teflaro®) and Europe (in 2012; Zinforo®). The approval was based on two phase 3 randomized, double-blinded, clinical trials for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI), which demonstrated non-inferiority to comparator agents. Ceftaroline fosamil has not been evaluated in randomized clinical trials for the treatment of bloodstream infections, and it is not approved by the US-FDA or by the European Medicine Agency for this indication, however, ceftaroline fosamil use has been reported for patients with MRSA bacteremia and endocarditis, especially as salvage therapy generally in combination with other antimicrobials.

In the present study, we evaluated the frequency of occurrence and antimicrobial susceptibility of bacterial organisms causing BSI in patients with skin and skin structure infections (SSSI) in US medical centers.

Methods

Organism Collection: Bacterial isolates were collected as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program, which was designed to establish the baseline and track post-approval activity of ceftaroline and comparator agents in the US. Participant centers submit clinical bacterial organisms (one per infection episode) that are consecutively collected according to a common protocol, which established the number of isolates for each bacterial species/genus, the target infection types and the period of time the isolates should be collected. Among 16,413 organisms consecutively collected from patients with bacteremia, 1,380 (8.4%) were from cases where the primary site of infection was the skin or skin structure. These organisms were collected in 2008-2014 from 24 USA medical centers. Isolates were identified at the participant medical center and sent to the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, US) for reference susceptibility testing. Species identification was confirmed at the coordinator laboratory by MALDI-TOF using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, US), where necessary.

Susceptibility Testing: Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by CLSI M07-A10, and susceptibility interpretations were based on CLSI (M100-S25) and EUCAST breakpoint criteria. Validated MIC panels were manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). Streptococcal isolates were tested in Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood, whereas all other organisms were tested in cation-adjusted Mueller-Hinton broth (Thermo Fisher Scientific). Ceftaroline and comparator agents were tested simultaneously using the same bacterial inoculum and testing reagents. Concurrent testing of quality control (QC) strains assured proper test conditions.

Results

- The most common organisms isolated from patients with bacteremia associated with SSSI were *Staphylococcus aureus* (670; 48.6%), *Escherichia coli* (200; 14.5%), β-hemolytic streptococci (BHS; 138; 10.0%) and *Klebsiella pneumoniae* (109; 7.9%; Figure 1).
- Among *S. aureus*, 50.6% of isolates were methicillin-resistant (MRSA), and ceftaroline was very active against both methicillin-susceptible *S. aureus* (MSSA; $MIC_{50/90}$, 0.25/0.25 μg/mL; highest MIC, 0.5 μg/mL; 100.0% susceptible) and MRSA ($MIC_{50/90}$, 1/1 μg/mL; 95.9% susceptible; highest MIC, 2 μg/mL).
- Ceftaroline was 16-, 4- and 4- to 8-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 μg/mL), vancomycin ($MIC_{50/90}$, 1/1 μg/mL) and linezolid ($MIC_{50/90}$, 1/2 μg/mL), respectively, when tested against MSSA (data not shown). Among MSSA, susceptibility rates to clindamycin ($MIC_{50/90}$, ≤0.25/≤0.25 μg/mL), and levofloxacin ($MIC_{50/90}$, ≤0.5/4 μg/mL) were 94.9 and 87.6%, respectively (data not shown).
- Ceftaroline inhibited 95.9% and 100.0% of MRSA strains ≤1 and ≤2 μg/mL, respectively (Table 1). All other β-lactams exhibited very limited activity against these organisms, and resistant rates to clindamycin ($MIC_{50/90}$, ≤0.25/>2 μg/mL) and levofloxacin ($MIC_{50/90}$, 4/>4 μg/mL) were 29.5 and 67.8%, respectively (data not shown). All MRSA isolates were susceptible to vancomycin ($MIC_{50/90}$, 1/1 μg/mL) and tigecycline ($MIC_{50/90}$, 0.06/0.25 μg/mL); and 99.7% were susceptible to daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; data not shown).
- Ceftaroline was highly active against β-hemolytic streptococci ($MIC_{50/90}$, ≤0.015/≤0.015 μg/mL; 100.0% susceptible). The highest MIC value was 0.12 μg/mL and 99.3% of strains were inhibited at ≤0.03 μg/mL of ceftaroline (Table 1).
- *E. coli* was the second most commonly isolated organism and exhibited an ESBL phenotype rate of 13.0%. Susceptibility to ceftaroline (85.0%) was slightly lower than that of ceftriaxone (89.0%) and gentamicin (86.5%); whereas only 67.0% of strains were susceptible to levofloxacin (Table 2).
- Among *K. pneumoniae* (4th most common organism), 10.1% of isolates showed an ESBL phenotype, and susceptibility rates to ceftaroline, ceftriaxone and ceftazidime were 86.2, 90.8 and 92.7%, respectively (Table 2).
- Other Enterobacteriaceae species isolated included *Enterobacter* spp. (36 isolates; 2.6%), *Proteus mirabilis* (32 isolates; 2.3%), *Klebsiella oxytoca* (22 isolates; 1.6%), *Serratia marcescens* (22 isolates; 1.6%), indole-positive Proteae (11 isolates; 0.8%) and *Citrobacter* spp. (seven isolates; 0.5%; Tables 1 and 2).

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against causing bacteremia in patients with skin and skin structure infections in US hospitals.

Organism/ antimicrobial agent	MIC (μg/mL)		CLSI[a]			EUCAST[a]		
	50%	90%	%S	%I	%R	%S	%I	%R
Staphylococcus aureus (670)								
Ceftaroline	0.5	1	97.9	2.1	0.0	97.9	-	2.1
Ceftriaxone	8	>8	49.4	-	50.6	-	-	-
Oxacillin	>2	>2	49.4	-	50.6	49.4	-	50.6
Clindamycin	≤0.25	>2	82.4	0.1	17.5	82.1	0.3	17.6
Daptomycin	0.25	0.5	99.7	-	-	99.7	-	0.3
Erythromycin	>2	>2	48.0	3.9	48.2	39.6	0.3	60.1
Levofloxacin	≤0.5	>4	59.0	1.0	40.0	59.0	1.0	40.0
Linezolid	1	2	99.9	-	0.1	99.9	-	0.1
Tigecycline[b]	0.06	0.25	100.0	-	-	100.0	-	0.0
TMP/SMX[c]	≤0.5	≤0.5	98.5	-	1.5	98.8	0.0	1.2
Vancomycin	1	1	100.0	0.0	0.0	100.0	-	0.0
β-hemolytic streptococci (138)[d]								
Ceftaroline	≤0.015	≤0.015	100.0	-	-	100.0	-	0.0
Ceftriaxone	≤0.25	≤0.25	100.0	-	-	100.0	-	0.0
Penicillin	≤0.06	≤0.06	100.0	-	-	100.0	-	0.0
Clindamycin	≤0.25	>2	84.8	0.0	15.2	84.8	-	15.2
Daptomycin	≤0.06	0.25	100.0	-	-	100.0	-	0.0
Erythromycin	≤0.25	>2	71.0	2.2	26.8	71.0	2.2	26.8
Levofloxacin	≤0.5	1	99.3	0.0	0.7	95.7	3.6	0.7
Linezolid	1	1	100.0	-	-	100.0	0.0	0.0
Tetracycline[b]	>8	>8	44.9	2.2	52.9	34.7	0.8	64.4
Tigecycline	≤0.03	0.06	100.0	-	-	100.0	0.0	0.0
TMP/SMX[c]	≤0.5	≤0.5	-	-	-	97.1	0.7	2.2
Vancomycin	0.5	0.5	100.0	-	-	100.0	-	0.0
Escherichia coli (200)								
Ceftaroline	0.12	16	85.0	1.5	13.5	85.0	-	15.0
Ceftriaxone	≤0.25	8	89.0	0.5	10.5	89.0	0.5	10.5
Ceftazidime	≤1	2	93.0	0.5	6.5	89.5	3.5	7.0
Ampicillin/sulbactam	16	>16	45.5	27.0	27.5	45.5	-	54.5
Piperacillin/tazobactam	2	8	97.0	1.0	2.0	94.5	2.5	3.0
Meropenem	≤0.12	≤0.12	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	≤0.5	>4	67.0	1.0	32.0	67.0	0.0	33.0
Gentamicin	≤2	>8	86.5	0.5	13.0	85.0	1.5	13.5
Tigecycline[b]	0.12	0.25	100.0	0.0	0.0	100.0	0.0	0.0
Klebsiella pneumoniae (109)								
Ceftaroline	0.12	4	86.2	2.8	11.0	86.2	-	13.8
Ceftriaxone	≤0.25	0.5	90.8	0.0	9.2	90.8	0.0	9.2
Ceftazidime	≤1	2	92.7	0.0	7.3	89.9	2.8	7.3
Ampicillin/sulbactam	4	>16	78.0	6.4	15.6	78.0	-	22.0
Piperacillin/tazobactam	2	16	92.7	2.8	4.6	89.9	2.8	7.3
Meropenem	≤0.12	≤0.12	99.1	0.0	0.9	99.1	0.0	0.9
Levofloxacin	≤0.5	1	91.7	0.9	7.3	90.8	0.9	8.3
Gentamicin	≤2	≤2	97.2	0.0	2.8	96.3	0.9	2.8
Tigecycline[b]	0.25	1	100.0	0.0	0.0	91.7	8.3	0.0
Other enterics (132)[e]								
Ceftaroline	0.25	>16	68.2	13.6	18.2	68.2	-	31.8
Ceftriaxone	≤0.25	8	84.1	1.5	14.4	84.1	1.5	14.4
Ceftazidime	≤1	16	89.4	0.0	10.6	86.4	3.0	10.6
Ampicillin/sulbactam	16	>16	49.2	13.7	37.1	49.2	-	50.8
Piperacillin/tazobactam	2	32	89.4	6.1	4.5	87.1	2.3	10.6
Meropenem	≤0.12	≤0.12	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	≤0.5	4	87.5	2.4	10.1	83.3	4.5	12.2
Gentamicin	≤2	4	93.2	3.8	3.0	89.4	3.8	6.8
Tigecycline[b]	0.5	2	100.0	6.0	0.8	78.8	14.4	6.8

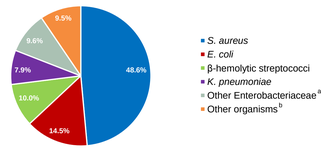
a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Breakpoints from US-FDA Package Insert.
c. TMP/SMX = Trimethoprim/sulfamethoxazole.
d. Include: *Streptococcus pyogenes* (49), *S. agalactiae* (57), Group C *Streptococcus* (8), Group G *Streptococcus* (17), *S. dysgalactiae* (7).
e. Includes: *Citrobacter braakii* (2), *C. freundii* (2), *C. koseri* (3), *Enterobacter aerogenes* (5), *E. cloacae* (30), *E. cancerogenus* (1), *Klebsiella oxytoca* (22), *Morganella morganii* (8), *Pantoea agglomerans* (1), *Proteus mirabilis* (32), *P. vulgaris* (2), *Providencia rettgeri* (1), *P. stuartii* (1), *Serratia marcescens* (22).

Table 1. Summary of ceftaroline activity tested against bacterial organisms causing bacteremia in patients with SSSI.

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline MIC in μg/mL of:											MIC (μg/mL)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	50%	90%
S. aureus (670)	--	--	--	25 (3.7)	289 (46.9)	175 (73.0)	167 (97.9)	14 (100.0)	--	--	--	--	0.5	1
MSSA (331)	--	--	--	25 (7.6)	283 (93.1)	23 (100.0)	--	--	--	--	--	--	0.25	0.25
MRSA (339)	--	--	--	--	6 (1.8)	152 (46.6)	167 (95.9)	14 (100.0)	--	--	--	--	1	1
β-hemolytic streptococci (138)	127 (92.0)	10 (99.3)	0 (99.3)	1 (100.0)	--	--	--	--	--	--	--	--	≤0.015	≤0.015
E. coli (200)	2 (1.0)	9 (5.5)	66 (38.5)	55 (66.0)	21 (76.5)	17 (85.0)	3 (86.5)	2 (87.5)	2 (88.5)	2 (89.5)	3 (91.0)	18 (100.0)	0.12	16
K. pneumoniae (109)	1 (0.9)	3 (3.7)	37 (37.6)	35 (69.7)	9 (78.0)	9 (86.2)	3 (89.0)	1 (89.9)	1 (90.8)	1 (91.7)	1 (92.7)	8 (100.0)	0.12	4
other Enterobacteriaceae (132)[a]	1 (0.8)	1 (1.5)	16 (13.6)	42 (45.5)	18 (59.1)	12 (68.2)	18 (81.8)	4 (84.8)	1 (85.6)	1 (86.4)	2 (87.9)	16 (100.0)	0.25	>16

a. Includes: *Citrobacter braakii* (2), *C. freundii* (2), *C. koseri* (3), *Enterobacter aerogenes* (5), *E. cloacae* (30), *E. cancerogenus* (1), *Klebsiella oxytoca* (22), *Morganella morganii* (8), *Pantoea agglomerans* (1), *Proteus mirabilis* (32), *P. vulgaris* (2), *Providencia rettgeri* (1), *P. stuartii* (1), *Serratia marcescens* (22).

Figure 1. Frequency of occurrence of organisms causing bacteremia in patients with skin and skin structure infections in United States hospitals.



a. Includes: *Citrobacter braakii* (2), *C. freundii* (2), *C. koseri* (3), *Enterobacter aerogenes* (5), *E. cloacae* (30), *E. cancerogenus* (1), *Klebsiella oxytoca* (22), *Morganella morganii* (8), *Pantoea agglomerans* (1), *Proteus mirabilis* (32), *P. vulgaris* (2), *Providencia rettgeri* (1), *P. stuartii* (1), *Serratia marcescens* (22).
b. Includes: *Acinetobacter* spp. (5), *Enterococcus* spp. (68), *Pseudomonas aeruginosa* (35) and viridans group streptococci (23).

Conclusions

- The results of this investigation demonstrated the potent in vitro activity of ceftaroline when tested against a large collection bacterial organisms causing bacteremia in patients with SSSI from US hospitals.
- Ceftaroline and tigecycline provided the best in vitro overall coverage across the collection of Gram-positive and negative organisms.

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