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Antimicrobial susceptibility patterns of community- and hospital-acquired methicillin-resistant *Staphylococcus aureus* from United States Hospitals: results from the AWARE Ceftaroline Surveillance Program (2012–2014)☆

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ABSTRACT

Among 8437 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates collected from 143 medical centers in the United States (2012–2014), 7116 and 1321 were reported as community-acquired (CA) and hospital-acquired (HA) MRSA, respectively. CA−/HA-MRSA were most often isolated from patients with skin and skin structure infections (SSSI; 68.4/26.9%), pneumonia (13.7/49.0%) and bacteremia (10.0/17.7%). Overall, susceptibility rates were generally lower among HA-MRSA compared to CA-MRSA strains, especially for clindamycin (44.6 vs. 66.1%) and levofloxacin (21.4 vs. 35.5%). Also, susceptibility rates were lower for these two compounds among isolates from pneumonia compared to SSSI and bacteremia. Ceftaroline was broadly active against 98.0% of CA-MRSA and 94.3% of HA-MRSA ($MIC_{50/90}$, 1 μg/mL for both; no resistant isolate) overall, with little variation among infection type subsets.

1. Introduction

The terms community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and hospital-acquired MRSA (HA-MRSA) have been used to refer both to the genotypic differences of certain MRSA isolates as well as to the epidemiological and clinical features of the infections that they cause (David and Daum, 2010). 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 (v) the clinical syndrome manifested by the patient (Chua et al., 2011). 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 (David and Daum, 2010).

Although the CA-MRSA strains initially described 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 (Diep et al., 2008). Furthermore, CA-MRSA clones have infiltrated hospitals and are rapidly replacing traditional HA-MRSA clones (Popovich et al., 2008). 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 (Sader et al., 2015b).

Ceftaroline fosamil, the prodrug of ceftaroline, is a broad-spectrum parenteral cephalosporin which has demonstrated potent binding affinity for multiple PBPs in *S. aureus* (including the mutated PBP2a form, which confers methicillin resistance) and *S. pneumoniae* (including PBP-1A, −2B and -2X, alterations of which are important in conferring penicillin resistance). The affinity of ceftaroline for PBP2a (half maximal inhibitory concentration [IC50], 0.01–1 μg/mL) is higher than that of penicillin G (2 to 64 μg/mL) or ceftriaxone (0.25 to >128 μg/mL) (Frampton, 2013). Ceftaroline 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) (Lodise and Low, 2012; TEFLARO®, 2015).

The Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) Program provides contemporary and longitudinal information on the activity of this agent against relevant pathogens. Continued monitoring is necessary to assure that the compound retain activity against indicated organisms, and previous reports from the AWARE program have provided analyses of ceftaroline activity against bacterial isolates recovered from indicated sites of infections, specific patient populations, and selected organism groups and resistant subsets, as well as yearly variation on its in vitro activity and potency (Sader

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et al., 2013, 2014, 2015a, 2016). 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 across the USA.

2. Materials and methods

2.1. 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 by infection type according to a common protocol, which established the number of isolates for each bacterial genus/species, the target infection types and the period of time the isolates should be collected.
- For this investigation, MRSA isolates from all infection types were categorized as CA- or HA-MRSA. 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 (David and Daum, 2010).
- These organisms were collected in 2012–2014 from 143 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 site by MALDI-TOF-MS using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA), where necessary.

2.2. Susceptibility testing

Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standard Institute (CLSI) M07-A10, and susceptibility interpretations were based on CLSI (M100-S26) and/or US-FDA breakpoint criteria (CLSI, 2015, 2016; EUCAST, 2016; TEFLARO®, 2015; Tygacil, 2014). 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 (CLSI, 2016).

2.3. Statistical analysis

The χ^2 test was applied to find significant differences between two groups. Statistical analyses were performed with the Epi Info™ 7 statistical package (US Centers for Disease Control and Prevention, Atlanta, GA). A *P*-value of <0.05 was considered statistically significant.

3. Results

Among 8437 MRSA strains collected by the AWARE program during the period of this investigation (2012–2014), 7116 were categorized as CA-MRSA and 1321 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 infection (BSI; 10.0%). In contrast, pneumonia was the most common infection type (49.0% of isolates) reported among HA-MRSA isolates, followed by SSSI (26.9%) 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 subsets) overall. Ceftaroline susceptibility rates were slightly lower among CA-MRSA strains from bloodstream infections (94.9%) compared to the other infection type subsets (97.1–98.7%; $P \leq 0.002$), and very similar when isolates from pneumonia were compared to SSSI (Tables 1 and 2). Ceftaroline MIC distributions were also very similar among CA-MRSA and HA-MRSA, with MIC values slightly lower ($P < 0.001$) among CA-MRSA (48.4% inhibited at ≤0.5 μg/mL) compared to HA-MRSA (38.6% inhibited at ≤0.5 μg/mL; Table 1). Interestingly, ceftaroline susceptibility rates for CA-MRSA were higher among isolates from the pediatric population (≤17 years old; 99.5%) compared to the adult population (≥18 years old; 97.7%); whereas for the HA-MRSA ceftaroline susceptibility rates were similar among pediatric (95.2%) and adult (94.3%) populations (data not shown).

Susceptibility rates were generally lower for non-β-lactam agents among HA-MRSA compared to CA-MRSA strains, especially for clindamycin (44.6 vs. 66.1%; $P < 0.001$) and levofloxacin (21.4 vs. 35.5%; $P < 0.001$; Table 2). Furthermore, susceptibility rates among isolates from pneumonia generally were lower compared to isolates from SSSI and bacteremia (Table 2). Among isolates from SSSI, clindamycin susceptibility was 74.6% for CA-MRSA, with 17.4% of isolates showing constitutive resistance and 7.9% having inducible resistance, whereas only 55.9% of HA-MRSA were susceptible to clindamycin (30.3% constitutive and 13.8% inducible resistance; Table 2).

Both CA- and HA-MRSA isolates exhibited high (>99.0%) susceptibility rates for daptomycin, linezolid, tigecycline and vancomycin; these high rates of susceptibility were independent of the infection type subset (Table 2). Tetracycline (94.0–96.4% susceptible) and trimethoprim/sulfamethoxazole (96.4–98.4% susceptible) also demonstrated 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).

Ceftaroline was also active against isolates that exhibited decreased susceptibility to daptomycin (n = 9), linezolid (n = 3) or vancomycin (139 isolates with vancomycin MIC of 2 μg/mL and one isolate with vancomycin MIC of 4 μg/mL). Isolates with decreased susceptibility to

Table 1
Summary of ceftaroline activity tested against CA- and HA-MRSA stratified by infection type (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 (7116)	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] (4870)	--	4 (0.1)	62 (1.4)	2393 (50.5)	2346 (98.7)	65 (100.0)	0.5	1
Other infection types (563)	--	--	6 (1.1)	246 (44.8)	297 (97.5)	14 (100.0)	1	1
HA-MRSA (1321)	--	--	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 infection types (84)	--	--	--	38 (45.2)	37 (89.3)	9 (100.0)	1	2

[a] SSSI = skin and skin structure infections.