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Antimicrobial Susceptibility of *S. aureus* from USA Hospitals According to the Site of Infection: Data from the Ceftaroline AWARE Surveillance Program (2008-2011)

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Abstract

Background: Ceftaroline, active form of ceftaroline fosamil, is a new, cephalosporin exhibiting broad-spectrum bactericidal *in vitro* activity including against methicillin-susceptible (MS) and -resistant (MR) *S. aureus*. We compared antimicrobial susceptibility of *S. aureus* from various sites of infections (SI).

Methods: 10,638 *S. aureus* were collected from 82 USA hospitals from 2008-2011 and susceptibility tested against ceftaroline and comparator agents by CLSI broth microdilution methodology. Isolates were from bloodstream (BSI; 3923), acute bacterial skin and skin structure (ABSSSI; 4385), respiratory tract (RTI; 1718), and other SIs (Other; 612).

Results: The overall MRSA rate was 51.9%, varying from 47.7 (BSI) to 58.0% (others). Ceftaroline was consistently active against *S. aureus* from all SI, with $MIC_{50/90}$ of 0.5/1 µg/mL and 97.0-99.2% susceptible (98.2% overall; Table 1). Ceftaroline demonstrated potent activity against MRSA ($MIC_{50/90}$, 0.5-1/1 µg/mL; 94.2-98.5% susceptible) with little variation by SI. The highest ceftaroline MIC was only 2 µg/mL. The activity of comparator agents against MSSA was consistent among SI; while MRSA from ABSSSI were slightly more susceptible to clindamycin (79.4%) and levofloxacin (42.2%) compared to those from other SI. The activities of tetracycline and trimethoprim/sulfamethoxazole did not vary substantially by SI or susceptibility to oxacillin. Vancomycin ($MIC_{50/90}$, 1/1 µg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), linezolid ($MIC_{50/90}$, 1/2 µg/mL), and tigecycline ($MIC_{50/90}$, 0.12/0.25 µg/mL) exhibited excellent anti-*S. aureus* activity overall (≥99.9% susceptible).

Conclusions: Our results demonstrate the potent *in vitro* activity of ceftaroline tested against a large collection of contemporary (2008-2011) *S. aureus* isolates from USA hospitals. Although the activity of some antimicrobials varied according to SI, ceftaroline exhibited consistent activity against MSSA and MRSA, independent of SI.

Introduction

Staphylococcus aureus, particularly methicillin-resistant strains (MRSA), represents a major cause of serious infections in the hospital environment. Furthermore, since the emergence of MRSA as a community-associated pathogen in the 1990s, community-acquired MRSA (CA-MRSA) strains have increasingly caused community-onset infections as well as hospital and health-care associated disease.

β-lactam antimicrobials have a long history of both safety and efficacy over a broad range of infections and organisms. Ceftaroline, the active form of ceftaroline fosamil, is a cephalosporin exhibiting broad-spectrum *in vitro* bactericidal activity against Gram-positive organisms, including MRSA and multidrug-resistant (MDR) *Streptococcus pneumoniae*, as well as common Gram-negative pathogens. Ceftaroline fosamil is approved by the United States Food and Drug Administration (USA-FDA) for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP). As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study, we evaluated the activity of ceftaroline against *S. aureus* from various sites of infections isolated in USA hospitals in 2008-2011.

Methods

Organism collection: A total of 10,638 clinically significant, nonduplicate isolates of *S. aureus* were collected from 82 USA hospitals from 2008-2011. The isolates were from bloodstream (BSI; 3923), ABSSSI (4385), respiratory tract (RTI; 1718), and other sites of infection (612).

Susceptibility testing methods: Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) methods were performed to determine antimicrobial susceptibility of ceftaroline and comparator antimicrobials used to treat ABSSSI. Validated MIC panels were manufactured by ThermoFisher Scientific®, Inc., formerly TREK Diagnostics® (Cleveland, Ohio, USA). The isolates were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. Susceptibility percentages and validation of QC results were based on CLSI documents (M100-S22) and EUCAST (2012). USA-FDA interpretive criteria for ceftaroline susceptibility were used, when available.

Results

- The overall MRSA rate was 51.9%, varying from 47.7% among isolates from bacteremia to 51.2, 55.2 and 58.0% for isolates from RTI, ABSSSI and other sites, respectively (Table 1)
- Ceftaroline was consistently active against *S. aureus* from all sites of infection, with $MIC_{50/90}$ of 0.5/1 µg/mL and overall susceptibility rates of 96.5% for MRSA and 100.0% for MSSA (98.2% overall; Tables 1 and 2)
- Ceftaroline demonstrated potent activity against MRSA with overall $MIC_{50/90}$ of 0.5/1 µg/mL (94.2-98.5% susceptibility rates) and little variation by site of infection. The highest ceftaroline MIC value was only 2 µg/mL (Tables 1 and 2), no resistant strains by CLSI (June 2012) breakpoint criteria of ≥4 µg/mL
- When tested against MSSA, ceftaroline ($MIC_{50/90}$, 0.25/0.25 µg/mL) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 µg/mL), four-fold more active than vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/2 µg/mL), and slightly more active than oxacillin ($MIC_{50/90}$, 0.5/0.5 µg/mL) and daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL; Table 2)
- The activity of comparator agents against MSSA was comparable across all sites of infections (Table 1)
- Among MRSA, susceptibility to levofloxacin varied from 16.2% for RTI strains to 42.2% for ABSSSI strains. Similarly, susceptibility to clindamycin was highest among MRSA strains from ABSSSI (79.4%) and lowest among MRSA strains from RTI (54.0%; Table 1)
- The activities of tetracycline and trimethoprim/sulfamethoxazole did not vary substantially by infection site or susceptibility to oxacillin (Table 1)
- Vancomycin ($MIC_{50/90}$, 1/1 µg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), linezolid ($MIC_{50/90}$, 1/2 µg/mL), and tigecycline ($MIC_{50/90}$, 0.12/0.25 µg/mL) exhibited excellent anti-*S. aureus* activity overall (0.0-0.1% resistance) and were most like ceftaroline (Table 2).

Table 1. Susceptibility rates to ceftaroline and comparator agents by site of infection

	% Susceptible (MSSA / MRSA)				
Antimicrobial agent	BSI[a]	ABSSSI[a]	RTI[a]	Other sites	All
Ceftaroline	100.0 / 95.2	100.0 / 98.5	100.0 / 94.2	100.0 / 95.5	100.0 / 96.5
Erythromycin	69.1 / 7.0	63.6 / 10.3	63.1 / 6.4	64.6 / 7.9	65.7 / 8.4
Clindamycin	94.2 / 60.0	95.2 / 79.4	92.0 / 54.0	92.2 / 61.7	94.1 / 67.7
Levofloxacin	88.8 / 20.6	88.8 / 42.2	88.4 / 16.2	87.6 / 26.5	88.7 / 29.7
Linezolid	100.0 / 99.9	100.0 / 99.9	100.0 / 99.4	100.0 / 100.0	100.0 / 99.8
Tetracycline	96.3 / 95.3	95.5 / 94.5	97.5 / 93.2	94.9 / 92.7	96.1 / 94.8
Tigecycline	100.0 / 99.9	100.0 / 100.0	100.0 / 100.0	100.0 / 100.0	100.0 / >99.9
Trimethoprim/sulfamethoxazole	98.2 / 97.7	99.2 / 98.6	98.7 / 97.4	98.8 / 97.5	98.7 / 98.0
Vancomycin	100.0 / 100.0	100.0 / 100.0	100.0 / 100.0	100.0 / 100.0	100.0 / 100.0
Daptomycin	100.0 / 99.5	100.0 / 100.0	100.0 / 100.0	100.0 / 100.0	100.0 / 99.8
No. of strains	2055 / 1868	1963 / 2422	839 / 879	257 / 355	5114 / 5524
MRSA rate (%)	47.7	55.2	51.2	58.0	51.9

a. Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; BSI, bloodstream infection; ABSSSI, acute bacterial skin and skin structure infection; RTI, respiratory tract infection

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against 10,638 isolates of *Staphylococcus aureus* (USA, 2008-2011)

	MIC (µg/mL)			CLSI[a]	EUCAST[a]
Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	Range	%S / %R	%S / %R
All isolates (10,638)					
Ceftaroline	0.5	1	≤0.008 – 2	98.2 / - (98.2 / 0.0)[b]	- / -
Ceftriaxone	>8	>8	≤0.25 – >8	46.6 / 51.9	48.1 / 51.9
Oxacillin	>2	>2	≤0.25 – >2	48.1 / 51.9	48.1 / 51.9
Erythromycin	>2	>2	≤0.25 – >2	36.0 / 62.9	36.2 / 63.4
Clindamycin	≤0.25	>2	≤0.25 – >2	80.4 / 19.4	80.0 / 19.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	58.1 / 40.8	58.1 / 40.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.3 / 1.7	98.3 / 1.6
Tetracycline	≤2	≤2	≤2 – >8	95.4 / 4.0	94.2 / 5.3
Tigecycline[c]	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	≤0.12 – >8	99.9 / 0.1	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	99.9 / -	99.9 / 0.1
MSSA (5,114)					
Ceftaroline	0.25	0.25	≤0.008 – 1	100.0 / - (100.0 / 0.0)[b]	- / -
Ceftriaxone	4	4	≤0.06 – >8	96.3 / 0.3	100.0 / 0.0
Oxacillin	0.5	0.5	≤0.25 – 2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	65.7 / 32.7	66.1 / 33.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	94.1 / 5.7	93.7 / 5.9
Levofloxacin	≤0.5	4	≤0.5 – >4	88.7 / 10.6	88.7 / 10.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.7 / 1.3	98.7 / 1.3
Tetracycline	≤2	≤2	≤2 – >8	96.1 / 3.1	95.5 / 4.3
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Linezolid	1	2	≤0.12 – 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
MRSA (5,524)					
Ceftaroline	0.5	1	0.12 – 2	96.5 / - (96.5 / 0.0)[b]	- / -
Erythromycin	>2	>2	≤0.25 – >2	8.4 / 90.9	8.5 / 91.2
Clindamycin	≤0.25	>2	≤0.25 – >2	67.7 / 32.1	67.2 / 32.3
Levofloxacin	4	>4	≤0.5 – >4	29.7 / 68.7	29.7 / 68.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.0 / 2.0	98.0 / 1.9
Tetracycline	≤2	≤2	≤2 – >8	94.8 / 4.8	93.0 / 6.2
Tigecycline[c]	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	≤0.12 – >8	99.8 / 0.2	99.8 / 0.2
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 4	99.8 / -	99.8 / 0.2

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-lactam susceptibility should be directed by the oxacillin test results. USA-FDA breakpoints were applied when available [Teflaro Product Insert, 2012].
b. Rates in parenthesis use CLSI approved criteria for 2013 publication (June 2012).
c. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2011].

Conclusions

- Our results document the potent *in vitro* activity of ceftaroline when tested against a large collection of contemporary (2008-2011) *S. aureus* isolates from USA hospitals
- Ceftaroline activity against *S. aureus* was comparable to those of daptomycin, linezolid, tigecycline and vancomycin
- Although the activity of some antimicrobials varied according to infection site, ceftaroline exhibited consistent *in vitro* activity against MSSA and MRSA, independent of site of infection.

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