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Antimicrobial Activity of Ceftaroline and Comparator Agents When Tested against Numerous Species of Coagulase-negative *Staphylococcus* (CoNS)

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Abstract

Background: CoNS is a major cause of bloodstream infections, especially in patients with intravenous catheters and prosthetic devices. We evaluated the *in vitro* activity of ceftaroline against a large collection of CoNS from United States (USA) hospitals.

Methods: 1593 CoNS isolates considered clinically significant (multiple infection types) were collected from 71 USA medical centers in 2013-2014 and tested for susceptibility (S) by CLSI reference broth microdilution methods against ceftaroline and numerous comparators. Species identification was performed by MALDI-TOF.

Results: Overall, 59.7% of isolates were oxacillin-resistant (MRCoNS). Ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/ml) inhibited 99.2% of CoNS at ≤1 µg/ml (S breakpoint for *S. aureus*), including 98.7% of MRCoNS. Ceftaroline activity was 4-fold greater than that of vancomycin ($MIC_{50/90}$, 1/2 µg/ml; 100.0% S) and similar to that of daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml; 99.9% S). The highest ceftaroline MIC value was only 2 µg/ml (13 strains); which was observed only among *S. cohnii* (1 of 7; 14.3%), *S. epidermidis* (0.1%), *S. haemolyticus* (13.0%) and *S. saprophyticus* (2.9%). *S. epidermidis* represented 60.3% of the CoNS collection and was highly S to ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/ml, 99.9% inhibited at ≤1 µg/ml). *S. lugdunensis* and *S. hominis* ($MIC_{50/90}$, 0.25/0.5 µg/ml for both) were the 2nd and 3rd most common CoNS species, respectively, and *S. capitis* ($MIC_{50/90}$, 0.06/0.25 µg/ml) ranked 4th; all isolates from these three species were inhibited at ceftaroline MIC of ≤1 µg/ml (Table 1). *S. haemolyticus* represented only 4.8%, was atypically less S to ceftaroline ($MIC_{50/90}$, 0.5/2 µg/ml, 87.0% inhibited at ≤1 µg/ml) and accounted for 76.9% (10/13) of isolates with ceftaroline MIC >1 µg/ml. Tigecycline and linezolid were also active against CoNS (≥99.3% S).

Conclusions: Ceftaroline exhibited potent *in vitro* activity against CoNS, including many uncommonly isolated species for which very limited susceptibility information is currently available to guide therapy. Ceftaroline may have a potential role in the treatment of CoNS infections as guided by reference MIC testing results.

Introduction

Ceftaroline fosamil, the prodrug of ceftaroline, is a broad-spectrum parenteral cephalosporin which was approved by the United States Food and Drug Administration (USA-FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), and by the European Medicines Agency (EMA) for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP). Ceftaroline has demonstrated potent *in vitro* bactericidal activity against resistant Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Streptococcus pneumoniae*, as well as prevalent Gram-negative organisms.

Coagulase-negative staphylococci (CoNS) represent the most common cause of bacteremia related to indwelling devices and most of these infections are hospital-acquired. Other important infections caused by CoNS include central nervous system shunt infections, native or prosthetic valve endocarditis, urinary tract infections, and endophthalmitis. Resistance to oxacillin and other β-lactams is widespread among CoNS associated with human infections, and although CoNS are usually susceptible to glycopeptides, increased MIC values for teicoplanin (≥4 µg/ml) and/or vancomcyin (≥2 µg/ml) are frequently reported and may relate to poor clinical treatment outcomes. We evaluated the *in vitro* activity of ceftaroline tested against a large collection of CoNS from USA hospitals.

Methods

Organism collection: A total of 1,593 CoNS isolates considered clinically significant (multiple infection types) were collected from 71 USA medical centers in 2013-2014 (one/patient episode) through the AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation) ceftaroline surveillance program. Isolates were submitted to a reference monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) where species identifications were confirmed using MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing: All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A10, 2015). Susceptibility testing was performed using validated broth microdilution panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). Categorical interpretation of MIC values was performed according to CLSI (M100-S25, 2015) and validation of MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) strains: *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

Results

- Among 1,593 CoNS isolates reported as clinically relevant; 602 (37.8%) were from bloodstream infections (BSI), 164 (10.3%) from urinary tract infections and 827 (51.9%) from other infection sites.
- The most frequently isolated species overall were *S. epidermidis* (960 isolates; 60.3%), *S. lugdunensis* (168 isolates; 10.5%), *S. hominis* (120 isolates; 7.5%) and *S. capitis* (103 isolates; 6.5%). Among isolates from BSI, the most common species were *S. epidermidis* (371; 61.6%), *S. hominis* (85; 14.1%) and *S. capitis* (103; 9.6%).
- Ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/ml) inhibited 99.2% of CoNS at ≤1 µg/ml (susceptible breakpoint for *S. aureus*), including 98.7% of oxacillin-resistant CoNS (Table 1). Among isolates from BSI, 99.3% (598/602) were inhibited at ceftaroline MIC of ≤1 µg/ml, and isolates with ceftaroline MIC >1 µg/ml were three *S. haemolyticus* and one *S. cohnii* isolates with ceftaroline MIC values of 2 µg/ml.
- Overall, 59.7% of isolates were oxacillin-resistant (MRCoNS). Oxacillin-resistance rates varied from as low as 1.8% for *S. lugdunensis* and 27.2% for *S. capitis* to 100.0% for *S. saprophyticus* and 76.3% for *S. warneri* (Table 2). Among *S. epidermidis,* the oxacillin resistance rate was slightly higher for BSI isolates (76.0%), compared to non-BSI isolates (68.4%).
- Ceftaroline activity was four-fold greater than that of vancomycin ($MIC_{50/90}$, 1/2 µg/ml; 100.0% susceptible) and similar to that of daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml; 99.9% susceptible; data not shown).
- The highest ceftaroline MIC value was 2 µg/ml; which was observed only among *S. cohnii* (1 of 7; 14.3%), *S. epidermidis* (0.1%), *S. haemolyticus* (13.0%) and *S. saprophyticus* (2.9%).
- *S. epidermidis* was highly susceptible to ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/ml, 99.9% inhibited at ≤1 µg/ml). *S. lugdunensis* and *S. hominis* ($MIC_{50/90}$, 0.25/0.5 µg/ml for both) were the 2nd and 3rd most common CoNS species, respectively, and *S. capitis* ($MIC_{50/90}$, 0.06/0.25 µg/ml) ranked 4th; all isolates from these 3 species were inhibited at ceftaroline MICs of ≤1 µg/ml (Tables 1 and 2).
- *S. haemolyticus* represented only 4.8% of CoNS, was atypically less susceptible to ceftaroline ($MIC_{50/90}$, 0.5/2 µg/ml, 87.0% inhibited at ≤1 µg/ml, 13.0% at 2 µg/ml) and accounted for 76.9% of isolates with ceftaroline MIC values of >1 µg/ml (Tables 1 and 2).
- Highest tigecycline MIC value was 0.5 µg/ml and 99.3% of isolates were susceptible to linezolid (MIC_{50} and MIC_{90}, 0.5 µg/ml; Table 2). All linezolid-non-susceptible isolates (n=11; 0.7%) were *S. epidermidis*, and seven of them (63.6%) were from BSI.

Table 1. Summary of ceftaroline activity tested against 1,593 clinical isolates of coagulase-negative staphylococci from USA medical centers (2013-2014).

Organism /	No. of isolates (cumulative %) inhibited at MIC (µg/ml) of:							MIC (µg/ml)	
no. tested	≤0.03	0.06	0.12	0.25	0.5	1	2	50%	90%
All isolates (1,593)	67 (4.2)	265 (20.8)	268 (37.7)	570 (73.4)	360 (96.0)	50 (99.2)	13 (100.0)	0.25	0.5
S. capitis (103)	36 (35.0)	43 (76.7)	5 (81.6)	10 (91.3)	6 (97.1)	3 (100.0)	-	0.06	0.25
S. epidermidis (960)	28 (2.9)	181 (21.8)	124 (34.7)	354 (71.6)	257 (98.3)	15 (99.9)	1 (100.0)	0.25	0.5
S. haemolyticus (77)	-	1 (1.3)	14 (19.5)	18 (42.9)	21 (70.1)	13 (87.0)	10 (100.0)	0.5	2
S. hominis (120)	-	6 (5.0)	37 (35.8)	26 (57.5)	43 (93.3)	8 (100.0)	-	0.25	0.5
S. lugdunensis (168)	-	4 (2.4)	24 (16.7)	121 (88.7)	17 (98.8)	2 (100.0)	-	0.25	0.5
S. saprophyticus (35)	-	-	7 (20.0)	18 (71.4)	6 (88.6)	3 (97.1)	1 (100.0)	0.25	1
S. warneri (38)	1 (2.6)	10 (28.9)	19 (78.9)	2 (84.2)	5 (97.4)	1 (100.0)	-	0.12	0.5
Other species (92)	2 (2.2)	20 (23.9)	38 (65.2)	21 (88.0)	5 (93.5)	5 (98.9)	1 (100.0)	0.12	0.5

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against 1,593 isolates of CoNS from USA medical centers (2013-2014).

Organism / Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
All (1,593)									
Ceftaroline	0.25	0.5	≤0.015 — 2	(99.2)[b]	-	-	-	-	-
Oxacillin	1	>2	≤0.25 — >2	40.3	-	59.7	40.3	-	59.7
Clindamycin	≤0.25	>2	≤0.25 — >2	68.6	1.4	30.0	66.1	2.5	31.4
Levofloxacin	0.25	>4	≤0.12 — >4	58.3	1.4	40.3	58.3	1.4	40.3
TMP/SMX[c]	≤0.5	>4	≤0.5 — >4	70.5	-	29.5	70.5	16.1	13.4
Tigecycline	0.06	0.12	≤0.015 — 0.5	-	-	-	100.0	-	0.0
Linezolid	0.5	0.5	≤0.12 — >8	99.3	-	0.7	99.3	-	0.7
Vancomycin	1	2	0.25 — 4	100.0	0.0	0.0	100.0	-	0.0
S. capitis (103)									
Ceftaroline	0.06	0.25	≤0.015 — 1	(100.0)[b]	-	-	-	-	-
Oxacillin	≤0.25	>2	≤0.25 — >2	72.8	-	27.2	72.8	-	27.2
Clindamycin	≤0.25	>2	≤0.25 — >2	85.4	1.0	13.6	83.5	1.9	14.6
Levofloxacin	0.25	>4	≤0.12 — >4	66.0	0.0	34.0	66.0	0.0	34.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 — >4	98.1	-	1.9	98.1	1.0	1.0
Tigecycline	0.06	0.12	0.03 — 0.25	-	-	-	100.0	-	0.0
Linezolid	0.5	1	0.25 — 1	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
S. epidermidis (960)									
Ceftaroline	0.25	0.5	≤0.015 — 2	(99.9)[b]	-	-	-	-	-
Oxacillin	2	>2	≤0.25 — >2	28.6	-	71.4	28.6	-	71.4
Clindamycin	≤0.25	>2	≤0.25 — >2	59.0	1.5	39.6	56.3	2.7	41.0
Levofloxacin	4	>4	≤0.12 — >4	46.5	1.8	51.8	46.5	1.8	51.8
TMP/SMX[c]	1	>4	≤0.5 — >4	60.0	-	40.0	60.0	22.2	17.8
Tigecycline	0.06	0.12	≤0.015 — 0.5	-	-	-	100.0	-	0.0
Linezolid	0.5	0.5	≤0.12 — >8	98.9	-	1.1	98.9	-	1.1
Vancomycin	2	2	0.25 — 4	100.0	0.0	0.0	100.0	-	0.0
S. haemolyticus (77)									
Ceftaroline	0.5	2	0.06 — 2	(87.0)[b]	-	-	-	-	-
Oxacillin	>2	>2	≤0.25 — >2	35.1	-	64.9	35.1	-	64.9
Clindamycin	≤0.25	>2	≤0.25 — >2	85.7	3.9	10.4	80.5	5.2	14.3
Levofloxacin	4	>4	≤0.12 — >4	41.6	0.0	58.4	41.6	0.0	58.4
TMP/SMX[c]	≤0.5	>4	≤0.5 — >4	62.3	-	37.7	62.3	1.3	36.4
Tigecycline	0.06	0.25	≤0.015 — 0.25	-	-	-	100.0	-	0.0
Linezolid	0.5	1	0.25 — 1	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	2	0.25 — 2	100.0	0.0	0.0	100.0	-	0.0
S. hominis (120)									
Ceftaroline	0.25	0.5	0.06 — 1	(100.0)[b]	-	-	-	-	-
Oxacillin	1	>2	≤0.25 — >2	40.0	-	60.0	40.0	-	60.0
Clindamycin	≤0.25	>2	≤0.25 — >2	76.7	0.8	22.5	75.8	0.8	23.3
Levofloxacin	≤0.12	>4	≤0.12 — >4	66.7	0.0	33.3	66.7	0.0	33.3
TMP/SMX[c]	≤0.5	4	≤0.5 — >4	62.5	-	37.5	62.5	30.8	6.7
Tigecycline	0.06	0.12	≤0.015 — 0.25	-	-	-	100.0	-	0.0
Linezolid	0.5	1	0.25 — 4	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
S. lugdunensis (168)									
Ceftaroline	0.25	0.5	0.06 — 1	(100.0)[b]	-	-	-	-	-
Oxacillin	1	1	≤0.25 — >2	98.2	-	1.8	98.2	-	1.8
Clindamycin	≤0.25	>2	≤0.25 — >2	87.5	0.0	12.5	86.9	0.6	12.5
Levofloxacin	0.25	0.25	≤0.12 — >4	98.2	0.6	1.2	98.2	0.6	1.2
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 — >4	99.4	-	0.6	99.4	0.0	0.6
Tigecycline	0.03	0.06	≤0.015 — 0.12	-	-	-	100.0	-	0.0
Linezolid	0.25	0.5	≤0.12 — 1	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
S. saprophyticus (35)									
Ceftaroline	0.25	1	0.12 — 2	(97.1)[b]	-	-	-	-	-
Oxacillin	1	>2	0.5 — >2	0.0	-	100.0	0.0	-	100.0
Clindamycin	≤0.25	>2	≤0.25 — >2	88.6	0.0	11.4	85.7	2.9	11.4
Levofloxacin	0.5	0.5	0.5 — 0.5	100.0	0.0	0.0	100.0	0.0	0.0
TMP/SMX[c]	≤0.5	1	≤0.5 — >4	94.3	-	5.7	94.3	0.0	5.7
Tigecycline	0.06	0.12	0.06 — 0.25	-	-	-	100.0	-	0.0
Linezolid	1	1	0.25 — 2	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
S. warneri (38)									
Ceftaroline	0.12	0.5	0.03 — 1	(100.0)[b]	-	-	-	-	-
Oxacillin	0.5	>2	≤0.25 — >2	23.7	-	76.3	23.7	-	76.3
Clindamycin	≤0.25	>2	≤0.25 — >2	81.6	2.6	15.8	81.6	0.0	18.4
Levofloxacin	0.25	0.25	≤0.12 — >4	94.7	0.0	5.3	94.7	0.0	5.3
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 — 4	97.4	-	2.6	97.4	2.6	0.0
Tigecycline	0.06	0.12	0.015 — 0.12	-	-	-	100.0	-	0.0
Linezolid	0.5	1	0.25 — 1	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	2	0.25 — 2	100.0	0.0	0.0	100.0	-	0.0
Other species (92)[d]									
Ceftaroline	0.12	0.5	0.03 — 2	(98.9)[b]	-	-	-	-	-
Oxacillin	0.5	>2	≤0.25 — >2	46.7	-	53.3	46.7	-	53.3
Clindamycin	≤0.25	>2	≤0.25 — >2	77.2	2.2	20.7	72.8	4.3	22.8
Levofloxacin	0.25	>4	≤0.12 — >4	72.8	4.3	22.8	72.8	4.3	22.8
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 — >4	93.5	-	6.5	93.5	4.3	2.2
Tigecycline	0.06	0.12	≤0.015 — 0.25	-	-	-	100.0	-	0.0
Linezolid	0.5	1	0.25 — 1	100.0	-	0.0	100.0	-	0.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Number in parenthesis indicate percentage inhibited at ≤1 µg/ml, the CLSI and USA-FDA susceptible breakpoint for *S. aureus*.
c. TMP/SMX = trimethoprim/sulfamethoxazole.
d. Organisms include: *S. arlettae* (1), *S. auricularis* (5), *S. capitis* (103), *S. schleiferi* (4), *S. cohnii* (7), *S. caprae* (13), *S. epidermidis* (960), *S. haemolyticus* (77), *S. hominis* (120), *S. intermedius* (4), *S. lentus* (3), *S. lugdunensis* (168), *S. pasteuri* (2), *S. pettenkoferi* (10), *S. pseudintermedius* (6), *S. pseudintermedius / intermedius* (5), *S. saprophyticus* (35), *S. sciuri* (2), *S. simulans* (27), Unspeciated *Staphylococcus* (2), *S. warneri* (38), *S. xylosus* (1).

Conclusions

- Ceftaroline exhibited potent *in vitro* activity against CoNS, including many uncommonly isolated species for which very limited susceptibility information is available to guide contemporary therapy.
- Ceftaroline may have a potential role in the treatment of CoNS infections as guided by reference MIC results.

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