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Profile of *Staphylococcus aureus* Isolated From United States (USA) Pediatric Patients During the 2009 Ceftaroline AWARE Surveillance Program

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Amended Abstract

Background: Ceftaroline, the active form of ceftaroline fosamil, is a new broad-spectrum cephalosporin active against MRSA. Ceftaroline fosamil was recently approved in the USA for treatment of adult patients with ABSSSI and CABP and is under review in Europe. This study compared *S. aureus* (SA) characteristics from adult and pediatric patients from the 2009 AWARE Surveillance Program.

Methods: Consecutive SA isolates (n = 2311) were collected from 52 sites representing the 9 USA Census regions. Isolates were stratified for analysis by patient age in years: ≤ 2 (n = 195), 3 - 5 (n = 52), 6 - 14 (n = 122), 15 - 17 (n = 47), 18 - 64 (n = 1232), ≥ 65 (n = 663). MICs were determined using CLSI methods.

Results: MRSA rates varied little across age groups, ranging from 42.3% (3 - 5 years) to 53.2% (15 - 17 years). Data on nosocomial or community-acquired status were available for 1511 of 2311 SA. Within this subset, the very young (age 0 - 2 years; 19%) and patients > 18 years (19.3%) were nearly 3x more likely to have a nosocomial SA than children and adolescents (3 - 17 years; 7.2%). Isolates from the very young and adults were 50.4% MDR (resistant [R] to ≥ 2 classes). Isolates from patients aged 3 - 17 were 38.5% MDR.

A correlation between patient age and levofloxacin (LEV)-R was noted. In patients from the following age groups (in years), LEV-R rates were ≤ 5, 19%; 6 - 14, 27%; 15 - 17, 29.8%; 18 - 64, 37.9%; and ≥ 65, 52.6%. Five linezolid-R (MIC ≥ 8 µg/mL) SA were recovered from patients aged 14, 17, 52, 53, and 68 years. Ceftaroline retained consistent activity against isolates with varying R phenotypes. Infection source and patient age also had no effect on ceftaroline MIC. The ceftaroline MIC_{90} results for the isolates evaluated in this study were 1 µg/mL for each analysis group.

Conclusion: Observed R patterns suggest differences in profiles of SA from USA pediatric and adult patients that may be attributable to frequency of hospital exposure or antibiotic prescribing patterns. Ceftaroline was consistently active in vitro independent of patient age groups. Further evaluation of ceftaroline in pediatric patients appears warranted.

Introduction

Cephalosporins have traditionally been considered amongst the best tolerated and most effective class of antibacterials. The increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has limited the use of cephalosporins in the management of certain severe and potentially life-threatening infections in many regions of the world. Ceftaroline, the active form of ceftaroline fosamil, is a new broad-spectrum cephalosporin with activity against MRSA. Like other β-lactams, ceftaroline binds to penicillin-binding proteins (PBPs) and interferes with new bacterial cell wall synthesis. Unlike other cephalosporins, ceftaroline has a strong affinity for PBP2a, which is responsible for resistance to other β-lactams in SA. Ceftaroline fosamil was recently approved by the United States Food and Drug Administration and is under review in Europe for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia in patients over 18 years of age.

The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance program has been initiated to monitor the susceptibility of ceftaroline and comparator agents against contemporary clinical isolates from around the world. The data for US SA isolates from the 2009 study were analyzed to determine if there were differences in susceptibility and isolate demographics across various patient age groups. Percentages of isolates that were MRSA and nosocomial or community-acquired in origin, resistance rates, and isolate antibiograms were compared.

Methods

Consecutive SA isolates (n = 2311) were collected from 52 sites representing the 9 USA Census Bureau regions. Only 1 isolate per patient was collected. Isolates were stratified for analysis by patient age in years: ≤ 2 (n = 195), 3 - 5 (n = 52), 6 - 14 (n = 122), 15 - 17 (n = 47), 18 - 64 (n = 1232), ≥ 65 (n = 663). MICs were determined using the CLSI method as outlined in document M7-A8 (2009) and using validated broth microdilution dry-form panels acquired from TREK Diagnostics (Cleveland, OH). Susceptibility interpretive criteria were as outlined in CLSI M100-S20 (2010) for all comparator agents. US FDA-approved MIC breakpoints (Teflaro® package insert) were used in lieu of CLSI breakpoints when the latter were unavailable (ie, for ceftaroline). Data were analyzed by patient age to identify trends in antibiotic resistance. In addition, other factors such as the source of the infection or whether the infection was nosocomial or community-acquired (determined by date of onset of infection compared to date of hospitalization) were evaluated.

Results

The number of isolates by body site is shown in Table 1. MICs for ceftaroline and comparator agents by age group are shown in Table 2.

- MRSA rates were consistent across all age groups. Only 42.3% of SA isolated from 52 patients aged 3 - 5 years were MRSA, whereas 53.3% of 47 isolates from patients aged 15 - 17 years were methicillin-resistant (Table 1 and Figure 1)
- Information on whether the isolates were nosocomial or community-acquired was available for 1511 of 2311 patients. Within this subset, 19% of isolates from patients aged 0 - 2 and 19.3% of isolates from patients > 18 years were nosocomial. These patients were nearly 3 times more likely to be infected with a nosocomial SA than children and adolescents (3 - 17 years; 7.2% of isolates) (Figure 2)
- Approximately half of the 1053 isolates (50.4%) collected from the very young and adults were multidrug-resistant (MDR; resistant to ≥ 2 classes of antibiotics). Only 38.5% of the 85 isolates from patients aged 3 - 17 were MDR (Figure 3)
- A correlation between increasing patient age and levofloxacin resistance rates was also noted. In patients from the following age groups (in years), levofloxacin resistance rates were ≤ 5, 19%; 6 - 14, 27.0%; 15 - 17, 29.8%; 18 - 64, 37.9%, and ≥ 65, 52.6% (Figure 4)
- No correlation was noted between patient age and isolate susceptibility to erythromycin or clindamycin. Erythromycin resistance rates were relatively high and ranged from 51.6% for patients aged 6 - 14 to 70.2% for patients aged 15 - 17. Clindamycin resistance was less frequently encountered, ranging from 5.7% for patients 6 - 14 years old to 28.1% for patients aged ≥ 65 years (Table 2)
- Resistance to trimethoprim-sulfamethoxazole (SXT) occurred in approximately 2% of isolates from patients > 15 years old. SXT resistance was not observed in younger patients. No SA resistant to daptomycin was recovered in this study (Table 2)
- Five linezolid-resistant (MIC ≥ 8 µg/mL) SA were recovered in this surveillance study from patients aged 14, 17, 52, 53, and 68 years. Ceftaroline MICs ranged from 0.25 - 2 µg/mL against these isolates (data not shown)
- Ceftaroline was consistently active across all age groups with 98.4% of isolates susceptible according to the US FDA breakpoints of 1 µg/mL.

Table 1. Numbers of *Staphylococcus aureus* Isolates Recovered by Infection Body Site

Body site	0 - 2 years (N = 195)	3 - 5 years (N = 52)	6 - 14 years (N = 122)	15 - 17 years (N = 47)	18 - 64 years (N = 1232)	≥ 65 years (N = 663)
Bloodstream	86	19	57	10	725	404
Respiratory tract	29	8	22	15	182	126
Skin/skin structure	75	21	42	20	284	112
Urinary tract	1	2	-	1	13	8
Other	4	2	1	1	28	13

Table 2. MIC_{90} Values of Ceftaroline and Comparator Agents Against *Staphylococcus aureus* From the 2009 AWARE Surveillance Program

Antimicrobial agent	MIC_{90} (µg/mL; % susceptible) 0 - 2 years (N = 195)	3 - 5 years (N = 52)	6 - 14 years (N = 122)	15 - 17 years (N = 47)	18 - 64 years (N = 1232)	≥ 65 years (N = 663)
Ceftaroline	1 (99.0)	1 (98.1)	1 (100)	1 (97.9)	1 (98.8)	1 (97.6)
Oxacillin	> 2 (49.7)	> 2 (57.7)	> 2 (57.4)	> 2 (46.8)	> 2 (53.7)	> 2 (50.1)
Ampicillin	> 16 (0.0)	> 16 (0.0)	> 32 (0.0)	> 16 (0.0)	> 16 (0.0)	> 16 (0.0)
Ceftriaxone	> 32 (48.2)	> 32 (55.8)	> 32 (54.9)	> 32 (46.8)	> 32 (51.8)	> 32 (48.3)
Clindamycin	≤ 0.25 (93.3)	> 2 (86.5)	≤ 0.25 (94.3)	> 2 (78.7)	> 2 (81.5)	> 2 (71.8)
Daptomycin	0.5 (100)	0.5 (100)	0.5 (100)	0.5 (100)	0.5 (100)	0.5 (100)
Erythromycin	> 2 (37.9)	> 2 (44.2)	> 2 (48.4)	> 2 (27.7)	> 2 (40.7)	> 2 (38.0)
Levofloxacin	4 (76.4)	> 4 (80.8)	> 4 (71.3)	> 4 (68.1)	> 4 (61.1)	> 4 (46.8)
Linezolid	2 (100)	2 (100)	2 (99.2)	2 (97.9)	2 (99.8)	2 (99.8)
Tigecycline	0.25 (100)	0.25 (100)	0.25 (100)	0.25 (100)	0.25 (99.9)	0.25 (100)
SXT	≤ 0.5 (100)	≤ 0.5 (100)	≤ 0.5 (100)	≤ 0.5 (97.9)	≤ 0.5 (98.3)	≤ 0.5 (98.0)
Vancomycin	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)

Abbreviations: AWARE = Assessing Worldwide Antimicrobial REsistance (AWARE) Surveillance program; MIC_{90} = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; SXT = trimethoprim-sulfamethoxazole.

Figure 1. MRSA Rates by Patient Age Group

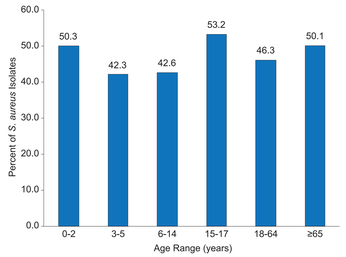
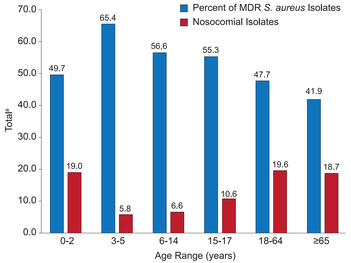


Figure 2. Occurrence of Community-acquired vs. Nosocomial *Staphylococcus aureus*



*The values shown above represent the percent of all *S. aureus* isolates (n = 2,311) that were either nosocomial or community-acquired in origin. The remaining isolates from each age group are of unknown origin (values not shown).

Figure 3. Frequency of Multidrug-resistant *Staphylococcus aureus*

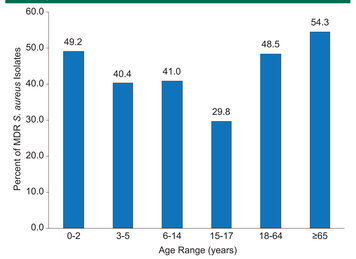
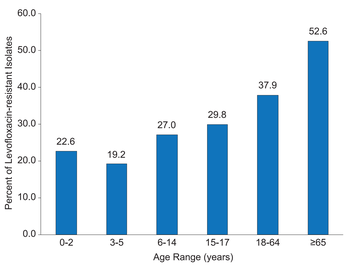


Figure 4. Frequency of Levofloxacin-resistant *Staphylococcus aureus*



Conclusions

- The data in this study suggest that MRSA isolates are recovered in approximately equal percentages from all patient age groups
- Resistance trends for most agents appeared to correlate with the frequencies of use in a given patient age group. For example, levofloxacin resistance appeared to increase with age, which correlates with the infrequent use of this drug in pediatric patients
- More frequent exposure to hospitals amongst infants and adults than adolescents may explain the more frequent isolation of nosocomial and multidrug-resistant SA in these age groups
- As expected, resistance to vancomcyin, daptomycin, linezolid, and SXT was uncommon amongst the SA in this study
- Ceftaroline maintained consistent activity against the SA isolates evaluated as part of the 2009 AWARE program, irrespective of patient age or infection source. The ceftaroline MIC_{90}s for the isolates evaluated in this study were 1 µg/mL for all analysis groups. These data support the further evaluation of ceftaroline for treatment of infections caused by SA, including those in pediatric patients.

References

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