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Activity of Ceftaroline and Comparator Agents Tested against *Staphylococcus aureus* from Patients with Bacteremia in United States (USA) Medical Centers (2009-2013)

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Amended Abstract

Background: Ceftaroline (CPT), the active metabolite of the prodrug CPT fosamil, is the first USA-FDA approved cephalosporin with potent activity against methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA). CPT fosamil is approved for treatment of community-acquired pneumonia and acute bacterial skin infections.

Methods: 4,426 *S. aureus* isolates from the AWARE CPT surveillance program were derived from patients with bacteremia in 2009-2013. Isolates were collected in 150 medical centers distributed through all 9 USA Census regions, and tested for susceptibility (S) against CPT and comparators by the CLSI broth microdilution method. S interpretations were determined per CLSI criteria.

Results: 45.5% of isolates were MRSA. CPT ($MIC_{50/90}$, 0.25/1 µg/mL) inhibited 97.9 and 100.0% of *S. aureus* at ≤1 and ≤2 µg/mL, respectively (Table 1). Daptomycin (DAP; $MIC_{50/90}$, 0.25/0.5 µg/mL), linezolid (LZD; $MIC_{50/90}$, 1/2 µg/mL) and vancomycin (VAN; $MIC_{50/90}$, 1/1 µg/mL) were active against ≥99.8% of isolates. S rates for erythromycin ($MIC_{50/90}$, >16/>16 µg/mL), clindamycin (CLI; $MIC_{50/90}$, ≤0.25/ >2 µg/mL) and levofloxacin (LEV; $MIC_{50/90}$, ≤0.5/>4 µg/mL) were 42.5, 80.8 and 59.2%, respectively. Against MSSA, CPT ($MIC_{50/90}$, 0.25/0.25 µg/mL; 100.0% S) was 16-, 4- and 4-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/mL), LZD ($MIC_{50/90}$, 1/2 µg/mL) and VAN ($MIC_{50/90}$, 1/1 µg/mL), respectively, and slightly more potent than DAP ($MIC_{50/90}$, 0.25/0.5 µg/mL). Among MRSA, 95.4 and 100.0% of strains were inhibited at ≤1 and ≤2 µg/mL of CPT, respectively. 35.8% and 75.4% of MRSA were resistant to CLI and LEV, respectively. 99.7% of MRSA strains were DAP-S ($MIC_{50/90}$, 0.25/0.5 µg/mL), and LZD ($MIC_{50/90}$, 1/2 µg/mL) and VAN ($MIC_{50/90}$, 1/1 µg/mL) were active against >99.9% of MRSA strains.

Conclusions: Our results demonstrate the potent in vitro activity of CPT when tested against a large collection of contemporary (2009-2013) *S. aureus* isolates causing bacteremias in USA hospitals.

Introduction

Staphylococcus aureus is a leading cause of community- and hospital-acquired bacteremia worldwide, and *S. aureus* bacteremia causes significant morbidity, mortality, and healthcare costs. *S. aureus* bacteremia can lead to seeding of virtually any body site, which may cause severe complications, such as infective endocarditis, vertebral osteomyelitis, epidural abscess, among others. Complications of *S. aureus* bacteremia carry poor prognosis because of the anatomic site or the difficulty in reaching a timely diagnosis. The most difficult cases are those that persist despite appropriate antimicrobial therapy and without an easily identified and removable focus.

Ceftaroline is the first cephalosporin with activity against MRSA approved for clinical use in the United States (USA; in 2010) and Europe (in 2012). Ceftaroline was approved based on two phase 3 randomized, double-blind, 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 has not been evaluated in the treatment of MRSA bacteremia and it is not approved by the USA Food and Drug Administration (FDA) for this indication, however, it has been sporadically used in patients with MRSA bacteremia and endocarditis, especially as salvage therapy in combination with other antimicrobials. We evaluated the in vitro activity of ceftaroline tested against a large collection of *S. aureus* isolated from patients with bacteremia in USA hospitals.

Methods

Organism collection: A total of 4,426 *S. aureus* isolates from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) ceftaroline surveillance program were derived from patients with bacteremia in 2009-2013. Isolates were collected in 150 medical centers distributed through all 9 USA Census regions. Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmatory identification and reference susceptibility testing. Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions.

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 CLSI (M100-S24) and EUCAST (2014) breakpoint criteria. Validated MIC panels were manufactured by ThermoFisher Scientific (Cleveland, Ohio, USA). Isolates were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control strains assured proper test conditions.

Results

- The majority of isolates (59.4%) were from patients >50 years old (18.0% from patients 50-64 year old and 31.4% from patients ≥75 years old). Isolates from patients ≤17 and 18-49 years old comprised 13.7 and 23.5% of strains, respectively. Patient age was not provided for 3.5% of the patients.
- Ceftaroline (MIC_{50}, 0.25 µg/mL and MIC_{90}, 1 µg/mL) inhibited 97.9 and 100.0% of *S. aureus* at ≤1 and ≤2 µg/mL, respectively (Table 1 and Figure 1).
- Overall, 45.5% of isolates were resistant to oxacillin (MRSA). Daptomycin (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL), linezolid (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL) were active against ≥99.8% of *S. aureus* isolates (Table 2).
- Susceptibility rates (CLSI) for *S. aureus* isolates for erythromycin (MIC_{50} and MIC_{90}, >16 µg/mL), clindamycin (MIC_{50}, ≤0.25 µg/mL and MIC_{90}, >2 µg/mL) and levofloxacin (MIC_{50}, ≤0.5 µg/mL and MIC_{90}, >4 µg/mL) were 42.5, 80.8 and 59.2%, respectively (Table 2).
- Against MSSA, ceftaroline (MIC_{50} and MIC_{90}, 0.25 µg/mL; 100.0% susceptible) was 16-, 4- and 4-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 µg/mL; Figure 2), linezolid (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL), respectively, and slightly more potent than daptomycin (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL; Table 2).
- Among MRSA, 95.4 and 100.0% of strains were inhibited at ≤1 and ≤2 µg/mL of ceftaroline (MIC_{50}, 0.5 µg/mL and MIC_{90}, 1 µg/mL), respectively (Table 1 and Figure 1).
- Susceptibility rates (CLSI) for clindamycin and levofloxacin when testing MRSA strains were 63.9 and 22.9%, respectively; whereas ≥99.7% of MRSA strains were susceptible to daptomycin (MIC_{50}, 0.25 µg/mL and MIC_{90}, 0.5 µg/mL) linezolid (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/mL; Table 2).
- Ceftaroline was active against *S. aureus* strains with decreased susceptibility to vancomycin (MIC, ≥2 µg/mL; n=123), with MIC_{50} of 0.5 µg/mL, MIC_{90} of 1 µg/mL and 91.1% susceptibility rate (Table 1 and Figure 3).
- Ceftaroline was also active against *S. aureus* strains nonsusceptible (CLSI) to levofloxacin (n=1,806; MIC_{50}, 0.5 µg/mL and MIC_{90}, 1 µg/mL; 94.9% susceptible), clindamycin (n=847; MIC_{50} and MIC_{90}, 1 µg/mL; 90.4% susceptible), trimethoprim/sulfamethoxazole (n=88; MIC_{50}, 0.5 µg/mL and MIC_{90}, 1 µg/mL; 93.2% susceptible) or daptomycin (n=7; MIC_{50}, 0.5 µg/mL and 100.0% susceptible; Table 1 and Figure 3). Only one strain, a MRSA, was non-susceptible to linezolid (MIC, >8 µg/mL) and exhibited a ceftaroline MIC of 0.5 µg/mL (data not shown).

Table 1. Summary of ceftaroline activity tested against 4,426 *S. aureus* strains from bacteremia (USA, 2009-2013)

Organism[a] (no.)	No. of isolates (cumulative % inhibited) at ceftaroline MIC (µg/mL) of: 0.03	0.06	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}	% Susc.[b]
S. aureus (4,426)	1 (<0.1)	12 (0.3)	222 (5.3)	2,105 (52.9)	1,113 (78.0)	880 (97.9)	93 (100.0)	0.25	1	97.9
MSSA (2,413)	1 (<0.1)	12 (0.5)	221 (9.7)	2,067 (95.4)	111 (>99.9)	1 (100.0)	--	0.25	0.25	100.0
MRSA (2,013)	--	--	1 (0.0)	38 (1.9)	1,002 (51.7)	879 (95.4)	93 (100.0)	0.5	1	95.4
LEV-NS (1,806)	--	3 (0.2)	21 (1.3)	243 (14.8)	709 (54.0)	737 (94.8)	92 (100.0)	0.5	1	94.8
CLI-NS (847)	--	--	13 (1.5)	110 (14.5)	247 (43.7)	396 (90.4)	81 (100.0)	1	1	90.4
VAN ≥2 (123)	--	2 (1.6)	5 (5.7)	29 (29.3)	29 (52.9)	47 (91.1)	11 (100.0)	0.5	1	91.1
T/S-NS (88)	--	1 (1.1)	2 (3.4)	24 (30.7)	22 (55.7)	33 (93.2)	6 (100.0)	0.5	1	93.2
DAP-NS (7)	--	--	--	--	5 (71.4)	2 (100.0)	--	0.5	--	100.0

a. Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; LEV-NS, levofloxacin-nonsusceptible (MIC, ≥2 µg/mL); CLI-NS, clindamycin-nonsusceptible (MIC, ≥1 µg/mL); VAN ≥2, includes isolates with vancomycin MIC of 2 µg/mL (122) or 4 µg/mL (one); T/S-NS, trimethoprim/sulfamethoxazole-nonsusceptible (MIC, ≥4 µg/mL) and DAP-NS, daptomycin-nonsusceptible (MIC, ≥2 µg/mL). Susceptibility defined according to CLSI breakpoint criteria (CLSI, 2014).
b. According to CLSI (2014), USA-FDA (2012) and EUCAST (2014) criteria.

Table 2. Antimicrobial activity of ceftaroline and comparator agents when tested against *S. aureus* isolates from bacteremia (USA, 2009-2013)

Antimicrobial agent (no. tested)	MIC (µg/mL) 50%	90%	Range	%S / %I / %R CLSI[a]	EUCAST[a]
S. aureus (4,426)					
Ceftaroline	0.25	1	0.03 – 2	97.9 / 2.1 / 0.0	97.9 / 0.0 / 2.1
Ceftriaxone	4	>8	0.5 – >8	54.5 / 0.0 / 45.5	54.5 / 0.0 / 45.5
Oxacillin	1	>2	≤0.25 – >2	54.5 / 0.0 / 45.5	54.5 / 0.0 / 45.5
Erythromycin	>16	>16	≤0.25 – >16	42.5 / 1.9 / 55.6	42.8 / 0.5 / 56.7
Clindamycin	≤0.25	>2	≤0.25 – >2	80.8 / 0.3 / 18.9	80.4 / 0.4 / 19.2
Levofloxacin	≤0.5	>4	≤0.5 – >4	59.2 / 1.1 / 39.7	59.2 / 1.1 / 39.7
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	98.0 / 0.0 / 2.0	98.0 / 0.2 / 1.8
Tetracycline	≤2	≤2	≤2 – >8	95.5 / 0.7 / 3.8	93.2 / 1.4 / 5.4
Linezolid	1	2	≤0.12 – >8	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
Vancomycin	1	1	0.25 – 4	>99.9 / <0.1 / 0.0	>99.9 / 0.0 / <0.1
Daptomycin	0.25	0.5	≤0.06 – 2	99.8 / - / -	99.8 / 0.0 / 0.2
MSSA (2,413)					
Ceftaroline	0.25	0.25	0.03 – 1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftriaxone	4	4	0.5 – >8	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.25	>16	≤0.25 – >16	69.9 / 2.4 / 27.7	70.3 / 0.8 / 28.9
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.0 / 0.2 / 4.8	94.8 / 0.2 / 5.0
Levofloxacin	≤0.5	2	≤0.5 – >4	89.5 / 0.6 / 9.9	89.5 / 0.6 / 9.9
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	98.8 / 0.0 / 1.2	98.8 / 0.1 / 1.1
Tetracycline	≤2	≤2	≤2 – >8	96.4 / 0.7 / 2.9	95.4 / 0.3 / 4.3
Linezolid	1	2	≤0.12 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / - / -	100.0 / 0.0 / 0.0
MRSA (2,013)					
Ceftaroline	0.5	1	0.12 – 2	95.4 / 4.6 / 0.0	95.4 / 0.0 / 4.6
Ceftriaxone	>8	>8	2 – >8	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Erythromycin	>16	>16	≤0.25 – >16	9.6 / 1.3 / 89.1	9.8 / 0.3 / 89.9
Clindamycin	≤0.25	>2	≤0.25 – >2	63.9 / 0.3 / 35.8	63.1 / 0.8 / 36.1
Levofloxacin	>4	>4	≤0.5 – >4	22.9 / 1.7 / 75.4	22.9 / 1.7 / 75.4
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	97.0 / 0.0 / 3.0	97.0 / 0.3 / 2.7
Tetracycline	≤2	≤2	≤2 – >8	94.3 / 0.9 / 4.8	90.6 / 2.7 / 6.7
Linezolid	1	2	0.25 – >8	>99.9 / 0.0 / <0.1	100.0 / 0.1 / 0.1
Vancomycin	1	1	0.5 – 4	>99.9 / <0.1 / 0.0	100.0 / 0.1 / 0.1
Daptomycin	0.25	0.5	≤0.06 – 2	99.7 / - / -	99.7 / 0.0 / 0.3

a. Criteria as published by the CLSI [2014] and EUCAST [2014].
b. TMP/SMX: trimethoprim/sulfamethoxazole.

Figure 1. Ceftaroline MIC distributions when tested against 4,426 *S. aureus* strains from bacteremia (USA, 2009-2013)

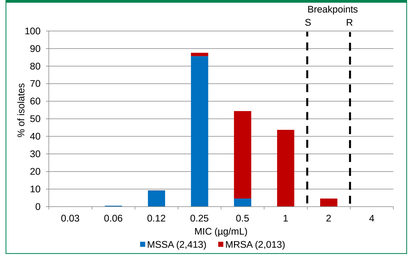


Figure 2. Antimicrobial activity of ceftaroline and ceftriaxone tested against 4,426 strains of MSSA from bacteremia (USA, 2009-2013)

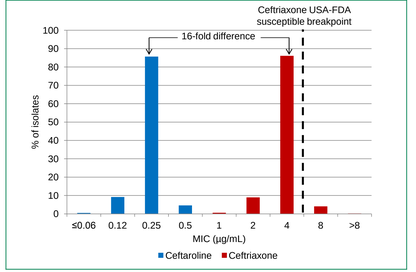
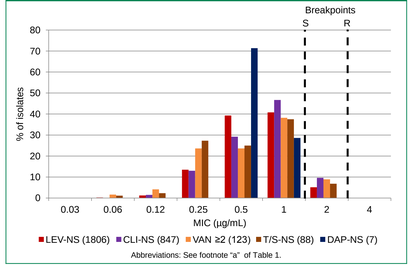


Figure 3. Ceftaroline MIC distribution when tested against various *S. aureus* resistant subsets (USA, 2009-2013)



Abbreviations: See footnote "a" of Table 1.

Conclusions

- Our results demonstrate the potent in vitro activity of ceftaroline when tested against a large collection of contemporary (2009-2013) *S. aureus* isolates causing bacteremias in USA hospitals.
- These in vitro data support the further clinical development of ceftaroline for treatment of bacteremia caused by *S. aureus*, including MRSA.

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