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Ceftaroline Activity Tested Against Organisms Causing Skin and Skin-Structure Infections (SSSI) Isolated in US and European Medical Centers in 2008

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Amended* Abstract

Background: Ceftaroline is the bioactive metabolite of ceftaroline fosamil, a N-phosphonoamino water-soluble cephalosporin prodrug. Ceftaroline is active against oxacillin-resistant *Staphylococcus aureus* (MRSA) and is under evaluation for treatment of SSSI in clinical trials. We assessed the activity of ceftaroline and comparator agents tested against SSSI pathogens.

Methods: Nonduplicate clinically significant strains of *S. aureus* (2791), *E. faecalis* (613), viridians group streptococci (VGS, 190), and β-hemolytic streptococci (βHS; 596) were consecutively collected from 49 medical centers in the USA and Europe (EU) and susceptibility tested by the CLSI broth microdilution methods (M7-A7; M100-S18) against ceftaroline and >20 antimicrobials currently available for SSSI treatment.

Results: 44.3% of *S. aureus* isolates were MRSA. Over 60% of *S. aureus* strains were from community origin and showed MRSA rate similar to health-care associated *S. aureus*. Ceftaroline was very active against oxacillin-susceptible *S. aureus* (MIC_{90}, 0.25 µg/mL) and MRSA (MIC_{90}, 1 µg/mL). Against oxacillin-susceptible *S. aureus*, ceftaroline was 16- and 4-fold more potent than ceftriaxone and vancomycin, respectively. 92.5% and 99.9% of oxacillin-susceptible *S. aureus* were inhibited at ≤0.25 and ≤0.5 µg/mL, respectively (highest ceftaroline MIC was 1 µg/mL). The percentages of MRSA inhibited at 1 and 2 µg/mL of ceftaroline were 95.3% and 100.0%, respectively. βHS (all strains inhibited at ≤0.06 µg/mL) and VGS (MIC_{90}, 0.06 µg/mL) were very susceptible to ceftaroline. More than 97% of *E. faecalis*, including all vancomycin-resistant isolates, were inhibited by ≤8 µg/mL of ceftaroline.

	MIC_{90} (µg/mL)/ % S					
Organism (no.)	**Ceftaroline**	**Ceftriaxone**	**Clindamycin**	**Levofloxacin**	**Co-trimoxazole**	**Vancomycin**
S. aureus						
Oxacillin-susc. (1554)	0.25/NA[a]	4/99.7	≤0.25/95.1	≤0.5/92.1	≤0.5/98.2	1/100.0
Oxacillin-res. (1237)	1/NA	>32/0.0	>2/68.1	>4/28.2	≤0.5/98.8	1/100.0
E. faecalis (613)	8/NA	>32/NA	>2/NA	>4/67.4	>2/NA	2/95.6
βHS (596)	0.015/NA[a]	≤0.25/100	≤0.25/90.3	1/99.3	≤0.5/NA	0.5/100.0
VGS (190)	0.06/NA[a]	0.5/93.7	≤0.25/91.6	2/92.6	2/NA	0.5/100.0

[a]NA = not assigned.

Conclusions: Ceftaroline showed high potency (MIC_{90} range, 0.015-1 µg/mL) and broad spectrum against the contemporary (2008) most common SSSI gram-positive pathogens, including MRSA and fluoroquinolones-resistant βHS, isolated in USA and EU medical centers. Based on these results, ceftaroline appears to be a promising agent for the treatment of organisms causing SSSI.

*Abstract was amended to update the number of strains tested.

Introduction

- Ceftaroline is a broad-spectrum cephalosporin in phase 3 development with activities that include resistant gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Streptococcus pneumoniae*, as well as many common gram-negative pathogens. Ceftaroline is currently in development for the treatment of complicated skin and skin structure infections (cSSSI). A successful phase 2 clinical trial of ceftaroline fosamil (formerly PPI–0903) for the treatment of patients with cSSSI was reported in 2007 (Talbot et al, 2007). Phase 3 trials (CANVAS 1 and 2) for cSSSI were recently completed. *S. aureus* and *Streptococcus pyogenes* are considered the most important pathogens associated with cSSSI. Ceftaroline demonstrates excellent in vitro activity against both of these species, including MRSA and penicillin-resistant streptococci (Sader et al, 2005). Enterococci and viridans group streptococci are also considered to be relevant pathogens associated with some types of cSSSI. Ceftaroline provides excellent in vitro activity against these gram-positive pathogens, including MDR strains
- The objective of this study was to generate susceptibility testing data for ceftaroline and ceftriaxone (as a class comparator agent), and the susceptibility profiles of several drug classes against *S. aureus* (including MRSA), *Enterococcus faecalis*, and β-hemolytic and viridans group streptococci. This multicenter study would establish the current susceptibility profiles of these important pathogens and determine the comparative activity of ceftaroline tested against nearly 5000 isolates collected from medical institutions geographically dispersed throughout the United States (USA) and Europe in 2008.

Materials and Methods

- The isolates tested in this study were collected from hospitalized patients in USA and European medical centers during early 2008. Twenty-seven medical centers in the USA and 22 sites from 12 European countries contributed isolates for analysis. A total of 4831 isolates, including *S. aureus* (2791 strains), coagulase-negative staphylococci (CoNS) (641 strains), *E. faecalis* (613 strains), β-hemolytic streptococci (596 strains), and viridans group streptococci (190 strains) were tested against ceftaroline and comparator agents. Nearly one third of the isolates in this collection were isolated from cSSSI, while the remaining strains were from other significant sources, including blood (45%) and respiratory tract cultures (7%)
- Broth microdilution methods that followed the Clinical and Laboratory Standards Institute (CLSI) documents were used to determine the antimicrobial susceptibility of each organism using validated panels manufactured by TREK Diagnostics (Cleveland, OH). *S. aureus* and *E. faecalis* were tested in Mueller-Hinton (MH) broth and *Streptococcus* spp. were tested in MH broth supplemented with 3% to 5% lysed horse blood (M7-A7, 2006). Concurrent testing of quality control (QC) isolates determined that proper test conditions and procedures were used. These strains included American Type Culture Collection (ATCC) strains, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S18, 2008).

Results

- Ceftaroline demonstrated excellent potency against MRSA isolates with all isolates inhibited by ≤2 µg/mL (minimum inhibitory concentration [MIC_{90}, 1 µg/mL). Methicillin-susceptible *S. aureus* (MSSA) isolates exhibited 4-fold lower ceftaroline MIC values (MIC_{90}, 0.25 µg/mL) compared with the MRSA strains (Table 1)
- Ceftaroline was at least 32-fold more active against MRSA isolates than ceftriaxone and 2-fold more active than linezolid (Table 2). Against MSSA, ceftaroline was 16-fold more potent than ceftriaxone
- Ceftaroline was the most active compound (MIC_{50}, 0.25 µg/mL and MIC_{90}, 1 µg/mL) tested against CoNS (74.7% oxacillin-resistant). Ceftaroline was 4-fold more active than linezolid (MIC_{50}, 1 µg/mL), 8-fold more active than vancomycin (MIC_{50}, 2 µg/mL), and 64-fold more active than ceftriaxone (MIC_{50}, 16 µg/mL) against this pathogen (Table 2)
- *E. faecalis* isolates had the highest ceftaroline MIC values compared with other cSSSI pathogens tested in this study, with MIC_{50} and MIC_{90} values of 2 and 8 µg/mL, respectively (Table 2)
- Ceftaroline had similar activity against vancomycin-resistant *E. faecalis* compared with vancomycin-susceptible strains (Table 2)
- β-hemolytic streptococci were highly susceptible to ceftaroline (MIC_{90}, 0.015 µg/mL). Ceftaroline was 4-fold more active than penicillin (MIC_{90}, 0.06 µg/mL) against this group of pathogens (Table 2)
- Ceftaroline had potent activity against viridans group streptococci, with a MIC_{90} value of 0.06 µg/mL (Table 2)
- Isolates of viridans group streptococci that were nonsusceptible to penicillin had higher ceftaroline MIC_{90} values of 0.5 µg/mL. Ceftaroline retained good activity against this group and was 16-fold more potent than ceftriaxone (Table 2).

Table 1. Activity of Ceftaroline Tested Against 4190 Bacterial Pathogens Associated With Skin and Skin-Structure Infections

	Cumulative % inhibited at MIC (µg/mL)											
Organism (no.)	**≤0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**≥ 16**
Staphylococcus aureus												
Oxacillin-susceptible (1554)	0.1	0.1	0.2	1.2	5.6	**92.5**[a]	99.9	100.0	-	-	-	-
Oxacillin-resistant (1237)	0.0	0.0	0.0	0.0	0.0	1.3	41.9	**95.3**	100.0	-	-	-
Coagulase-negative staphylococci (641)	0.3	0.5	3.6	17.3	27.3	52.4	85.5	**94.1**	98.6	100.0	-	-
Enterococcus faecalis (613)	0.0	0.0	0.0	0.0	0.3	0.8	2.6	29.2	71.3	85.2	**97.2**	100.0
β-hemolytic streptococci (596)	56.4	**92.3**	99.7	100.0	-	-	-	-	-	-	-	-
Viridans group streptococci (190)	21.1	45.3	85.3	**91.6**	92.6	94.7	99.0	100.0	-	-	-	-

[a]MIC_{90} values in bold.

Table 2. Activity of ceftaroline and comparator agents tested against *S. aureus, E. faecalis* and *Streptococcus* spp., including resistant phenotypes.

	MIC (µg/ml)				
Organism group/susceptibility subset (no. tested Antimicrobial agent	**50%**	**90%**	**Range**	**% susceptible[a]**	**% resistant**
S. aureus					
Oxacillin-susceptible (1,554)					
Ceftaroline	0.25	0.25	≤0.008-1	-	-
Ceftriaxone	4	4	1->32	99.7	0.0
Erythromycin	≤0.25	>2	≤0.25->2	73.1	26.1
Clindamycin	≤0.25	≤0.25	≤0.25->2	95.3	4.6
Levofloxacin	≤0.5	≤0.5	≤0.5->4	91.4	7.9
Gentamicin	≤2	≤2	≤2->8	99.2	0.8
Tetracycline	≤2	≤2	≤2->8	95.4	3.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	99.0	1.0
Linezolid	2	2	0.25-2	100.0	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Oxacillin-resistant (1,237)					
Ceftaroline	1	1	0.25-2	-	-
Ceftriaxone	32	>32	1->32	0.0	100.0
Erythromycin	>2	>2	≤0.25->2	12.4	87.1
Clindamycin	≤0.25	>2	≤0.25->2	68.6	31.4
Levofloxacin	>4	>4	≤0.5->4	27.6	71.8
Gentamicin	≤2	≤2	≤2->8	95.8	3.9
Tetracycline	≤2	≤2	≤2->8	93.6	5.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	99.2	0.8
Linezolid	2	2	0.25-2	100.0	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Coagulase-negative staphylococci (641)					
Ceftaroline	0.25	1	≤0.008-4	-	-
Ceftriaxone	16	>32	≤0.25->32	25.3	74.7
Oxacillin	>2	>2	≤0.25->2	25.3	74.7
Erythromycin	>2	>2	≤0.25->2	35.1	64.6
Clindamycin	≤0.25	>2	≤0.25->2	64.6	33.9
Levofloxacin	4	>4	≤0.5->4	43.4	54.9
Gentamicin	≤2	>8	≤2->8	64.4	28.7
Tetracycline	≤2	>8	≤2->8	87.4	12.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	61.3	38.7
Linezolid	1	1	0.12->8	99.2	-
Vancomycin	2	2	≤0.12-4	100.0	0.0
E. faecalis					
All isolates (613)					
Ceftaroline	2	8	0.12->16	-	-
Ceftriaxone	>32	>32	1->32	-	-
Ampicillin	≤1	2	≤1-8	100.0	0.0
Erythromycin	>2	>2	≤0.25->2	6.2	65.6
Levofloxacin	1	>4	≤0.5->4	67.4	32.5
Tetracycline	>8	>8	≤1->8	25.0	75.0
Gentamicin (HL)[c]	≤500	>1000	≤500->1000	71.1	28.9
Linezolid	1	2	0.25-2	100.0	0.0
Vancomycin	1	2	0.5->16	95.6	4.1
Vancomycin-resistant (25)					
Ceftaroline	4	8	0.5-8	-	-
Ceftriaxone	>32	>32	16->32	-	-
Ampicillin	≤1	2	≤1-2	100.0	0.0
Erythromycin	>2	>2	≤0.25->2	4.0	84.0
Levofloxacin	>4	>4	1->4	4.0	96.0
Tetracycline	>8	>8	≤2->8	16.0	84.0
Gentamicin (HL)[c]	>1000	>1000	≤500->1000	29.2	70.8
Linezolid	1	2	0.5-2	100.0	0.0
Teicoplanin	>16	>16	>16	24.0	76.0
β-hemolytic streptococci (596)					
Ceftaroline	≤0.008	0.015	≤0.008-0.06	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	-
Penicillin	≤0.015	0.06	≤0.015-0.12	100.0	-
Amoxicillin-clavulanate	≤1	≤1	≤1	100.0	-
Erythromycin	≤0.25	>2	≤0.25->2	78.9	20.5
Clindamycin	≤0.25	≤0.25	≤0.25->2	90.3	9.4
Levofloxacin	≤0.5	1	≤0.5->4	99.3	0.7
Tetracycline	≤2	>8	≤2->8	53.0	44.3
Linezolid	1	1	0.5-2	100.0	-
Vancomycin	0.5	0.5	0.25-1	100.0	-
Viridans group streptococci					
All isolates (190)					
Ceftaroline	0.03	0.06	≤0.008-1	-	-
Ceftriaxone	≤0.25	0.5	≤0.25-16	93.7	4.2
Penicillin	0.06	1	≤0.015-16	77.9	4.2
Amoxicillin-clavulanate	≤1	2	≤1-16	77.9	4.2
Erythromycin	≤0.25	>2	≤0.25->2	55.8	41.1
Clindamycin	≤0.25	≤0.25	≤0.25->2	91.6	8.4
Levofloxacin	1	2	≤0.5->4	92.6	6.3
Tetracycline	≤2	>8	≤2->8	72.6	22.1
Linezolid	1	1	0.25-2	100.0	-
Vancomycin	0.5	0.5	0.25-1	100.0	-
Penicillin-non-susceptible (42)					
Ceftaroline	0.03	0.5	≤0.008-1	-	-
Ceftriaxone	≤0.25	8	≤0.25-16	71.4	19.0
Penicillin	0.5	8	0.25-16	0.0	19.0
Amoxicillin-clavulanate	2	16	≤1-16	0.0	19.0
Erythromycin	2	>2	≤0.25->2	14.3	85.7
Clindamycin	≤0.25	≤0.25	≤0.25->2	90.5	9.5
Levofloxacin	1	1	≤0.5->4	90.5	9.5
Tetracycline	≤2	>8	≤2->8	71.4	23.8
Linezolid	0.5	1	0.5-1	100.0	-
Vancomycin	0.5	0.5	0.25-0.5	100.0	-

a. Susceptibility criteria of the CLSI (M100-S18, 2008) were used where available.
b. - = no breakpoint criteria have been recommended by the CLSI.
c. HL = High level.

Conclusions

- Ceftaroline showed high activity (MIC range, 0.015-1 µg/mL) against many common gram-positive cSSSI pathogens, including MRSA
- Ceftaroline activity was noted to be ≥8-fold that of ceftriaxone against the common gram-positive pathogens associated with cSSSI
- All MRSA isolates were inhibited by ≤2 µg/mL of ceftaroline
- The potent activities of ceftaroline demonstrated here against a large collection of recent gram-positive skin infection isolates, including MRSA and drug-resistant β-hemolytic streptococci, support the continued development of ceftaroline for treatment of cSSSI.

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