Antimicrobial Activity of Ceftaroline Tested Against *Staphylococcus aureus* From the United States and Europe, 2008-2009

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Amended Abstract

Objectives: To evaluate the potency and spectrum of ceftaroline against contemporary *S. aureus* strains and the correlation between SCC*mec* type and ceftaroline MICs. Ceftaroline is a novel, parenteral cephalosporin currently under review in the US for treatment of community-acquired pneumonia and complicated skin and skin structure infections. Ceftaroline exhibits broad-spectrum activity against Gram-negative and -positive organisms, including methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant *S. pneumoniae*.

Methods: A total of 8742 unique clinical *S. aureus* strains were consecutively collected in 2008-2009 from 29 hospitals located in Europe (EU; 3899 strains) and 27 in the USA (4843 strains). Strains were tested for susceptibility (S) to ceftaroline and numerous comparators by CLSI broth microdilution methods. Additionally, 100 strains for which SCC*mec* types had been previously characterized by PCR were tested for S to ceftaroline and selected beta-lactams.

Results: MRSA rates were 55.2% in the USA and 25.8% in EU, ranging from 0.8% in Sweden to 59.5% in Greece. Ceftaroline (MIC_{50}, 0.25 mg/L) was 16-fold more active than ceftriaxone (MIC_{50}, 4 mg/L) against methicillin-S *S. aureus* (MSSA) and showed potent activity against MRSA (MIC_{50}, 1 mg/L and MIC_{90}, 1-2 mg/L; see Table). All MRSA collected in 2009 were inhibited at ≤2 mg/L of ceftaroline, while in 2008, 4 clonally related strains from a Greek hospital exhibited MIC of 4 mg/L. In EU and the USA, 37.1% and 34.6% of MRSA strains were resistant (R) to clindamycin, and 85.9% and 65.9% were R to levofloxacin, respectively. In contrast, trimethoprim/sulfamethoxazole (98.4%-98.6% S), linezolid (100.0% S), and vancomycin (100.0% S) remained very active against MRSA. Ceftaroline MIC values were lowest among MRSA strains with SCC*mec* type IV, followed by those with SCC*mec* types II, III, and I.

Organism (no. of strains)	Cumulative % inhibited at ceftaroline MIC (mg/L) of:						
	≤0.06	0.12	0.25	0.5	1	2	4
MSSA							
(2895)	0.9	5.9	88.3	99.9	100.0	-	-
(2169)	0.7	4.5	88.4	99.9	100.0	-	-
MRSA							
(1004)	0.0	0.0	2.2	31.6	83.9	99.6	100.0[a]
(2674)	0.0	0.1	1.1	34.3	94.7	100.0	-

a. 4 strains ()

Conclusions: Ceftaroline was very active against a large collection of MSSA and MRSA strains recently (2008-2009) isolated in EU and USA hospitals. Based on its favourable antimicrobial profile, ceftaroline is a very promising anti-staphylococcal therapeutic option widely applicable to EU and the USA. MRSA isolates with SCC*mec* type IV, which are found in USA pandemic clone USA300 and several clones circulating in EU, exhibited the lowest ceftaroline MIC results.

Introduction

Ceftaroline is a novel, parenteral cephalosporin currently in late-stage clinical development for the treatment of community-acquired bacterial pneumonia (CABP) and complicated skin and skin structure infections (cSSSI). Encouraging results have been reported from Phase 2 and 3 clinical trials on the efficacy and safety profile of ceftaroline.

The bioactive compound ceftaroline is released upon in vivo hydrolysis of the phosphonate group from ceftaroline fosamil, the N-phosphonoamino water-soluble prodrug. Ceftaroline demonstrates broad-spectrum antimicrobial activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* (MDRSP), as well as common Gram-negative organisms.

The present study was conducted to evaluate the potency and spectrum of ceftaroline and comparator agents against contemporary (2008-2009) clinical *S. aureus* strains from Europe and the USA, including methicillin-susceptible *S. aureus* (MSSA), MRSA, and SCC*mec*-type characterized strains.

Materials and Methods

Bacterial Isolates

A total of 8742 unique and clinically significant *S. aureus* isolates were consecutively collected in 2008-2009 from 29 hospitals in 11 European countries, Turkey, and Israel (3899 strains; 25.8% MRSA), and 27 hospitals in the United States (4843 strains; 55.2% MRSA). In addition, a collection of 100 isolates of MRSA selected from various geographic regions (USA, Europe, and South America) and for which SCC*mec* types had been previously determined by PCR, were evaluated.

Susceptibility Testing

Broth microdilution methods were performed according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) to determine the antimicrobial susceptibility of each strain to ceftaroline and comparators. Commercially prepared MIC panels were produced by TREK Diagnostics (Cleveland, Ohio, USA) and all strains were tested in cation-adjusted Mueller-Hinton (MH) broth. Susceptibility and resistance percentage rates were based on CLSI M100-S19 and EUCAST breakpoints. Quality assurance was monitored with concurrent testing of ATCC quality control (QC) strains: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

Results

- Ceftaroline was very active against *S. aureus*, with >99.9% of strains inhibited at ≤2 mg/L (95.9% of European strains and 97.1% of US strains inhibited at ≤1 mg/L). The highest ceftaroline MIC value (4 mg/L) was observed in 4 clonally related *S. aureus* strains isolated from 1 medical center in Greece (Table 1)
- Against MSSA, ceftaroline MIC_{50} and MIC_{90} values were 0.25 mg/L and 0.5 mg/L, respectively. No difference was noted between European and USA MSSA strains (Tables 1 and 2)
- Ceftaroline was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 mg/L) against MSSA (Table 2). Activity of ceftaroline was greater than that of linezolid (MIC_{50} and MIC_{90}, 2 mg/L) or vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) and comparable to that of daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) against MSSA (Table 2)
- Among MSSA, rates of resistance to erythromycin (14.7% vs 34.9%), clindamycin (2.2% vs 6.4%), levofloxacin (5.5% vs 10.5%), and trimethoprim/sulfamethoxazole (0.6% vs 1.3%) were lower in Europe than in the USA
- The MRSA rate was significantly higher in the USA (55.2%) than in Europe (25.8%; Table 2). However, MRSA rates varied substantially among individual European nations, ranging from only 0.8% in Sweden to 59.5% in Greece (data not shown)
- Against MRSA strains, ceftaroline (MIC_{50}, 1 mg/L and MIC_{90}, 1 mg/L and 2 mg/L for USA and European isolates, respectively) was at least 64-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, >32 mg/L). Ceftaroline exhibited activity comparable to that of linezolid (MIC_{50} and MIC_{90}, 2 mg/L) and vancomycin (MIC_{50} and MIC_{90}, 1 mg/L). Ceftaroline was slightly less active than daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) (Table 2). Ceftaroline demonstrated greater activity against USA MRSA isolates than European MRSA isolates (94.7% of USA isolates and 83.9% of European isolates with MIC ≤1 mg/L; Table 1)
- Vancomycin, linezolid, and daptomycin provided complete coverage (100.0% susceptibility) against European MRSA strains, whereas low levels of linezolid (0.1%; 3 strains) and daptomycin (0.3%; 9 strains) nonsusceptibility were observed in USA MRSA strains (Table 2)
- Among MRSA, rates of resistance to comparator agents were comparable between European and USA strains, excepting erythromycin (66.1% vs 92.5%; lower in Europe) and levofloxacin (85.9% vs 69.5%; lower in the USA; Table 2)
- Ceftaroline MIC_{90} results were lowest for MRSA strains with SCC*mec* type IV elements (MIC_{50} and MIC_{90}, 1 mg/L), with an apparent trend towards increased MICs for type II (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L), type III (MIC_{50} and MIC_{90}, 2 mg/L), and type I (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L; Table 3)

Table 1. Frequency of Occurrence of Ceftaroline MIC Values for All *Staphylococcus aureus* Strains Tested

Organisms (no. tested)	No. (cumulative %) of isolates inhibited at ceftaroline MIC (mg/L):									
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4
Europe										
S. aureus (3899)	2 (0.1)	0 (0.1)	4 (0.2)	21 (0.7)	144 (4.4)	2407 (66.1)	632 (82.3)	527 (95.9)	158(99.9)	4 (100.0)
Oxacillin-susceptible (2895)	2 (0.1)	0 (0.1)	4 (0.2)	21 (0.9)	144 (5.9)	2385(88.3)	337 (99.9)	2 (100.0)	-	-
Oxacillin-resistant (1004)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (2.2)	295 (31.6)	525 (83.9)	158 (99.6)	4 (100.0)
United States										
S. aureus (4843)	1 (<0.1)	2 (0.1)	1 (0.1)	12 (0.3)	85 (2.1)	1845 (40.2)	1137 (63.7)	1618 (97.1)	142 (100.0)	-
Oxacillin-susceptible (2169)	1 (0.1)	2 (0.1)	1 (0.2)	12 (0.7)	82 (4.5)	1820 (88.4)	249(99.9)	2 (100.0)	-	-
Oxacillin-resistant (2674)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	25 (1.1)	888 (34.3)	1616 (94.7)	142 (100.0)	-

Table 2. Antimicrobial Activity of Ceftaroline and Comparator Agents When Tested Against Methicillin-susceptible and Methicillin-resistant *S. aureus* Strains From European and United States Medical Centers

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S/%R	EUCAST[a] %S/%R
Europe					
S. aureus (3899)					
Ceftaroline	0.25	1	≤0.008 – 4	-[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	74.2 / 25.8	74.2 / 25.8
Ceftriaxone	4	>32	≤0.25 – >32	74.2 / 25.8	74.2 / 25.8
Imipenem	≤0.12	4	≤0.12 – >8	74.2 / 25.8	74.2 / 25.8
Erythromycin	≤0.25	>2	≤0.25 – >2	70.7 / 28.0	71.7 / 28.0
Clindamycin	≤0.25	>2	≤0.25 – >2	88.7 / 11.0	88.0 / 11.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	73.2 / 26.2	73.2 / 26.2
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >2	99.2 / 0.8	99.2 / 0.8
Linezolid	2	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin-susceptible (2895)					
Ceftaroline	0.25	0.5	≤0.008 – 1	- / -	- / -
Ceftriaxone	4	4	≤0.25 – 32	99.8 / 0.0	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	83.9 / 14.7	84.9 / 14.7
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.7 / 2.2	97.2 / 2.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.0 / 5.5	94.0 / 5.5
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	99.4 / 0.6	99.4 / 0.6
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin-resistant (1004)					
Ceftaroline	1	2	0.25 – 4	- / -	- / -
Ceftriaxone	>32	>32	4 – >32	0.0 / 100.0	0.0 / 100.0
Imipenem	2	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	32.7 / 66.1	33.7 / 66.1
Clindamycin	≤0.25	>2	≤0.25 – >2	62.8 / 36.6	61.8 / 37.2
Levofloxacin	>4	>4	≤0.5 – >4	13.3 / 85.9	13.3 / 85.9
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.6 / 1.4	98.6 / 1.4
Linezolid	2	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S/%R	EUCAST[a] %S/%R
United States					
S. aureus (4843)					
Ceftaroline	0.5	1	≤0.008 – 2	- / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	44.8 / 55.2	44.8 / 55.2
Ceftriaxone	16	>32	≤0.25 – >32	44.8 / 55.2	44.8 / 55.2
Imipenem	≤0.12	8	≤0.12 – >8	44.8 / 55.2	44.8 / 55.2
Erythromycin	>2	>2	≤0.25 – >2	32.7 / 66.7	32.9 / 66.7
Clindamycin	≤0.25	>2	≤0.25 – >2	77.9 / 21.8	77.5 / 22.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	56.3 / 43.1	56.3 / 43.1
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5	98.5 / 1.5
Linezolid	2	2	≤0.06 – >8	99.9 / 0.0	99.9 / 0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 4	99.8 / -	99.8 / 0.2
Oxacillin-susceptible (2169)					
Ceftaroline	0.25	0.5	≤0.008 – 1	- / -	- / -
Ceftriaxone	4	4	0.5 – 32	99.4 / 0.0	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	64.4 / 34.9	64.7 / 34.9
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	93.3 / 6.4	93.0 / 6.7
Levofloxacin	≤0.5	4	≤0.5 – >4	89.0 / 10.5	89.0 / 10.5
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.7 / 1.3	98.7 / 1.3
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin-resistant (2674)					
Ceftaroline	1	1	0.12 – 2	- / -	- / -
Ceftriaxone	>32	>32	≤0.25 – >32	0.0 / 100.0	0.0 / 100.0
Imipenem	0.5	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	6.9 / 92.5	7.1 / 92.5
Clindamycin	≤0.25	>2	≤0.25 – >2	65.4 / 34.2	64.9 / 34.6
Levofloxacin	>4	>4	≤0.5 – >4	29.8 / 69.5	29.8 / 69.5
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.4 / 1.6	98.4 / 1.6
Linezolid	2	2	0.25 – >8	99.9 / 0.0	99.9 / 0.1
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 4	99.7 / -	99.7 / 0.3

a. Criteria as published by the CLSI [2009] and EUCAST [2009] for staphylococci. Only β-lactam susceptibility should be directed by the oxacillin test results
b. - = No breakpoint has been established by CLSI or EUCAST
c. TMP/SMX = Trimethoprim/sulfamethoxazole

Table 3. Ceftaroline MIC Distributions for 100 Methicillin-resistant *S. aureus* Strains Having Various Types of SCC*mec* Elements (I-IV and variants)

SCC*mec* type (no. tested)	Occurrences at MIC (mg/L):				MIC (mg/L):		
	0.5	1	2	4	50%	90%	Geometric mean
I (19)	-	1	16	2	2	4	2.07
II (20)	3	14	3	-	1	2	1.00
III (20)	2	7	11	-	2	2	1.37
IV (21)	9	12	-	-	1	1	0.74
IV variants (20)	11	9	-	-	0.5	1	0.68
All (100)	25	43	30	2	1	2	1.06

Conclusions

- Ceftaroline was very active against a large collection of MSSA and MRSA strains recently (2008-2009) isolated in European and USA medical centers (56 sites)
- Ceftaroline was 16-fold more active than ceftriaxone against MSSA and demonstrated strong activity against MRSA (MIC_{90}, 1-2 mg/L)
- MRSA isolates with SCC*mec* type IV, which is found in USA pandemic community-associated MRSA clone USA300 and several clones circulating in Europe, exhibited the lowest ceftaroline MICs
- The favorable antimicrobial profile of ceftaroline suggests its promise as an antistaphylococcal therapeutic option widely applicable to Europe and the USA patient populations

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