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Comparative Evaluation of the Antimicrobial Susceptibility Patterns of Community- and Hospital-Acquired Methicillin-Resistant *S. aureus* from United States Hospitals by Site of Infection: Results from the Ceftaroline Surveillance Program AWARE (2012-2014)

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Abstract

Background:
MRSA has been increasingly identified as a cause of community-onset infections. Although the initial community-acquired (CA)-MRSA strains were more susceptible (S) to antimicrobial agents compared to traditional hospital-acquired (HA)-MRSA strains, CA-MRSA variants with multidrug resistance patterns have been increasingly reported.

Methods:
Among 8,437 MRSA strains collected through the ceftaroline (CPT) AWARE program (2012-2014), 7,116 and 1,321 were reported as CA- and HA-MRSA, respectively. Organisms were collected from 145 medical centers in the United States and tested for S against CPT and comparators by the broth microdilution method.

Results:
CA-/HA-MRSA were isolated mainly from patients with skin and skin structure infections (SSSI; 68.4/27.0%), pneumonia (13.7/49.0%) and bacteremia (10.0/17.7%). Overall, S rates were generally lower among HA-MRSA compared to CA-MRSA strains (Table), especially for clindamycin (CLI; 61.4 vs. 76.6%) and levofloxacin (LEV; 21.4 vs. 35.5%). CPT was active against 98.0% of CA-MRSA and 94.3% of HA-MRSA ($MIC_{50/90}$, 1 µg/mL for both) overall, with little variation among infection type subsets. Among SSSI and bacteremia isolates, S rates for CLI and LEV were lower among HA-MRSA compared to CA-MRSA. Further, S rates among isolates from pneumonia were generally lower compared to isolates from SSSI and bacteremia. Tetracycline (TET) and trimethoprim/sulfamethoxazole (T/S) exhibited good in vitro activity against CA- and HA-MRSA from all infection types. Erythromycin (ERY) S was generally low.

Conclusion:
CPT exhibited potent in vitro activity against CA- and HA-MRSA isolates independent of infection type. S rates were generally lower among HA-MRSA and varied according to the type of infection.

Site of infection no. (CA-/HA-MRSA)	% Susceptible (CA-MRSA / HA-MRSA)					
	CPT	CLI	ERY	LEV	TET	T/S
All (7116/1321)	98.0/94.3	76.6/61.4	10.6/9.8	35.5/21.4	95.3/96.0	97.6/97.7
SSSI (4870/356)	98.7/95.5	82.5/69.7	11.0/9.3	40.9/24.4	95.6/96.3	98.2/98.3
Pneumonia (974/647)	97.1/95.2	57.9/55.7	7.7/9.3	18.4/19.8	94.5/96.4	96.4/97.7
Bacteremia (709/234)	94.9/91.9	68.6/62.4	13.8/11.1	26.0/18.8	94.8/94.8	97.5/96.6
Other (563/84)	97.5/89.3	68.6/67.9	8.9/13.1	30.2/28.6	95.0/94.0	98.4/97.6

Introduction

The terms community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and hospital-acquired MRSA (HA-MRSA) have been used to call attention both to the genotypic differences of certain MRSA isolates as well as to the epidemiological and clinical features of the infections that they cause. These definitions are based on various factors, including (i) the setting in which the MRSA infection begins, (ii) current or prior patient exposure to health care settings, (iii) genetic characteristics and antimicrobial susceptibility profiles of the causative MRSA isolate; and (iv) the clinical syndrome manifested by the patient. However, a simpler temporal definition is often used to designate CA-MRSA. By this criterion, all infections occurring among outpatients or among inpatients with a MRSA isolate obtained earlier than 48 hours after hospitalization would be considered CA-MRSA.

Although the initial CA-MRSA strains were more susceptible to antimicrobial agents compared to HA-MRSA strains, variants of traditional CA-MRSA clones with multidrug resistance (MDR) patterns have more recently been identified. Furthermore, CA-MRSA clones have infiltrated hospitals and are rapidly replacing the traditional HA-MRSA clones. In summary, major changes in the epidemiology and susceptibility patterns of *S. aureus* have been observed in recent years. Since initial antimicrobial therapy is usually selected empirically, results of large multicenter surveillance programs, such as the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) program, are valuable to guide appropriate selection of antimicrobial treatment.

Ceftaroline fosamil, the prodrug of ceftaroline, is a broad-spectrum parenteral cephalosporin which was approved by the United States (USA) Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI), including those caused by MRSA, and community-acquired bacterial pneumonia (CABP). In the present study, we evaluated the in vitro activity of ceftaroline and comparator agents tested against a large collection of CA- and HA-MRSA from hospitals in the USA.

Methods

Organism Collection: Bacterial isolates were collected as part of the AWARE program, which was designed to establish the baseline and track post-approval activity of ceftaroline and comparator agents in the USA.

- Participant centers submit clinical bacterial organisms (one per infection episode) that are consecutively collected according to a common protocol, which established the number of isolates for each bacterial species/genus, the target infection types and the period of time the isolates should be collected.
- For this investigation, a MRSA isolate obtained from an outpatient or earlier than 48 hours after hospitalization was considered CA-MRSA; whereas MRSA isolates obtained later than 48 hours after hospitalization were considered HA-MRSA.
- These organisms were collected in 2012-2014 from 145 medical centers in the US. Isolates identified at the participant medical centers were sent to the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing. Species identification was confirmed at the coordinator laboratory by MALDI-TOF using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA), where necessary.

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-A10, and susceptibility interpretations were based on CLSI (M100-S25) and EUCAST (2015) breakpoint criteria. Validated MIC panels were manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). Organisms were tested in cation-adjusted Mueller-Hinton broth (Thermo Fisher Scientific). Ceftaroline and comparator agents were tested simultaneously using the same bacterial inoculum and testing reagents. Concurrent testing of quality control (QC) strains assured proper test conditions. All QC results were within CLSI published ranges.

Results

- Among 8,437 MRSA strains collected, 7,116 were categorized as CA-MRSA and 1,321 were categorized as HA-MRSA.
- CA-MRSA isolates were most frequently collected from patients with skin and skin structure infections (SSSI; 68.4%), followed by pneumonia (13.7%) and bloodstream infections (BSI; 10.0%). In contrast, pneumonia was the most common reported site of infection (49.0% of isolates) among HA-MRSA isolates, followed by SSSI (27.0%) and BSI (17.7%; Table 1).
- Ceftaroline was active against 98.0% of CA-MRSA and 94.3% of HA-MRSA ($MIC_{50/90}$, 1 µg/mL for both) overall, with little variation among infection type subsets (Tables 1 and 2).
- Ceftaroline MIC distributions were also very similar among CA-MRSA and HA-MRSA, with MIC values only slightly lower among CA-MRSA (48.6% inhibited at ≤0.5 µg/mL) compared to HA-MRSA (38.6% inhibited at ≤0.5 µg/mL; Table 1 and Figure 1).
- Susceptibility rates were generally lower among HA-MRSA compared to CA-MRSA strains, especially for clindamycin (61.4 vs. 76.6%) and levofloxacin (21.4 vs. 35.5%; Table 2 and Figure 2).
- Susceptibility rates among isolates from pneumonia were lower compared to isolates from SSSI and bacteremia (Table 2 and Figure 3).
- CA- and HA-MRSA isolates exhibited high (>99.0%) susceptibility rates for daptomycin, linezolid, tigecycline and vancomycin; and were independent of the infection type subset (data not shown).
- Tetracycline (94.5-96.4% susceptible) and trimethoprim/sulfamethoxazole (96.4-98.4% susceptible) exhibited potent in vitro activity against CA- and HA-MRSA from all infection types; whereas erythromycin susceptibility rates were generally low (7.7-13.8% susceptible; Table 2 and Figure 3).

Table 1. Summary of ceftaroline activity against CA- and HA-MRSA stratified by site of infection (USA, 2012-2014).

Organism/ Infection type (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline MIC (µg/mL) of:						MIC (µg/mL)	
	0.06	0.12	0.25	0.5	1	2	50%	90%
CA-MRSA (7,116)	1 (<0.1)	5 (0.1)	91 (1.4)	3350 (48.4)	3526 (98.0)	143 (100.0)	1	1
bloodstream infection (709)	1 (0.1)	0 (0.1)	11 (1.7)	305 (44.7)	356 (94.9)	36 (100.0)	1	1
pneumonia (974)	--	1 (0.1)	12 (1.3)	406 (43.0)	527 (97.1)	28 (100.0)	1	1
SSSI[a] (4,870)	--	4 (0.1)	62 (1.4)	2393 (50.5)	2346 (98.7)	65 (100.0)	0.5	1
Other sites (563)	--	--	6 (1.1)	246 (44.8)	297 (97.5)	14 (100.0)	1	1
HA-MRSA (1,321)	--	--	14 (1.1)	496 (38.6)	736 (94.3)	75 (100.0)	1	1
bloodstream infection (234)	--	--	2 (0.9)	79 (34.6)	134 (91.9)	19 (100.0)	1	1
pneumonia (647)	--	--	8 (1.2)	231 (36.9)	377 (95.2)	31 (100.0)	1	1
SSSI[a] (356)	--	--	4 (1.1)	148 (42.7)	188 (95.5)	16 (100.0)	1	1
Other sites (84)	--	--	--	38 (45.2)	37 (89.3)	9 (100.0)	1	2

a. SSSI= skin and skin structure infections

Table 2. Antimicrobial susceptibility rates for CA-MRSA and HA-MRSA stratified by infection type.

Antimicrobial agent/ organism[a]	% Susceptible [CLSI criteria]				
	BSI	Pneumonia	SSSI	Others	All
Ceftaroline					
CA-MRSA	94.9	97.1	98.7	97.5	98.0
HA-MRSA	91.9	95.2	95.5	89.3	94.3
Clindamycin					
CA-MRSA	68.6	57.9	82.5	68.6	76.6
HA-MRSA	62.4	55.7	69.7	67.9	61.4
Erythromycin					
CA-MRSA	13.8	7.7	11.0	8.9	10.6
HA-MRSA	11.1	9.3	9.3	13.1	9.8
Levofloxacin					
CA-MRSA	26.0	18.4	40.9	30.2	35.5
HA-MRSA	18.8	19.8	24.4	28.6	21.4
Tetracycline					
CA-MRSA	94.8	94.5	95.6	95.0	95.3
HA-MRSA	94.8	96.4	96.3	94.0	96.0
TMP/SMX					
CA-MRSA	97.5	96.4	98.2	98.4	97.9
HA-MRSA	96.6	97.7	98.3	97.6	97.7

a. Abbreviations: BSI= bloodstream infections, SSSI= skin and skin structure infections and TMP/SMX = trimethoprim/sulfamethoxazole.

Figure 1. Ceftaroline MIC distributions for CA- and HA-MRSA strains from USA hospitals.

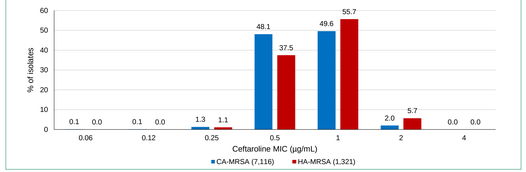


Figure 2. Antimicrobial susceptibility rates of CA- and HA-MRSA from USA hospitals.

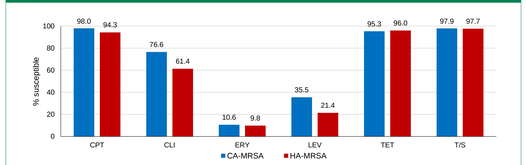
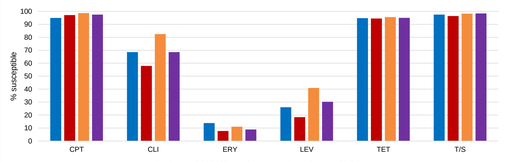


Figure 3. Antimicrobial susceptibility rates of CA-MRSA strains stratified by site of infection.



Abbreviations: CPT= ceftaroline; CLI= clindamycin; ERY= erythromycin; LEV= levofloxacin; TET= tetracycline; T/S= trimethoprim/sulfamethoxazole; BSI= bloodstream infections, and SSSI= skin and skin structure infections

Conclusions

- Ceftaroline exhibited potent in vitro activity against CA- and HA-MRSA isolates (MIC_{90}, 1 µg/mL) independent of infection type.
- Susceptibility rates for some comparator agents, especially clindamycin and levofloxacin, were lower among HA-MRSA and varied according to the type of infection.

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