Reduced Ceftaroline Susceptibility Among Invasive MRSA Isolates at a Tertiary Children's Hospital

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ABSTRACT

Background: The emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in the late 1990s-early 2000s complicated the empiric management of suspected staphylococcal infection in children. Rising clindamycin resistance rates in many communities adds further to management challenges. Ceftaroline, an anti-MRSA cephalosporin, represents an attractive therapy option. Little data are available, however, regarding the frequency of reduced susceptibility (RS) to ceftaroline among MRSA isolates from a general pediatric population.
Methods: Isolates were selected from an ongoing *S. aureus* surveillance study at Texas Children's Hospital. Invasive MRSA isolates from 2015-2018 were included. Isolates were initially screened for ceftaroline RS with E-test; all isolates with a ceftaroline E-test MIC ≥ 1.5µg/ml underwent ceftaroline broth dilution. Ceftaroline RS was regarded as an MIC ≥ 2 µg/ml; full ceftaroline resistance was defined as an MIC ≥ 8 µg/ml. Accessory gene regulator (*agr*) groups were characterized by PCR.
Results: 201 viable isolates were included. The ceftaroline MIC_{50} and MIC_{90} were 0.5 and 1 µg/ml, respectively. Six isolates had MIC ≥ 2 µg/ml (2.9%) with two having MIC ≥ 8 µg/ml (0.9%). All ceftaroline RS isolates were from healthcare associated infections. Ceftaroline RS isolates were more often associated with clindamycin-resistance and *agr* group II. Infections with ceftaroline RS were associated with central venous lines, recent ICU admission, preceding antibiotic exposure (specifically cephalosporins) and prior MRSA infection. One subject with MRSA CLABSI had a ceftaroline susceptible MRSA infection followed < 1 month later by a ceftaroline resistant infection (MIC =32 µg/ml); the isolates were identical by PFGE. Only 3 subjects had previously received ceftaroline, none of which subsequently developed a ceftaroline RS isolate.
Conclusions: Ceftaroline RS occurs in 2.9% of invasive MRSA isolates in children and is most prominent among healthcare-associated infections. These isolates were associated with clindamycin resistance and *agr* group II. While ceftaroline RS is rare among invasive MRSA infections, the lack of preceding ceftaroline exposure is concerning and warrants careful surveillance.

AIMS

1. **To define the frequency of reduced susceptibility (RS) to ceftaroline among invasive MRSA infections in children.**
2. **To describe the microbiologic and clinical features of MRSA isolates with ceftaroline RS.**

INTRODUCTION

- Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has represented a major child health problem since the late 1990s-early 2000s
- Vancomycin is generally regarded as the drug of choice for serious MRSA in children but carries with it a risk of nephrotoxicity.
- Clindamycin is a commonly used for non-life threatening MRSA infections in children, however, rising rates of resistance in many communities creates challenges for empiric therapy.
- Ceftaroline, a novel cephalosporin with activity against MRSA is an attractive alternative.
- Resistance and/or reduced susceptibility (RS) to ceftaroline has rarely been reported, most commonly in isolates from the cystic fibrosis population.
- Little data are available regarding the prevalence of or clinical risk factors for ceftaroline RS in a general pediatric population.

PATIENTS AND METHODS

Patients/Isolates. Isolates were selected from an ongoing *S. aureus* surveillance study at Texas Children's Hospital. All invasive MRSA isolates from 2015-2018 were included.
Microbiology. All isolates were initially screened with ceftaroline E-test. Any isolate with a ceftaroline E-test MIC ≥ 1.5µg/ml underwent ceftaroline broth dilution..

PATIENTS AND METHODS

Definitions. Susceptibility breakpoints for ceftaroline are defined by CLSI and for this study as the following:

CLSI Definition	S	SDD	R
Study Definition	Susceptible	Reduced Susceptibility	
Ceftaroline MIC (µg/ml)	≤ 1	2-4	≥8

Molecular Studies. All isolates underwent PCR for *agr* group and the presence of *pvl*. Select isolates were characterized by PFGE.
Clinical Data: Medical records corresponding to each isolate were reviewed. The electronic medical record was reviewed for 90 days prior to the infection of interest for history of hospitalization, ICU admission, antibiotic use, MRSA infection and surgery
Statistical Analysis. Continuous variables were examined with Kruskal-Wallis and Mann-Whitney U tests, dichotomous variables with χ^2 and Fisher's exact tests with the use of STATA ver 12.

RESULTS

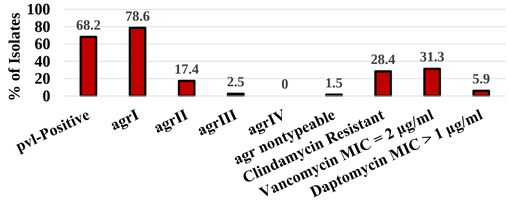
- During the study period, 5,175 *S. aureus* isolates were collected of which 2,327 were MRSA. 201 viable invasive MRSA isolates were included in the study.
- The median age of patients was 3.5 years (**Table 1**.)
- 28.4% of isolates were clindamycin resistant and the majority were *pvl*-positive and belonged to *agr*I. (**Figure 1**.)

Table 1. General Characteristics of Patients

	All Isolates, n=201
Age, years (IQR)*	3.5 (0.8-9.6)
Female Gender, n (%)*	80 (39.8)
Comorbidities	109 (54.2)
Acquisition	
Community-Acquired	97 (48.3)
Community-Onset Healthcare Associated	61 (30.3)
Hospital Acquired	43 (21.4)
CVL in Place	55 (27.4)
Median Symptom Duration, days	2 (1-5)
Hospitalization in Prior 90 Days	94 (46.8)
ICU Stay in Prior 90 Days	65 (32.3)
Surgery in Prior 90 Days	61 (30.3)
Antibiotics in Prior 90 Days	123 (61.2)
Cephalosporin in Prior 90 Days	66 (32.8)
Previous Ceftaroline	3 (1.5)
MRSA Infection in Prior 90 Days	21 (10.4)
Relapse of Infection at End of Therapy	13 (6.5)

*All continuous variables expressed as medians with interquartile ranges (IQR), categorical variables as n (%)

Figure 1. Characteristics of Isolates



RESULTS

- The ceftaroline MIC_{50} and MIC_{90} were 0.5 and 1 µg/ml, respectively (**Figure 2**). Six isolates had MIC ≥ 2 µg/ml (2.9%) with two having MIC ≥ 8 µg/ml (0.9%).
- RS isolates differed from susceptible isolates in a number of ways (**Figures 3-4** and **Table 2**).

Figure 2. Ceftaroline MICs

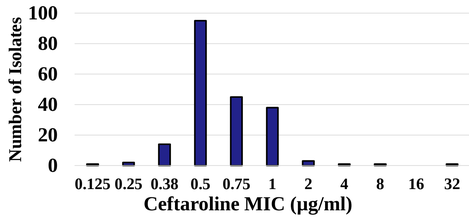


Figure 3. Characteristics of Isolates With and Without Ceftaroline RS

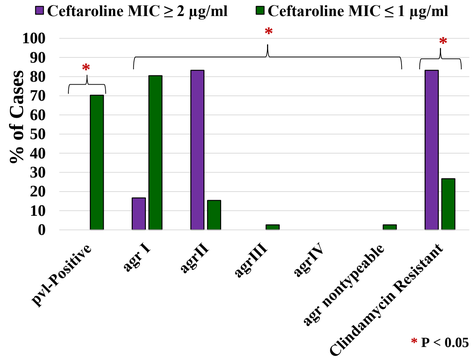
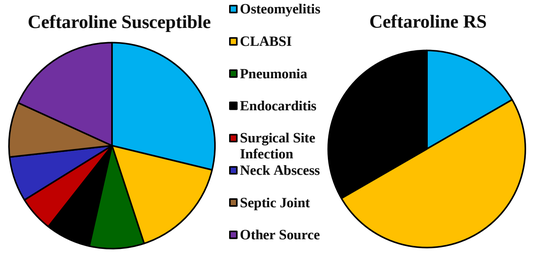


Figure 4. Infectious Diagnoses



RESULTS

Table 2. Comparison of Cases by Ceftaroline MIC

	Ceftaroline MIC ≥ 8 µg/ml n=2	Ceftaroline MIC 2-4 mcg/ml n=4	Ceftaroline MIC ≤ 1 µg/ml, n=195	P value
Age, years	5.4 (0.8-10.1)	9.3 (1.4-17)	3.5 (0.8-9.5)	0.5
Female Gender	0	2 (50)	78 (40)	0.66
Medical Comorbidities	2 (100)	4 (100)	105 (53.8)	0.08
Malignancy	0	2 (50)	13 (6.7)	
Prematurity	0	1 (25)	22 (11.3)	
Short Gut	1 (50)	0	9 (4.6)	
Spina Bifida	0	1 (25)	5 (2.6)	
S/p Solid Organ Transplant	1 (50)	0	6 (3.1)	
Acquisition				0.02
Community-Acquired	0	0	97 (49.7)	
Community-Onset Healthcare Associated	2 (100)	3 (75)	56 (28.7)	
Hospital Acquired	0	1 (25)	42 (21.5)	
CVL *in situ*	2 (100)	3 (75)	50 (25.6)	0.009
Hospitalization in Prior 90 days	2 (100)	3 (75)	89 (45.6)	0.17
ICU Stay in Prior 90 Days	2 (100)	3 (75)	60 (30.8)	0.019
Surgery in Prior 90 Days	1 (50)	3 (75)	57 (29.2)	0.09
Antibiotics in Prior 90 Days	2 (100)	4 (100)	117 (60)	0.11
Cephalosporin in Prior 90 Days	2 (100)	3 (75)	63 (32.3)	0.001
Any Ceftaroline Exposure	0	0	3 (1.5)	1
MRSA Infection in Prior 90 days	2 (100)	1 (25)	18 (9.2)	0.007
Length of Stay, days	11 (8-14)	10.5 (10-112)	12.5 (6-40)	0.8
Relapse of Infection	0	1 (25)	12 (6.2)	0.33
Thrombosis	1 (50)	1 (25)	25 (12.8)	0.18
Attributable Mortality	0	1 (25)	10 (5.1)	0.29
Clindamycin Resistant	2 (100)	3 (75)	52 (26.7)	0.01
Daptomycin MIC > 1 mcg/ml	0	0	12 (6.2)	1
Vancomycin MIC = 2 mcg/ml	2 (100)	2 (50)	59 (62.1)	0.07

Table 3 and Figure 5. Emergence of Ceftaroline Resistance in a Patient

Comorbidity	Diagnosis	Isolate	Date	Ceftaroline MIC (µg/ml)	Treatment
Short Gut	CLABSI	A	May 19, 2017	0.75	Vancomycin, Line Retention
	CLABSI	B	June 25, 2017	>32	Vancomycin, Line Removal

- 1 subject had a ceftaroline susceptible infection followed 1 month later by a ceftaroline resistant infection; isolates were identical by PFGE (**Table 3, Figure 5**).
- None of the ceftaroline RS isolates occurred in patients with prior ceftaroline exposure.

CONCLUSIONS

- Ceftaroline RS is relatively rare in pediatric MRSA, occurring in ~3% of invasive isolates. <1% of isolates exhibited full resistance.
- Ceftaroline RS was only seen in healthcare-associated infections and was associated clindamycin resistance and *agr*II. All CA-MRSA were ceftaroline susceptible.
- Clinicians should be aware that MRSA infections with ceftaroline RS may occur in the absence of history of prior ceftaroline use. Given these findings, providers should perform susceptibility testing rather than assuming all healthcare-associated MRSA are susceptible to ceftaroline.

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