Penicillin-Susceptibility among *Staphylococcus aureus* Skin and Soft-Tissue Infections at a Children's Hospital

J Chase McNeil, Lauren M Sommer, Marritta Joseph, Kristina G Hulten, Sheldon L Kaplan

Department of Pediatrics, Division of Infectious Diseases, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

Contact Info:
Chase McNeil, MD.
Texas Children's Hospital
1102 Bates St., Suite 1150
Houston, TX 77030, USA
E-mail:
jm140109@bcm.tmc.edu

ABSTRACT

Background: Shortly after its introduction into clinical practice, *Staphylococcus aureus* isolates gained resistance to penicillin via the acquisition of β-lactamases. By the 1960s, these strains became the dominant staphylococci in clinical practice. However, a number of centers have recently described an increase in the proportion of methicillin susceptible *S. aureus* (MSSA) which are also susceptible to penicillin (PSSA). In our center we have recently observed the emergence of PSSA in osteoarticular infections. Little data are available regarding the prevalence or impact of PSSA in pediatric skin-and-soft-tissue infections (SSTI).
Methods: MSSA SSTI isolates were obtained through an ongoing surveillance study at Texas Children's (TCH) from 1/2017-12/2021. Twenty community-acquired MSSA SSTI isolates were chosen at random from every six-month interval during the study period, for a total of 200 isolates to be screened. All isolates underwent PCR for *blaZ* β-lactamase, PVL genes and *agr* group. All *blaZ* negative isolates then underwent penicillin susceptibility testing using macrobroth dilution. Isolates which were *blaZ* negative and had a penicillin MIC ≤ 0.125 μg/ml were regarded as PSSA with the remainder regarded as penicillin-resistant MSSA (PR-MSSA).
Results: During the study period 1701 MSSA SSTI isolates were collected with 200 examined for penicillin susceptibility. The overall median age of subjects was 4.1 years (IQR: 1.6-10.4). PSSA accounted for 9% of isolates during the study period; the annual frequency of PSSA varied from 5-17.5%. PSSA and PR-MSSA cases were similar with respect to age, demographics, anatomic site of infection and rates of prior antibiotic exposure. Subjects with SSTI secondary to PSSA were more often admitted to the hospital and underwent operative debridement/drainage. Among PSSA, 94.4% belonged to *agr*I and 33.3% were PVL positive.
Conclusions: PSSA account for a small but significant proportion of MSSA SSTI in children. Clinically distinguishing patients with PSSA and PR-MSSA SSTI is challenging. However, PSSA SSTI were associated with a greater frequency of hospital admission and operative drainage, suggesting a high clinical impact of these infections. Further studies are needed to understand the optimal management of these infections.

AIMS

1. **To determine the frequency of penicillin-susceptibility among methicillin-susceptible *Staphylococcus aureus* skin-and-soft tissue infections in children.**
2. **To examine the clinical and microbiologic associations of penicillin-susceptibility in *S. aureus***

INTRODUCTION

- Starting in the late 1940s, *Staphylococcus aureus* isolates began developing resistance to penicillin-largely through the acquisition of β-lactamase genes.
- In recent years, many centers (Kanjilal S et al *J Clin Microbiol*. 2018; 56:300160) have noted an increase in the proportion of methicillin-susceptible *S. aureus* (MSSA) which are also penicillin-susceptible (PSSA).
- We recently reported an increase in PSSA among *S. aureus* osteoarticular infections in children (McNeil et al. IDWeek 2021).
- Skin and soft tissue infections (SSTI) represent the most common manifestation of *S. aureus* infection in children.
- Little data are available regarding the frequency of penicillin-susceptibility among *S. aureus* SSTI isolates.
- We to sought to define the prevalence of PSSA in pediatric *S. aureus* SSTI.

PATIENTS AND METHODS

Subjects/Isolates. MSSA SSTI isolates were selected from an ongoing *S. aureus* surveillance study at Texas Children's Hospital (TCH). Twenty community-acquired SSTI isolates were randomly selected from every 6-month interval from Jan 1, 2017-Dec 31, 2021, for a total of 200 isolates.
Molecular Studies. All isolates underwent PCR for *blaZ*, *agr* group and the presence of genes associated with PVL.
Microbiology Studies. Isolates negative for *blaZ* underwent penicillin broth dilution testing; cefazolin and oxacillin MICs were determined.

PATIENTS AND METHODS

Definitions. Isolates lacking *blaZ* and with a penicillin MIC ≤ 0.125 μg/ml were regarded as PSSA. All other isolates were considered penicillin-resistant (PR)-MSSA.
Statistical Analysis. Continuous variables were examined with Mann-Whitney U tests, dichotomous variables with χ^2 and Fisher's exact tests.

RESULTS

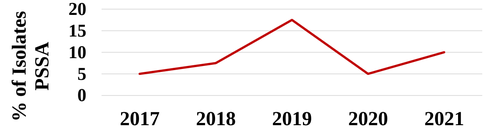
- During the study period, 3,331 *S. aureus* SSTI isolates were recovered of which 1701 were MSSA. 200 random MSSA isolates were screened.
- The median age of patients was 4.2 years and overall patient demographics were representative of the Houston area (**Table 1).**
- Overall, 9% of MSSA SSTI isolates were penicillin susceptible. The frequency of PSSA varied from 5-17.5% annually (**Figure 1**).

Table 1. General Characteristics of the Study Population

Clinical Characteristics	N=200
Median Age, y*	4.2 (1.6-10.5)
Female Gender	91 (45.9)
Race	
White	130 (60)
African American	50 (25)
Asian	7 (3.5)
Other Race	2 (1)
Unknown/Not Answered	11 (5.5)
Hispanic Ethnicity	81 (40.5)
History of Eczema	39 (19.5)
Previous SSTI	42 (21)
Antibiotics in Prior 90 Days	72 (36)
β-lactam Antibiotics in Prior 90 Days	25 (12.5)
SSTI Diagnosis	
Abscess	105 (52.5)
Superinfected Eczema	27 (13.5)
Cellulitis	25 (12.5)
Felon/Paronychia	20 (10)
Impetigo	16 (8)
Lymphadenitis	11 (5.5)
Traumatic Wound Infection	8 (4)

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

Figure 1. Proportion of Penicillin Susceptible Isolates



RESULTS

- Children with PSSA & PR-MSSA SSTI were of similar demographics.
- PSSA infections were more often associated with hospital admission as well as operative intervention (**Table 2**).
- For PSSA, MICs to oxacillin and cefazolin were determined (**Figure 2**).
- PSSA isolates were more often PVL-negative (**Figure 3**).
- Penicillin susceptibility was independently associated with hospital admission (**Table 3**)

Figure 2. β-lactam MICs among PSSA

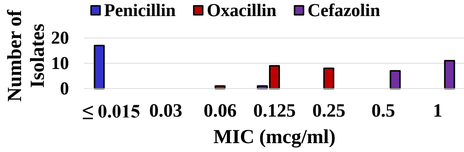


Table 2. Comparison of Clinical Characteristics Between PSSA And PR-MSSA

Clinical Characteristics	PSSA, n=18	PR-MSSA, n=182	P value
Median Age, y	3.2 (0.8-6.2)	4.2 (1.6-10.6)	0.2
Female Gender	8 (44.4)	83 (45.6)	1
History of Eczema	3 (16.7)	36 (19.8)	1
Previous SSTI	6 (33.3)	36 (19.8)	0.22
Antibiotics in Prior 90 Days	7 (38.9)	65 (35.7)	0.81
Prior β-lactam	4 (22.2)	65 (35.7)	0.25
SSTI Diagnosis			
Abscess	11 (61.1)	82 (45.5)	0.17
Superinfected Eczema	0	27 (14.8)	0.14
Cellulitis	2 (11.1)	23 (12.6)	1
Felon/Paronychia	1 (5.6)	19 (10.4)	1
Impetigo	1 (5.6)	15 (8.2)	1
Lymphadenitis	1 (5.6)	10 (5.5)	0.15
Traumatic Wound Infection	2 (11.1)	6 (3.3)	0.15
Infection Prompting Admission	12 (66.7)	74 (41.2)	0.04
Length of Stay, days	2 (1-3)	2 (1-3)	1
I&D/Debridement Required	13 (72.2)	116 (63.7)	0.61
Operative Surgical Intervention	11 (61.1)	55 (30.2)	0.01
Recurrence of SSTI in 30 Days	1 (5.6)	22 (12.1)	0.7

RESULTS

Figure 3. Molecular, Microbiologic Characteristics of PSSA vs. PR-MSSA

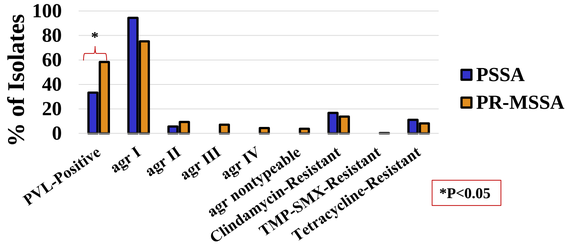


Table 3. Clinical Associations with Hospital Admission for MSSA SSTI

	Hospital Admission, n=86	No Admission, n=114	Uni-P	Multi-P	aOR
Age, y	2.4 (0.9-9.9)	5.6 (2.1-10.7)	0.002		
Age < 4 y	53 (61.7)	45 (39.5)	0.003	0.01	2.18 (1.2-4.0)
Prior Antibiotics	36 (41.8)	36 (31.5)	0.14		
Dx of Abscess	57 (66.3)	46 (40.4)	<0.001	0.26	1.49 (0.7-3.0)
Required Source Control	66 (76.7)	63 (55.3)	0.002	0.007	2.75 (1.3-5.8)
PSSA	12 (13.9)	6 (5.3)	0.04	0.03	3.24 (1.1-9.8)
PVL +	46 (53.4)	64 (56.1)	0.7		
Infection Site: Face	10 (11.6)	16 (14.1)	0.68		
Genitals	12 (13.9)	3 (2.6)	0.005	0.03	4.7 (1.2-18.9)
Hand	1 (1.2)	17 (14.9)	0.47		

- The most commonly prescribed antibiotics were clindamycin (55%), trimethoprim-sulfamethoxazole (31%) and cephalexin (19.5%). No subject received penicillin.

CONCLUSIONS

- PSSA account for 9% of random MSSA SSTI isolates in children.
- Clinically distinguishing patients with PSSA and PR-MSSA SSTI is challenging.
- PSSA are associated with more frequent operative intervention as well as hospital admission, emphasizing the clinical impact of these infections. Further work is needed to understand the reasons for more severe disease associated with PSSA strains.
- Likewise, additional studies are needed to evaluate the optimal management of these infections.

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