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Antimicrobial Activity of Ceftaroline Tested Against Staphylococci with Reduced Susceptibility to Linezolid, Daptomycin or Vancomycin from USA Hospitals (2008–2011)

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Amended Abstract

Background: Ceftaroline fosamil is a USA-FDA approved parenteral cephalosporin, and the active metabolite ceftaroline has potent *in vitro* activity against staphylococci, including methicillin-resistant (MR) strains. Vancomycin (VAN), linezolid (LZD) and daptomycin (DAP) remain very active against staphylococci, but isolates with decreased susceptibility (S) to these drugs are isolated sporadically.

Methods: 19,350 *S. aureus* (SA; 51% MRSA) and 3,270 coagulase-negative staphylococci (CoNS) were collected consecutively from 82 USA medical centers in 2008-2011 and tested for susceptibility against ceftaroline and comparator agents by CLSI broth microdilution methods. Among SA, 14 (0.07%), 18 (0.09%) and 369 (1.9%) exhibited decreased susceptibility to LZD (LZD-R; MIC, ≥8 µg/mL), DAP (DAP-NS; MIC, ≥2 µg/mL) and VAN (MIC, ≥2 µg/mL; 368 at 2 and 1 at 4 µg/mL), respectively. Among CoNS, 51 (1.6%) were LZD-R and 4 (0.12%) were DAP-NS.

Results: Ceftaroline was very active against SA overall ($MIC_{50/90}$, 0.5/1 µg/mL; 98.5% susceptible by USA-FDA breakpoint), including MRSA (9,875 strains tested; $MIC_{50/90}$, 0.5/1 µg/mL; 97.2% susceptible). All DAP-NS and 85.7% of LZD-R SA were susceptible to ceftaroline (Table 1). Against SA with VAN MIC of ≥2 µg/mL, 91.9, 96.1 and 98.9% were susceptible to ceftaroline, DAP and LZD respectively; ceftaroline and DAP ($MIC_{50/90}$, 0.5/1 µg/mL for both) were 2-fold more active than LZD ($MIC_{50/90}$, 1/2 µg/mL). CoNS strains were very susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/mL; 99.1% inhibited at ≤1 µg/mL), including MR (2,268 strains tested; $MIC_{50/90}$, 0.25/0.5 µg/mL), LZD-R ($MIC_{50/90}$, 0.25/0.5 µg/mL) and DAP-NS (MIC range, 0.03-0.12 µg/mL) strains (see Table 1).

Conclusions: Ceftaroline exhibited excellent activity *in vitro* against a large contemporary collection of SA and CoNS from USA hospitals, including MRSA and MRCoNS. Ceftaroline also retained significant activity against staphylococci with reduced susceptibility to LZD, DAP or VAN, and could potentially represent a valuable treatment option for infections caused by multidrug-resistant staphylococci.

Introduction

Staphylococcus aureus represents a major cause of both community-acquired and healthcare-associated infections. *S. aureus* is associated with a wide range of infections, including skin and skin structure infections, pneumonia, bacteremia, endocarditis, osteomyelitis, prosthetic joint infections, and catheter-related infections. The prevalence of nosocomial infections caused by methicillin-resistant *S. aureus* (MRSA) has increased substantially in the United States (USA) in the last decade. Furthermore, since its appearance in the 1990s, community-acquired MRSA (CA-MRSA) strains have increasingly caused community-onset infections as well as hospital and healthcare-associated disease in various USA regions.

Prompt and appropriate antibacterial therapy plays an important role in the management of MRSA infections. Vancomycin has been used for treatment of MRSA infections for more than 50 years, and although susceptibility rates remain high (>99%) in the USA and worldwide, there have been increasing reports of treatment failure in the last few years, which appears to be related to increased vancomycin MIC within the susceptibility range (2 µg/mL). Linezolid and daptomycin have been increasingly used in the last decade. Although reported only sporadically, resistance to these compounds is still uncommon among *S. aureus* isolated in USA hospitals.

Ceftaroline fosamil is approved by the USA Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). The European Medicines Agency (EMA) has approved ceftaroline fosamil for the treatment of complicated skin and soft tissue infections (cSSTI) or community-acquired pneumonia (CAP). The active metabolite, ceftaroline, is a new cephalosporin with potent bactericidal activity against resistant Gram-positive organisms, including MRSA and common Gram-negative organisms. We report here the activity of ceftaroline tested against a large collection of staphylococci, including strains with reduced susceptibility to vancomycin, linezolid or daptomycin.

Methods

Organisms collection: A total of 19,350 *S. aureus* (51.0% MRSA) and 3,270 coagulase-negative staphylococci (CoNS) were collected from 82 USA medical centers in 2008-2011. Organisms were consecutively collected from clinical infections and target numbers of strains for each of the requested bacterial species/genus were predetermined in the study protocol. Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance. Among *S. aureus*, 14 (0.07%), 18 (0.09%) and 369 (1.9%) strains exhibited decreased susceptibility to linezolid (MIC, ≥8 µg/mL), daptomycin (MIC, ≥2 µg/mL) and vancomycin (MIC, ≥2 µg/mL; 368 at 2 and 1 at 4 µg/mL) respectively. Among CoNS, 51 (1.6%) strains were linezolid-resistant and 4 (0.12%) were daptomycin-non-susceptible.

Susceptibility testing: Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) and CLSI interpretations were based on M100-S22 (2012) breakpoints, while ceftaroline interpretations were based on the breakpoint criteria established by the USA-FDA. *S. aureus* isolates were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains assured proper test conditions.

Results

- Ceftaroline was very active against *S. aureus* overall ($MIC_{50/90}$, 0.5/1 µg/mL; 98.5% susceptible), including MRSA (9,875 strains tested; $MIC_{50/90}$, 0.5/1 µg/mL; 97.2% susceptible; Tables 1 and 2)
- Overall, 51.0% of *S. aureus* strains were resistant to oxacillin (MRSA), and MRSA strains exhibited low susceptibility to erythromycin (8.9%), levofloxacin (29.5%) and clindamycin (67.9%; Table 2)
- Ceftaroline was very active against daptomycin-non-susceptible ($MIC_{50/90}$, 0.5/1 µg/mL and 100.0% susceptible) and linezolid-resistant ($MIC_{50/90}$, 1/2 µg/mL and 85.7% susceptible) strains of *S. aureus* (Tables 1 and 2)
- Against *S. aureus* strains with vancomycin MIC values of ≥2 µg/mL, 91.9, 96.2 and 98.9% were susceptible to ceftaroline, daptomycin and linezolid, respectively. Ceftaroline and daptomycin ($MIC_{50/90}$, 0.5/1 µg/mL for both) were 2-fold more active than linezolid ($MIC_{50/90}$, 1/2 µg/mL; Table 2)
- CoNS strains were very susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/mL; 99.1% inhibited at ≤1 µg/mL), including methicillin-resistant strains (2,268 strains tested; $MIC_{50/90}$, 0.25/0.5 µg/mL; Tables 1 and 3)
- 69.4% of CoNS strains were resistant to oxacillin. Resistance rates were also elevated for erythromycin (63.5%), levofloxacin (50.5%), trimethoprim/sulfamethoxazole (38.2%) and clindamycin (29.3%; Table 3)
- Linezolid-resistant ($MIC_{50/90}$, 0.5/0.5 µg/mL and 96.1% inhibited at ≤1 µg/mL) and daptomycin-non-susceptible (MIC range, 0.03-0.12 µg/mL) strains of CoNS were very susceptible to ceftaroline (Tables 1 and 3).

Table 1. Summary of Ceftaroline Tested Against *S. aureus* and CoNS from USA Hospitals (2008–2011), Including Strains with Reduced Susceptibility to Linezolid, Daptomycin or Vancomycin

	no. of strains (cumulative %) inhibited at ceftaroline MIC (µg/mL) of:					
Organism (no. tested)	≤0.06	0.12	0.25	0.5	1	2
S. aureus						
All strains (19,350)	63 (0.3)	1,027 (5.6)	8,122 (47.6)	5,853 (77.8)	4,004 (98.5)	281 (100.0)
MSSA (9,475)	61 (0.6)	1,020 (11.4)	7,928 (95.1)	460 (99.9)	6 (100.0)	-
MRSA (9,875)	2 (0.2)	7 (0.9)	194 (2.1)	5,393 (56.7)	3,998 (97.1)	281 (100.0)
Linezolid-resistant (14)	-	-	1 (7.1)	5 (42.9)	6 (85.7)	2 (100.0)
Daptomycin-non-susceptible (18)	1 (5.6)	0 (5.6)	2 (16.7)	7 (55.6)	8 (100.0)	-
Vancomycin MIC of ≥2 µg/mL (369)	5 (1.4)	10 (4.1)	89 (28.2)	92 (53.1)	143 (91.9)	30 (100.0)
CoNS						
All strains (3,270)	689 (21.1)	467 (35.3)	1,086 (68.5)	882 (95.5)	118 (99.1)	28 (100.0)
Methicillin-susceptible (1,002)	631 (63.0)	293 (92.2)	74 (99.6)	2 (99.8)	2 (100.0)	-
Methicillin-resistant (2,268)	58 (2.6)	174 (10.2)	1,012 (54.8)	880 (93.6)	116 (98.7)	28 (100.0)
Linezolid-resistant (51)	1 (2.0)	3 (7.8)	7 (21.6)	37 (94.1)	1 (96.1)	2 (100.0)
Daptomycin-non-susceptible (4)	2 (50.0)	2 (100.0)	-	-	-	-

Table 2. Activity of Ceftaroline and Comparator Antimicrobial Agents when Tested Against 19,350 *Staphylococcus aureus* (USA)

Antimicrobial agent (no. tested)	MIC (µg/mL)		%S / %R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
Staphylococcus aureus (19,350)				
Ceftaroline[b]	0.5	1	98.5 / -	- / -
Ceftriaxone	8	>8	49.0 / 51.0	49.0 / 51.0
Oxacillin	>2	>2	49.0 / 51.0	49.0 / 51.0
Erythromycin	>2	>2	36.6 / 61.8	36.8 / 62.6
Clindamycin	≤0.25	>2	80.9 / 18.9	80.5 / 19.1
Levofloxacin	≤0.5	>4	58.4 / 40.1	58.4 / 40.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.4 / 1.6	98.4 / 1.5
Tetracycline	≤2	≤2	95.5 / 3.9	93.9 / 5.1
Tigecycline[c]	0.06	0.25	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	99.9 / 0.1	99.9 / 0.1
Vancomycin	1	1	>99.9 / 0.0	>99.9 / <0.1
Daptomycin	0.25	0.5	99.9 / -	99.9 / 0.1
MSSA (9,475)				
Ceftaroline[b]	0.25	0.25	100.0 / -	- / -
Ceftriaxone	4	4	99.8 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	65.5 / 32.2	65.8 / 33.3
Clindamycin	≤0.25	≤0.25	94.4 / 5.4	94.0 / 5.6
Levofloxacin	≤0.5	4	88.5 / 10.7	88.5 / 10.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.9 / 1.1	98.9 / 1.0
Tetracycline	≤2	≤2	96.1 / 3.3	95.2 / 4.6
Tigecycline[c]	0.06	0.25	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	>99.9 / -	>99.9 / <0.1
MRSA (9,875)				
Ceftaroline[b]	0.5	1	97.2 / -	- / -
Erythromycin	>2	>2	8.9 / 90.2	9.0 / 90.6
Clindamycin	≤0.25	>2	67.9 / 31.8	67.5 / 32.1
Levofloxacin	4	>4	29.5 / 68.4	29.5 / 68.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.0 / 2.0	98.0 / 1.9
Tetracycline	≤2	≤2	95.0 / 4.6	92.7 / 5.6
Tigecycline[c]	0.12	0.25	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	99.9 / 0.1	99.9 / 0.1
Vancomycin	1	1	>99.9 / 0.0	>99.9 / <0.1
Daptomycin	0.25	0.5	99.8 / -	99.8 / 0.2
Linezolid-resistant (MIC, ≥8 µg/mL; 14)				
Ceftaroline[b]	1	2	85.7 / -	- / -
Oxacillin	>2	>2	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	0.0 / 100.0	0.0 / 100.0
Clindamycin	>2	>2	21.4 / 71.4	14.3 / 78.6
Levofloxacin	>4	>4	14.3 / 85.7	14.3 / 85.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	92.9 / 7.1	92.9 / 7.1
Tetracycline	≤2	>8	78.6 / 21.4	71.4 / 28.6
Tigecycline[c]	0.12	0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Daptomycin-non-susceptible (MIC, ≥2 µg/mL; 18)				
Ceftaroline[b]	0.5	1	100.0 / -	- / -
Ceftriaxone	>8	>8	5.6 / 94.4	5.6 / 94.4
Oxacillin	>2	>2	5.6 / 94.4	5.6 / 94.4
Erythromycin	>2	>2	5.6 / 94.4	5.6 / 94.4
Clindamycin	>2	>2	33.3 / 66.7	33.3 / 66.7
Levofloxacin	>4	>4	27.8 / 72.2	27.8 / 72.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Tigecycline[c]	0.06	0.25	100.0 / -	100.0 / 0.0
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Vancomycin	2	2	100.0 / 0.0	100.0 / 0.0
Vancomycin MIC ≥2 µg/mL (369)				
Ceftaroline[b]	0.5	1	91.9 / -	- / -
Oxacillin	>2	>2	29.8 / 70.2	29.8 / 70.2
Erythromycin	>2	>2	24.9 / 74.5	24.9 / 74.5
Clindamycin	≤0.25	>2	57.5 / 42.5	56.6 / 42.5
Levofloxacin	>4	>4	37.7 / 61.2	37.7 / 61.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	96.7 / 3.3	96.7 / 3.3
Tetracycline	≤2	≤2	95.7 / 4.1	89.7 / 6.2
Tigecycline[c]	0.12	0.25	100.0 / -	100.0 / 0.0
Linezolid	1	2	98.9 / 1.1	98.9 / 1.1
Vancomycin	2	2	99.7 / 0.0	99.7 / 0.3
Daptomycin	0.5	1	96.2 / -	96.2 / 3.8

a. Criteria as published by the CLSI [2012] and EUCAST [2012]. β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied [Teflaro Package Insert, 2012].
c. USA-FDA breakpoints were applied [Tygacil Package Insert, 2011].

Table 3. Activity of Ceftaroline and Comparator Antimicrobial Agents when Tested Against 3,270 Isolates of Coagulase-negative Staphylococci[a] (CoNS; USA)

Antimicrobial agent (no. tested)	MIC (µg/mL)		%S / %R	
	MIC_{50}	MIC_{90}	CLSI[b]	EUCAST[b]
CoNS (3,270)				
Ceftaroline[c]	0.25	0.5	- / -	- / -
Ceftriaxone	8	>8	30.6 / 69.4	30.6 / 69.4
Oxacillin	2	>2	30.6 / 69.4	30.6 / 69.4
Erythromycin	>2	>2	34.8 / 63.5	35.3 / 64.1
Clindamycin	≤0.25	>2	68.5 / 29.3	67.1 / 31.5
Levofloxacin	4	>4	47.9 / 50.5	47.9 / 50.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	61.8 / 38.2	61.8 / 28.7
Tetracycline	≤2	>8	85.6 / 13.6	78.1 / 15.6
Tigecycline[d]	0.12	0.25	- / -	100.0 / 0.0
Linezolid	0.5	1	98.4 / 1.6	98.4 / 1.6
Vancomycin	1	2	100.0 / 0.0	99.6 / 0.4
Daptomycin	0.25	0.5	99.9 / -	99.9 / 0.1
Methicillin-susceptible (1,002)				
Ceftaroline[c]	0.06	0.12	- / -	- / -
Ceftriaxone	2	4	99.3 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	56.7 / 42.3	57.0 / 42.5
Clindamycin	≤0.25	>2	88.1 / 10.1	87.0 / 11.9
Levofloxacin	≤0.5	>4	78.5 / 20.5	78.5 / 20.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	82.4 / 17.6	82.4 / 15.2
Tetracycline	≤2	8	89.0 / 9.4	83.9 / 11.7
Tigecycline[d]	0.06	0.25	- / -	100.0 / 0.0
Linezolid	0.5	1	99.7 / 0.3	99.7 / 0.3
Vancomycin	1	2	100.0 / 0.0	99.8 / 0.2
Daptomycin	0.25	0.5	99.8 / -	99.8 / 0.2
Methicillin-resistant (2,268)				
Ceftaroline[c]	0.25	0.5	- / -	- / -
Erythromycin	>2	>2	25.2 / 72.9	25.7 / 73.6
Clindamycin	≤0.25	>2	59.8 / 37.8	58.2 / 40.2
Levofloxacin	>4	>4	34.3 / 63.8	34.3 / 63.8
Trimethoprim/sulfamethoxazole	2	>2	52.7 / 47.3	52.7 / 34.6
Tetracycline	≤2	>8	84.1 / 15.5	75.6 / 17.4
Tigecycline[d]	0.12	0.25	- / -	100.0 / 0.0
Linezolid	0.5	1	97.9 / 2.1	97.9 / 2.1
Vancomycin	2	2	100.0 / 0.0	99.5 / 0.5
Daptomycin	0.25	0.5	99.9 / -	99.9 / 0.1
Linezolid-resistant (MIC, ≥8 µg/mL; 51)				
Ceftaroline[c]	0.5	0.5	- / -	- / -
Oxacillin	>2	>2	5.9 / 94.1	5.9 / 94.1
Erythromycin	>2	>2	15.7 / 52.9	19.6 / 70.6
Clindamycin	1	>2	39.2 / 19.6	23.5 / 60.8
Levofloxacin	>4	>4	2.0 / 98.0	2.0 / 98.0
Trimethoprim/sulfamethoxazole	>2	>2	9.8 / 90.2	9.8 / 72.5
Tetracycline	≤2	≤2	96.1 / 3.9	88.2 / 3.9
Tigecycline[d]	0.12	0.25	- / -	100.0 / 0.0
Vancomycin	2	2	100.0 / 0.0	98.0 / 2.0
Daptomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Daptomycin-non-susceptible (MIC, ≥2 µg/mL; 4)				
Ceftaroline[c]	0.06	-	- / -	- / -
Oxacillin	≤0.25	-	50.0 / 50.0	50.0 / 50.0
Erythromycin	≤0.25	-	75.0 / 0.0	100.0 / 0.0
Clindamycin	≤0.25	-	75.0 / 25.0	75.0 / 25.0
Levofloxacin	≤0.5	-	100.0 / 0.0	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	-	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	-	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.12	-	- / -	100.0 / 0.0
Linezolid	0.5	-	100.0 / 0.0	100.0 / 0.0
Vancomycin	2	-	100.0 / 0.0	75.0 / 25.0

a. Includes: *Staphylococcus auricularis* (18 strains), *S. capitis* (65 strains), *S. carnosus* (1 strain), *S. cohnii* (2 strains), *S. epidermidis* (924 strains), *S. haemolyticus* (66 strains), *S. hominis* (119 strains), *S. intermedius* (5 strains), *S. lentus* (1 strain), *S. lugdunensis* (87 strains), *S. saccharolyticus* (2 strains), *S. saprophyticus* (26 strains), *S. sciuri* (5 strains), *S. simulans* (6 strains), *S. succinus* (1 strain), *S. warneri* (38 strains), *S. xylosus* (2 strains), and unspecieated CoNS (1902 strains).
b. Criteria as published by the CLSI [2012] and EUCAST [2012]. β-lactam susceptibility should be directed by the oxacillin test results.
c. USA-FDA breakpoints were applied [Teflaro Package Insert, 2012].
d. USA-FDA breakpoints were applied [Tygacil Package Insert, 2011].

Conclusions

- Ceftaroline exhibited potent *in vitro* activity against a large contemporary collection of *S. aureus* and CoNS from USA hospitals, including MRSA and MRCoNS, collected between 2008 and 2011
- Ceftaroline also retained significant activity against staphylococci with reduced susceptibility to linezolid, daptomycin and vancomycin, and could potentially represent a valuable treatment option for infections caused by these multidrug-resistant staphylococci in the USA.

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