Journal of Microbiology, Immunology and Infection 55 (2022) 728–739

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

# Etiology, clinical features, management, and outcomes of skin and soft tissue infections in hospitalized children: A 10-year review

Chih-Ming Yueh [a,b], Hsin Chi [a,c,d], Nan-Chang Chiu [a,d], Fu-Yuan Huang [a], Daniel Tsung-Ning Huang [a], Lung Chang [a], Yen-Hsin Kung [a], Ching-Ying Huang [a,c,*]

[a] *Department of Pediatrics, MacKay Children's Hospital and MacKay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Pediatrics, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei, Taiwan*
[c] *Department of Medicine, MacKay Medicine College, New Taipei, Taiwan*
[d] *MacKay Junior College of Medicine, Nursing and Management, Taipei, Taiwan*

Received 15 August 2021; received in revised form 25 November 2021; accepted 20 January 2022
Available online 3 March 2022

**KEYWORDS**
Children;
MRSA;
Skin and soft tissue infections;
*Staphylococcus aureus*

**Abstract** *Purpose:* This study aimed to describe the etiology, clinical features, hospital course, and outcomes of hospitalized children with skin and soft tissue infections (SSTIs) and to test if clinical and laboratory variables at admission could differentiate between community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and community-acquired methicillin-sensitive *S. aureus* (CA-MSSA).
*Methods:* We reviewed the clinical, laboratory, treatment, and outcome data for children hospitalized with SSTIs, aged 0–18 years at MacKay Children's Hospital between 2010 and 2019. Multivariable logistic regression was used to identify independent predictors of CA-MRSA and CA-MSSA SSTIs.
*Results:* A total of 1631 patients were enrolled. Erysipelas/cellulitis (73.8%) was the most common pediatric SSTI type, followed by acute lymphadenitis (13.6%) and abscess/furuncle/carbuncle (8.6%). Among the 639 culture-positive isolates (purulent SSTIs), 142 (22.2%) were CA-MSSA and 363 (56.8%) were CA-MRSA. The age group 0–1 month (OR, 6.52; 95% CI 1.09–38.92; $P = 0.04$) and local lymph node reaction (OR, 2.47; 95% CI 1.004–6.08; $P = 0.049$) were independent factors for differentiating children with CA-MSSA from those with CA-MRSA SSTIs. MRSA isolates in our cohort were highly susceptible to glycopeptides (100%), linezolid (100%), daptomycin (100%), and sulfamethoxazole/trimethoprim (98.6%) but were significantly less susceptible to clindamycin compared with MSSA (34.2% vs. 78.2%, $P < 0.001$).

* Corresponding author. Department of Pediatrics, MacKay Children's Hospital, No. 92, Sec. 2, Zhongshan N. Road, Zhongshan Dist., Taipei, 10449, Taiwan. Fax: +886 2 2523 2448.
*E-mail address:* 4846.4846@mmh.org.tw (C.-Y. Huang).

https://doi.org/10.1016/j.jmii.2022.01.007

*Conclusion:* *S. aureus* is the leading pathogen of culture-proven SSTIs in hospitalized children with MRSA accounting for more than half. Determining the optimal empirical antibiotics in CA-SSTIs may rely on the patient's age, disease severity, and local epidemiologic data.


## Introduction

Children are frequently affected by skin and soft tissue infections (SSTIs), which require inpatient management. SSTIs can differ in clinical presentation, microbial etiology, and severity. Risk factors for admission include a history of atypical exposures, rapidly progressing infection, extensive or severe site of involvement, failure of oral antibiotics, need for surgical management, comorbidities, or signs of sepsis/systemic infection.

The hospitalizations and medical burden of SSTIs have increased nationwide since the emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[1—3] CA-MRSA strains are genetically different from the hospital-acquired MRSA (HA-MRSA) strains. They have been recognized as a novel pathogen group. The CA-MRSA strains are usually characterized by limited antibiotic resistance (except to β-lactams). They possess different exotoxin gene profiles (e.g., Panton-Valentine leucocidin (PVL) genes) and carry the type IV staphylococcal cassette chromosome (SCCmec IV).[4] Presence of PVL has some major clinical therapeutic impacts, such as the association with deep-seated abscess, multiple lesions, recurring SSTI episodes, multiple antibiotic resistances and outbreaks of SSTIs.[5] Prompt recognition, timely usage of appropriate therapy, and judicious antibiotic usage may improve patients' outcomes.

In Taiwan, the local epidemiological data for pediatric SSTIs is limited. Consequently, the purpose of this study was to describe the clinical features, management, etiology, and antibiotic resistance patterns of *S. aureus*, as well as the outcomes of SSTIs in hospitalized children. We also aimed to identify any independent factors that could differentiate between children with CA-MSSA and CA-MRSA SSTIs.

## Methods

### Patient identification and medical chart review

A retrospective observational study was performed for patients in Mackay Children's Hospital between January 1st 2010 and December 31st 2019. A list of patients with International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) discharge diagnosis codes indicative of SSTIs was obtained. From January 2010 to December 2015, the ICD-9 CM diagnostic codes were used in Mackay Children's Hospital. The ICD-10 CM diagnostic codes have been used since January 1st 2016. A list of ICD-9/10 CM diagnostic codes about SSTIs was shown in Supplementary Table S1. Electronic hospital records were the primary source of this information. However, paper charts were examined if the electronic records were incomplete. We included patients <18 years of age with CA-SSTIs. Patients were excluded if they were >18 years of age, had healthcare-related SSTIs, or had insufficient data available.

We collected information on the patients' demographics (including their gender and age), clinical presentation (including pre-hospitalization fever, systemic inflammation response syndrome (SIRS), recurrent infection, comorbidities, foreign body in lesion, insect/animal bite, previous trauma, previous surgery, symptoms of erythema, swelling, warmth and tenderness, local lymph node reaction, petechiae, vesicle/bullae and purulent lesion), and hospitalization course (including the length of stay, presence and duration of fever during hospitalization, the course of antibiotics used, the site of infection and surgical treatment). In addition, laboratory evaluations at presentation (including the white blood cell [WBC] count, differential count of segment/lymphocyte/band, absolute neutrophil count [ANC], blood hemoglobin and hematocrit percentage, platelet count, and C-reactive protein [CRP] value), pus cultures, blood cultures, and antimicrobial susceptibility test results were reviewed.

### Bacterial species identification

A total of 505 *S. aureus* isolates were identified using the VITEK MS system (BioMerieux Vitek, Hazelwood, MO, USA). Blood cultures were also processed using the VITEK MS system.

### Antimicrobial susceptibility testing

The antimicrobial susceptibility and minimum inhibitory concentration to cefazolin, clindamycin, erythromycin, fusidic acid, linezolid, oxacillin, penicillin, rifampicin, teicoplanin, tigecycline, trimethoprim-sulfamethoxazole (TMP-SMX), ampicillin/sulbactam, daptomycin, and vancomycin were assessed using the VITEK 2 system (BioMerieux Vitek).

### Definitions

We classified *S. aureus*-infected patients as CA and healthcare-associated (HA) using the U.S. Centers for Disease Control and Prevention definition for MRSA.[6] "HA" infection was defined as patients with SSTIs which were

identified after 48 h hospitalization or those with a prior healthcare exposure history within 1 year before the SSTI episode, including residence in a long-term care facility, the use of central intravenous catheters or long-term venous access devices, the use of urinary catheters, the use of other long-term percutaneous devices, and/or the requirement of dialysis. "CA" infection was defined as patients with SSTIs which were identified within 48 h of hospitalization and without the aforementioned history within 1 year before the episode.

Pediatric systemic inflammatory response syndrome (SIRS) was defined as below.[7] The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core body temperature of >38.5 °C or <36 °C.
- Tachycardia, defined as a mean heart rate >2 standard deviation (SD) above average for the patient's age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5–4 h period; or for children <1 year-old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5 h period.
- Mean respiratory rate >2 SD above average for the patient's age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for the patient's age (not secondary chemotherapy-induced leukopenia) or >10% immature neutrophils.

The age-specific cutoffs for each criterion were based on a previous study.[7] These values were chosen after careful review of the medical literature and cited references. As no evidence-based values for abnormal vital signs and laboratory values were found, the values cited were based on expert opinion from the cited references.[7]

Antibiotic use was calculated as days of therapy (DOT). DOT was a description of antibiotic use and calculated independently of the patient-days and combination drugs. It was calculated by multiplying the number of doses by the dosing interval and dividing this by 24 (hours).[8] Empiric antibiotic accuracy was defined to see if the empiric antibiotic usage was compatible with the antimicrobial susceptibility result of the pus culture.

### Statistical analysis

A chi-squared test or Fisher's exact test was used for categorical variables, and a Student's *t*-test was used for continuous variables with normal distribution. The Mann–Whitney U test was used for continuous variables with non-normal distribution. The variables found to be significantly related to the dependent variable were used in collinearity diagnostics of linear regression to examine the multicollinearity. After checking and removing multicollinearity, univariate logistic regression analysis was performed. The statistically significant variables were then used in the multivariate logistic regression to find the best predictors for differential diagnosis between CA-MSSA and CA-MRSA SSTIs. Values for numerical variables were provided as the mean ± SD, median (range), or median (interquartile range; IQR) depending on the normality of the distribution. Categorical variables were provided as absolute values or percentages. A P value $< 0.05$ was considered to indicate a statistically significant difference. SPSS (Version 26.0, IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

### Ethical considerations

This study was approved by the Institutional Review Board of Mackay Memorial Hospital (approval no. 20MMHIS329e).

## Results

The case records of 2250 hospitalized children with SSTI as a discharge diagnosis, as determined by their ICD9 and ICD10 codes between 2010 and 2019, were reviewed. A total of 1631 children were enrolled in our study, including 639 who had culture-positive isolates. We identified 363 MRSA and 142 MSSA among the 505 *S. aureus* isolates (Fig. 1). The other bacterial isolates were *Acinetobacter baumannii* complex, *Aeromonas hydrophila/caviae*, Alpha-Streptococcus species, *Bacteroides fragilis* group, *Citrobacter freundii*, Coagulase (−) *Staphylococcus*, *Corynebacterium* species, *Eikenella corrodens*, *Enterobacter kobei*, *Enterobacter cloacae*, *Enterococcus* species, *Escherichia coli*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae* ssp *pneumoniae*, *Morganella morganii* ssp *morganii*, *Pasteurella canis*, *Pasteurella multocida*, *Pasteurella pneumotropica*, *Peptostreptococcus* species, *Prevotella* species, *Propionibacterium* species, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Raoultella ornithinolytica*, *Streptococcus agalactiae* and *Streptococcus pyogenes*. The numbers of other bacteria are shown in Supplementary Table S2.

### Patient characteristics

The characteristics of all included patients are presented in Table 1. Patients with a positive pus culture were significantly younger ($P < 0.001$), especially <24 months old; and had a significantly higher initial WBC count ($P < 0.001$), platelet value ($P < 0.001$), CRP value ($P < 0.05$) and a longer length of hospital stay ($P < 0.001$).

The characteristics of patients with MRSA versus MSSA isolates are shown in Table 2. Hospitalized patients with MRSA infections were generally older (median age: 21.4 months vs. 17.5 months, $P = 0.037$), were significantly more likely to be between the ages of 2 and 5 years (25.9% vs. 16.2%, $P < 0.001$), had a higher frequency of fever before (65% vs. 54.9%, $P = 0.036$) and after hospitalization (54.8% vs 42.3%, $P = 0.011$), had an erythematous change at the lesion (91.7% vs. 82.4%, $P = 0.002$), had lesions at on the buttocks (27.8% vs. 6.3%, $P < 0.001$), had cellulitis as the type of SSTI (88.2% vs. 69.7%, $P < 0.001$), and had a

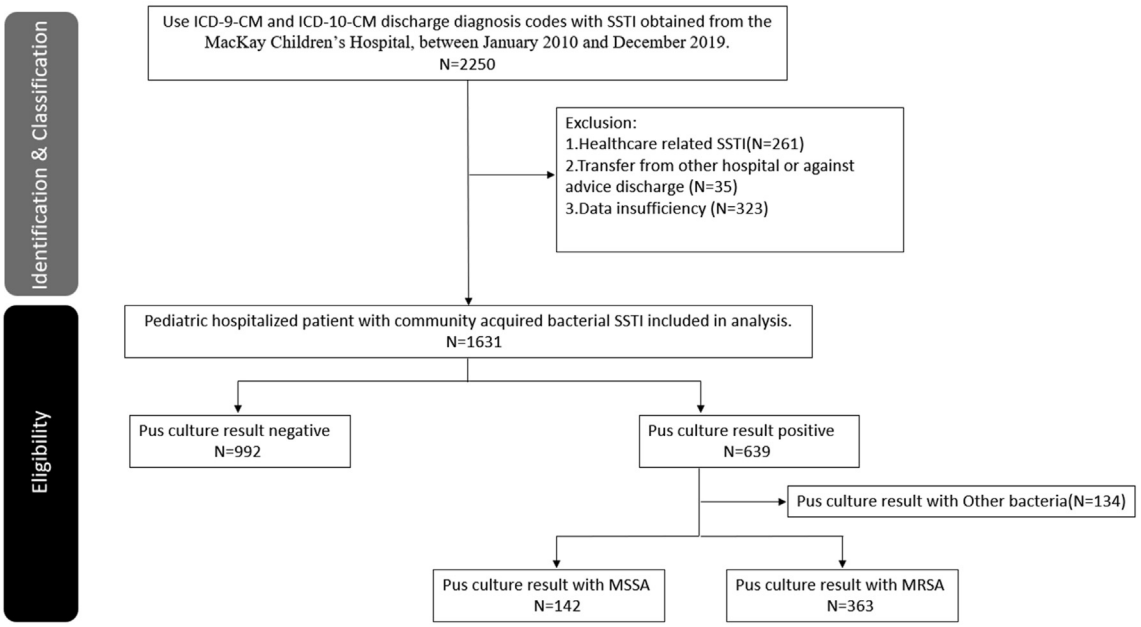


**Figure 1.** Flow chart of data extraction.

**Table 1** Demographics and characteristics of hospitalized children with SSTIs at Mackay Children's Hospital between 2010 and 2019.

| Characteristic | Pus culture negative (N = 992) | Pus culture positive (N = 639) | *P* value |
|---|---|---|---|
| **Demographic** | | | |
| Male | 551 (55.5%) | 353 (55.2%) | 0.905 |
| Age group, month | | | <0.001* |
| <1 | 17 (1.7%) | 36 (5.6%) | |
| 2 – <24 | 259 (26.1%) | 315 (49.3%) | |
| 24 – <72 | 303 (30.6%) | 135 (21.1%) | |
| 72 – <156 | 270 (27.2%) | 86 (13.5%) | |
| 156 – <228 | 143 (14.4%) | 67 (10.5%) | |
| Age, median (IQR) | 56.9 (21.8–109.4) | 20.6 (9.1–65.1) | <0.001* |
| **Laboratory data at presentation** | | | |
| WBC count ($10^3/\mu L$) | 12.6 ± 4.8 | 15.7 ± 6.5 | <0.001* |
| Segment (%) | 57.7 ± 19.6 | 57.4 ± 18.2 | 0.799 |
| Lymphocyte (%) | 30.3 ± 17.5 | 30.1 ± 16.1 | 0.765 |
| Band (%), median (range) | 0 (0–24) | 0 (0–33) | 0.034* |
| ANC ($10^3/\mu L$) | 7.6 ± 4.3 | 9.3 ± 5.2 | <0.001* |
| Hb (g/dL) | 12.4 ± 1.4 | 12.2 ± 1.4 | 0.004* |
| Hct (%) | 37.4 ± 10.3 | 36.4 ± 4.2 | 0.021* |
| Platelet count ($10^3/\mu L$) | 309.3 ± 103.8 | 343.1 ± 117.8 | <0.001* |
| CRP (mg/dL), median (IQR) | 1.3 (0.3–3.6) | 1.6 (0.5–4.0) | 0.003* |
| Bacteremia | 3 (0.3%) | 4 (0.6%) | 0.082 |
| **Hospital course** | | | |
| Oral antibiotic before admission | 381 (38.4%) | 246 (38.5%) | 0.97 |
| LOS (days) | 6.1 ± 3.0 | 7.1 ± 3.2 | <0.001* |
| Fever at admission | 446 (45.0%) | 302 (47.3%) | 0.362 |
| Duration to defervescence, median (range) | 0 (0–8) | 0 (0–14) | 0.466 |
| ICU admission | 3 (0.3%) | 1 (0.2%) | 0.57 |

Data are presented as N (%) or mean ± SD unless otherwise indicated.
**Abbreviations:** ANC, absolute neutrophil count; CRP, C-reactive protein; Hb, hemoglobulin; Hct, hematocrit; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SSTIs, skin and soft tissue infections; WBC, white blood cell count.
*$P < 0.05$, as determined by Student's t-distribution, Mann–Whitney U test, Chi-squared test or Fisher's exact test.

**Table 2** Comparison between hospitalized children with MSSA and MRSA isolates from 2010 to 2019.

| Characteristic | MSSA (N = 142) | MRSA (N = 363) | *P* value |
|---|---|---|---|
| **Demographic** | | | |
| Male | 87 (61.3%) | 170 (46.8%) | 0.004* |
| Age group, month | | | 0.001* |
| <1 | 11 (7.7%) | 5 (1.4%) | |
| 1 − < 24 | 75 (52.8%) | 189 (52.1%) | |
| 24 − <72 | 23 (16.2%) | 94 (25.9%) | |
| 72 − <156 | 19 (13.4%) | 49 (13.5%) | |
| 156 − <228 | 14 (9.9%) | 26 (7.2%) | |
| Age, median (IQR) | 17.5 (6.2−65.4) | 21.4 (11.9−49.4) | 0.037* |
| **Clinical presentation** | | | |
| Pre-hospitalization fever | 78 (54.9%) | 236 (65.0%) | 0.036* |
| SIRS reaction | 52 (36.6%) | 129 (35.5%) | 0.820 |
| Recurrent | 4 (2.8%) | 6 (1.7%) | 0.399 |
| Foreign body | 0 (0%) | 0 (0%) | − |
| Insect/animal bite | 11 (7.7%) | 48 (13.2%) | 0.085 |
| Previous trauma | 1 (0.7%) | 6 (1.7%) | 0.412 |
| Previous surgery | 3 (2.1%) | 1 (0.3%) | 0.036* |
| Erythema | 117 (82.4%) | 333 (91.7%) | 0.002* |
| Swelling | 115 (81.0%) | 315 (86.8%) | 0.100 |
| Warmth | 43 (30.3%) | 136 (37.5%) | 0.129 |
| Tenderness | 72 (50.7%) | 209 (57.6%) | 0.162 |
| Local lymph node reaction | 31 (21.8%) | 14 (3.9%) | <0.001* |
| Purulent lesion | 67 (47.2%) | 186 (51.2%) | 0.412 |
| Petechiae | 0 (0%) | 0 (0%) | − |
| Vesicle/bulla | 9 (6.3%) | 19 (5.2%) | 0.626 |
| **Type of SSTI** | | | <0.001* |
| SSSS | 1 (0.7%) | 2 (0.6%) | |
| Impetigo | 1 (0.7%) | 4 (1.1%) | |
| Abscess/Furuncle/Carbuncle | 11 (7.7%) | 34 (9.4%) | |
| Cellulitis | 99 (69.7%) | 320 (88.2%) | |
| Acute lymphadenitis | 23 (16.2%) | 2 (0.6%) | |
| Omphalitis | 7 (4.9%) | 1 (0.3%) | |
| Necrotizing fasciitis | 0 (0%) | 0 (0%) | |
| **Location** | | | <0.001* |
| Extremities | 53 (37.3%) | 114 (31.4%) | |
| Head/Neck | 30 (21.1%) | 23 (6.3%) | |
| Groin/Perineum | 14 (9.9%) | 21 (5.8%) | |
| Buttock | 9 (6.3%) | 101 (27.8%) | |
| Torso | 22 (15.5%) | 46 (12.7%) | |
| Face | 11 (7.7%) | 52 (14.3%) | |
| Multiple sites | 3 (2.1%) | 6 (1.7%) | |
| **Laboratory data at presentation** | | | |
| WBC count ($10^3/\mu L$) | 15.0 ± 6.8 | 16.3 ± 6.6 | 0.046* |
| Segment (%) | 53.6 ± 21.2 | 59.9 ± 15.0 | <0.001* |
| Lymphocyte (%) | 32.6 ± 18.7 | 28.1 ± 13.6 | 0.003* |
| Band (%), median (range) | 0 (0−21) | 0 (0−33) | 0.966 |
| ANC ($10^3/\mu L$) | 8.5 ± 5.6 | 9.9 ± 5.0 | 0.005* |
| Hb (g/dL) | 11.9 ± 1.7 | 12.2 ± 1.2 | 0.01* |
| Hct (%) | 35.7 ± 5.1 | 36.6 ± 3.4 | 0.02* |
| Platelet count ($10^3/\mu L$) | 379.4 ± 140.3 | 326.9 ± 101.8 | <0.001* |
| CRP (mg/dL), median (IQR) | 1.6 (0.4−4.5) | 1.7 (0.6−3.8) | 0.47 |
| Bacteremia | 3 (2.1%) | 0 (0%) | 0.005* |
| **Comorbidities**[a] | | | 0.009* |
| Negative | 121 (85.2%) | 338 (93.1%) | |
| Hematology/Malignancy | 6 (4.2%) | 1 (0.3%) | |
| Endocrine disease | 0 (0%) | 1 (0.3%) | |
| Neurologic disease | 2 (1.4%) | 2 (0.6%) | |
| Dermatologic disease | 3 (2.1%) | 11 (2.9%) | |

**Table 2** (*continued*)

| Characteristic | MSSA (N = 142) | MRSA (N = 363) | *P* value |
|---|---|---|---|
| Renal disease | 0 (0%) | 0 (0%) | |
| Genetic syndrome/Metabolic disease | 3 (2.1%) | 2 (0.6%) | |
| Immune deficiency/Rheumatologic disease | 5 (3.6%) | 7 (1.9%) | |
| Infectious disease | 1 (0.7%) | 1 (0.3%) | |
| ENT anomalies | 1 (0.7%) | 0 (0%) | |
| CV disease/Chest disease | 0 (0%) | 0 (0%) | |
| GI disease | 0 (0%) | 0 (0%) | |
| **Hospital course** | | | |
| LOS | 7.6 ± 4.4 | 6.6 ± 2.5 | 0.004* |
| Fever during hospitalization | 60 (42.3%) | 199 (54.8%) | 0.011* |
| Fever days during hospitalization, median (range) | 0 (0–14) | 1 (0–10) | 0.013* |
| ICU admission | 1 (0.7%) | 0 (0%) | 0.110 |
| **Treatment** | | | |
| DOTs (intravenous + oral) | 8.1 ± 6.1 | 7.2 ± 4.4 | 0.059 |
| Empiric antibiotic[b] | | | 0.25 |
| Glycopeptides only | 10 (7.1%) | 23 (6.3%) | |
| Glycopeptides combination | 2 (1.4%) | 7 (1.9%) | |
| β-lactams | 97 (68.3%) | 232 (63.9%) | |
| β-lactams combination | 25 (17.6%) | 91 (25.1%) | |
| Others | 8 (5.6%) | 10 (2.8%) | |
| Empiric antibiotic accuracy | 124 (87.3%) | 40 (11.0%) | <0.001* |
| Use 1 empiric antibiotic | 90 (63.4%) | 206 (56.7%) | 0.174 |
| Use ≥2 empiric antibiotics | 52 (36.6%) | 157 (43.3%) | |
| Take home antibiotic | 124 (87.3%) | 324 (89.3%) | 0.537 |
| Need for surgery | 46 (32.4%) | 60 (16.5%) | <0.001* |

[a] **Comorbidities:** - Hematology/malignancy: acute lymphoblastic leukemia, acute myeloid leukemia, aplastic anemia, rhabdomyosarcoma, osteosarcoma. - Endocrine disease: diabetes mellitus, type I. - Neurologic disease: congenital myopathy, adrenoleukodystrophy, cerebral palsy, epilepsy, congenital insensitivity to pain with anhidrosis. - Dermatologic disease: atopic dermatitis. - Genetic syndrome/metabolic disease: Down's syndrome, Treacher Collins syndrome, mucopolysaccharidosis. - Immune deficiency/rheumatologic disease: hyper IgE syndrome, hyper IgM syndrome, juvenile rheumatoid arthritis. - Infectious disease: herpangina, tinea pedis. - ENT anomalies: pre-auricular fistula.

[b] **Empiric antibiotic:** - β-lactams: penicillin, oxacillin, amoxicillin/clavulanate, or cephalosporins. - β-lactams combination: aβ-lactam plus either an aminoglycoside (gentamicin or amikacin) and/or clindamycin or metronidazole and/or TMP-SMX. - Glycopeptide: vancomycin or teicoplanin. - Glycopeptide combination: a glycopeptide plus either an aminoglycoside and/or clindamycin or metronidazole. - Others: clindamycin, daptomycin, linezolid, TMP-SMX, or fluoroquinolones (moxifloxacin or levofloxacin).

Data are presented as N (%) or mean ± SD unless otherwise indicated.

**Abbreviations:** ANC, Absolute neutrophil count; CRP, C-reactive protein; CV, cardiovascular; DOTs, Days of antibiotic therapy; ENT, Ear nose throat; GI, gastrointestinal; Hb, hemoglobulin; Hct, hematocrit; ICU, intensive care center; LOS, length of stay; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; SIRS, systemic inflammatory response syndrome; SSTIs, skin and soft tissue infections; SSSS, staphylococcal scalded skin syndrome; TMP-SMX, trimethoprim/sulfamethoxazole; WBC, white blood cell count.

—, not applicable.

*P < 0.05, as determined by Student's t-distribution, Mann–Whitney U test, Chi-squared test or Fisher's exact test.

higher WBC count ($1.6 \times 10^3/\mu L$ vs. $1.5 \times 10^3/\mu L$, $P = 0.046$) and absolute neutrophil count ($9.9 \times 10^3/\mu L$ vs. $8.5 \times 10^3/\mu L$, $P = 0.005$) at admission compared with patients with MSSA infections. In comparison with MRSA isolates, patients with MSSA isolates were significantly more likely to be < 1 month old (7.7% vs. 1.4%, $P < 0.001$), male ($P = 0.004$), have a local lymph node reaction (21.8% vs. 3.9%, $P < 0.001$), have lesions at the head and neck (21.1% vs. 6.3%, $P < 0.001$), have lymphadenitis and omphalitis as the type of SSTI ($P < 0.001$), have bacteremia (2.1% vs. 0%, $P = 0.005$), comorbidities ($P = 0.009$), a longer length of hospital stay ($P = 0.004$), a need for surgical intervention (32.4% vs. 16.5%, $P = 0.009$), and have a higher accuracy to the empiric antibiotic (87.3% vs. 11.0%, $P < 0.001$).

## Clinical manifestations

Erysipelas/cellulitis (1204 cases; 73.8%) was the most common pediatric SSTI infection type, followed by acute lymphadenitis (222 cases; 13.6%), abscess/furuncle/carbuncle (140 cases; 8.6%), impetigo (25cases; 1.5%), staphylococcal scalded skin syndrome (23 cases; 1.4%), omphalitis (15 cases; 0.9%), and necrotizing fasciitis (2 cases; 0.1%) (Supplementary Fig. S1).

Detailed location distribution of all SSTIs is shown in Supplementary Fig. S2. The extremities (36%) accounted for the largest proportion of cases, followed by head/neck (18%), face (17%), buttocks (15%), torso (7%), groin/perineum (4%), and multiple locations (3%).

### Recurrent *S. aureus* SSTIs

Ten patients had recurrent SSTIs caused by *S. aureus*. Compared with patients without recurrent SSTIs, patients with recurrent *S. aureus* SSTIs had more local lymph node reaction (40% vs. 8.3%, $P < 0.001$), had lesions over head and neck (50% vs. 9.7%, $P = 0.003$), had longer length of hospital stays (12.0 $\pm$ 10.7 days vs. 6.8 $\pm$ 2.8 days, $P < 0.001$), received more days of antibiotic therapy (14.6 $\pm$ 12.1 vs. 7.3 $\pm$ 4.6, $P < 0.001$), had more need for surgical intervention (60% vs. 20.2%, $P = 0.002$), had a high frequency of comorbidities (80.0% vs. 7.7%, $P < 0.001$), had more TMP-SMX for take-home antibiotic (60.0% vs. 34.3%, $P = 0.024$), had a higher WBC count (22.2 $\times$ $10^3/\mu L$ vs. 15.8 $\times$ $10^3/\mu L$, $P = 0.002$), absolute neutrophil count (15.0 $\times$ $10^3/\mu L$ vs. 9.4 $\times$ $10^3/\mu L$, $P = 0.001$), and generally high CRP level (4.38 mg/dL vs. 1.68 mg/dL, $P = 0.001$) at admission.

### Risk factors

We used logistic regression modeling to identify risk factors for CA-MSSA and CA-MRSA SSTIs (Table 3). The variables used in the logistic model were the features identified as being significantly different between the MRSA and MSSA isolate groups, as shown in Table 2. In addition, we also used the collinearity diagnostics of linear regression to check and remove any multicollinearity. After removing multicollinearity, we used the remaining variables one by one in univariate logistic regression. We then took the statistically significant variables from the univariate logistic regression to perform multivariate logistic regression.

As shown in Table 3, the age group 0—1 month (OR, 6.52; 95% CI 1.09—38.92; $P = 0.04$) and local lymph node reaction (OR, 2.47; 95% CI 1.004—6.08; $P = 0.049$) were significant risk factors associated with CA-MSSA SSTIs. In addition, if the hemoglobin value at presentation (OR, 0.79; 95% CI 0.65—0.97; $P = 0.022$) was increased by 1 g/dL, we expected to see a 21% decrease in the odds of it being CA-MSSA SSTI.

### Bacterial culture and antibiotic susceptibility results

Fig. 2 demonstrates the microbial distribution at each location. MRSA isolates were more prevalent than MSSA isolates in all locations except for head/neck.

Fig. 3 demonstrates the frequency of *S. aureus* (included MRSA and MSSA) isolates from 2010 to 2019. The rate of MRSA isolates each year was always more frequent than MSSA isolates from 2010 to 2019.

The results of antimicrobial susceptibility testing are shown in Table 4. The MSSA isolates exhibited low susceptibility to penicillin and erythromycin but high susceptibility to oxacillin, cefazolin, TMP-SMX, and ampicillin/sulbactam. The MRSA isolates were susceptible to most antimicrobial agents except for oxacillin and clindamycin. Significantly more MRSA isolates were resistant to clindamycin than MSSA isolates ($P < 0.001$). Both MSSA and MRSA were mostly susceptible to TMP-SMX, and there was no significant difference noted between them.

## Discussion

Several previous studies have reported that ambulatory care visits for SSTIs have increased over the past 20 years.[1,3] CA-MRSA strains have emerged worldwide and have made the management of *S. aureus* SSTIs more challenging and complicated.[2] A clinical approach for identifying risk factors that can predict and possibly differentiate between infections with MRSA and MSSA, is required. Our hospital-based 10-year study provides detailed information about children with SSTIs in Taiwan.

In the current study, the clinical and demographic characteristics of SSTIs in hospitalized children were analyzed. A significant number of culture-positive SSTIs occurred in patients between birth and two years of age (54.9%); they primarily had SSTIs caused by MRSA. Some previous studies on *S. aureus* infections in children had similar findings.[9,10] On the other hand, some previous studies have reported different results regarding the prevalent age range. For example, a previous study reported a higher prevalence of *S. aureus* infection in children aged 2—5 years in Colombia.[11] Infections in different age groups may be determined by the characteristics of each population and by the risk factors to which children are exposed. The microbiology of SSTIs in our study showed that MRSA (56.8%) was the most common cultured pathogen, followed by MSSA (22.2%) and mixed infection (8.8%). Some previous studies have also reported an association with this finding, and our results supported this finding.[9,12] However, there are some studies which reported opposite results.[13,14]

Our study found that no predictors were associated with CA-MRSA SSTIs. Several previous studies also found that there were no specific risk factors for children with CA-MRSA and CA-MSSA SSTIs.[10,15,16] However, two studies on adult populations identified obesity as an independent risk factor for MRSA SSTIs compared with patients with SSTIs due to other bacterial etiologies.[17,18] Due to the amount of anthropometric data lost in our study, we excluded this variable from the analysis. The age group 0—1 month and local lymph node reaction appear to be risk factors for CA-MSSA SSTIs in our study. A previous study indicated that MSSA colonization of the nares, umbilical stump, and skin is a normal process.[19] However, staphylococcal infection occurs ten times more frequently in otherwise healthy infants colonized with *S. aureus*.[20] The relationship between colonization, infection, and transmission is a dynamic process, and no doubt is influenced by numerous factors, including host factors, intrinsic microbial factors, and infection control practices. A pediatric study observed that 43% of newborns of *S. aureus*-colonized mothers were also colonized in contrast to 7% of the newborns of *S. aureus*-negative mothers by 100 h of hospitalization.[21] The previous study also found that most *S. aureus* carriage in the parturient mothers was MSSA.[22] We might hypothesize that increased CA-MSSA SSTIs among the <1 month age group are partially explained by possibly increased MSSA colonization in this age group. A previous study also supports the finding that lymphadenitis is more commonly associated with patients with CA-MSSA SSTIs compared with patients with CA-MRSA SSTIs.[23] Another study regarding pediatric

**Table 3** Logistic regression analysis of significantly different factors between MRSA and MSSA isolates from 2010 to 2019.

| Variables | MSSA vs MRSA (ref) | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| | Adjusted OR (95% CI) | *P value* | Adjusted OR (95% CI) | *P value* |
| **Demographic** | | | | |
| Female (ref: male) | 0.56 (0.38—0.83) | 0.004* | 0.62 (0.38—1.003) | 0.051 |
| Age, month (ref:156—228) | | 0.004* | | 0.012* |
| <1 | 4.09 (1.18—14.13) | 0.026* | 6.52 (1.09—38.92) | 0.04* |
| 1 — <24 | 0.74 (0.37—1.49) | 0.395 | 0.44 (0.18—1.08) | 0.074 |
| 24 — <72 | 0.45 (0.21—1.01) | 0.051 | 0.39 (0.16—0.99) | 0.046* |
| 72 — <156 | 0.72 (0.31—1.67) | 0.443 | 0.59 (0.24—1.49) | 0.272 |
| **Clinical presentation (ref: Negative)** | | | | |
| Pre-hospitalization fever | 0.66 (0.44—0.97) | 0.036* | 1.09 (0.66—1.83) | 0.733 |
| Previous surgery | 7.81 (0.81—75.75) | 0.076 | | |
| Erythema | 0.42 (0.24—0.75) | 0.003* | 0.78 (0.37—1.64) | 0.52 |
| Local lymph node reaction | 6.96 (3.58—13.56) | <0.001* | 2.47 (1.004—6.08) | 0.049* |
| **Type (ref: SSSS)** | | <0.001* | | 0.025* |
| Impetigo | 0.5 (0.02—12.89) | 0.68 | 0.14 (0.004—5.69) | 0.301 |
| Abscess/Furuncle/Carbuncle | 0.65 (0.05—7.84) | 0.73 | 1.09 (0.06—18.87) | 0.952 |
| Cellulitis | 0.62 (0.06—6.89) | 0.69 | 0.60 (0.04—8.98) | 0.713 |
| Acute lymphadenitis | 23 (1.39—378.89) | 0.028* | 5.6 (0.23—137.45) | 0.291 |
| Omphalitis | 14 (0.58—338.78) | 0.105 | 6.1 (0.18—212.43) | 0.318 |
| Necrotizing fasciitis | — | — | — | — |
| **Location (ref: Multiple)** | | <0.001* | | 0.003* |
| Extremities | 0.93 (0.22—3.86) | 0.92 | 1.30 (0.24—7.16) | 0.76 |
| Head/Neck | 2.61 (0.59—11.56) | 0.207 | 1.08 (0.17—6.89) | 0.936 |
| Groin/Perineum | 1.33 (0.29—6.23) | 0.715 | 1.64 (0.25—10.63) | 0.605 |
| Buttock | 0.18 (0.04—0.84) | 0.029* | 0.25 (0.04—1.59) | 0.142 |
| Torso | 0.96 (0.22—4.19) | 0.953 | 0.77 (0.13—4.53) | 0.771 |
| Face | 0.42 (0.09—1.96) | 0.271 | 0.54 (0.09—3.27) | 0.502 |
| **Laboratory data at presentation** | | | | |
| WBC count ($10^3/\mu L$) | 1 (1—1) | 0.047* | 1 (1—1) | 0.045* |
| Hb (g/dL) | 0.83 (0.72—0.96) | 0.011* | 0.79 (0.65—0.97) | 0.022* |
| Platelet count ($10^3/\mu L$) | 1.004 (1.002—1.005) | <0.001* | 1.002 (1.0—1.004) | 0.119 |
| **Comorbidities (ref: Negative)** | | 0.155 | | |
| Hematology/Malignancy | 16.76 (1.99—140.64) | 0.009* | | |
| Endocrine disease | — | 1 | | |
| Neurologic disease | 2.79 (0.39—20.05) | 0.307 | | |
| Dermatologic disease | 0.76 (0.21—2.78) | 0.68 | | |
| Renal disease | — | — | | |
| Genetic syndrome/Metabolic disease | 4.19 (0.69—25.38) | 0.12 | | |
| Immune deficiency/Rheumatologic disease | 1.99 (0.62—6.41) | 0.25 | | |
| Infectious disease | 2.79 (0.17—45.01) | 0.47 | | |
| ENT anomaly | — | 1 | | |
| CV disease/Chest disease | — | — | | |
| GI disease | — | — | | |

**Abbreviations:** ENT, Ear nose throat; Hb, hemoglobulin; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; SSTIs, skin and soft tissue infections; SSSS, staphylococcal scalded skin syndrome; WBC, white blood cell count.
—, Not applicable.
*$P < 0.05$.

patients with community-acquired bacterial lymphadenitis also have the similar result.[24] However, the association between age or local lymph node reaction and CA-MSSA SSTIs has not been widely recognized.

The pathogenesis of human infections caused by the *S. aureus* has been previously shown to rely on acquiring iron from host hemoproteins.[25] The iron-regulated surface determinant system (Isd) encodes a heme transport apparatus to scavenge iron from hemoglobin. It represents avital virulence strategy for *S. aureus* replication in host tissues and the establishment of persistent staphylococcal infections.[25] Some studies point that exotoxin production of *S. aureus* would be shut down due to high exposure to hemoglobin components whenever it gets access to the

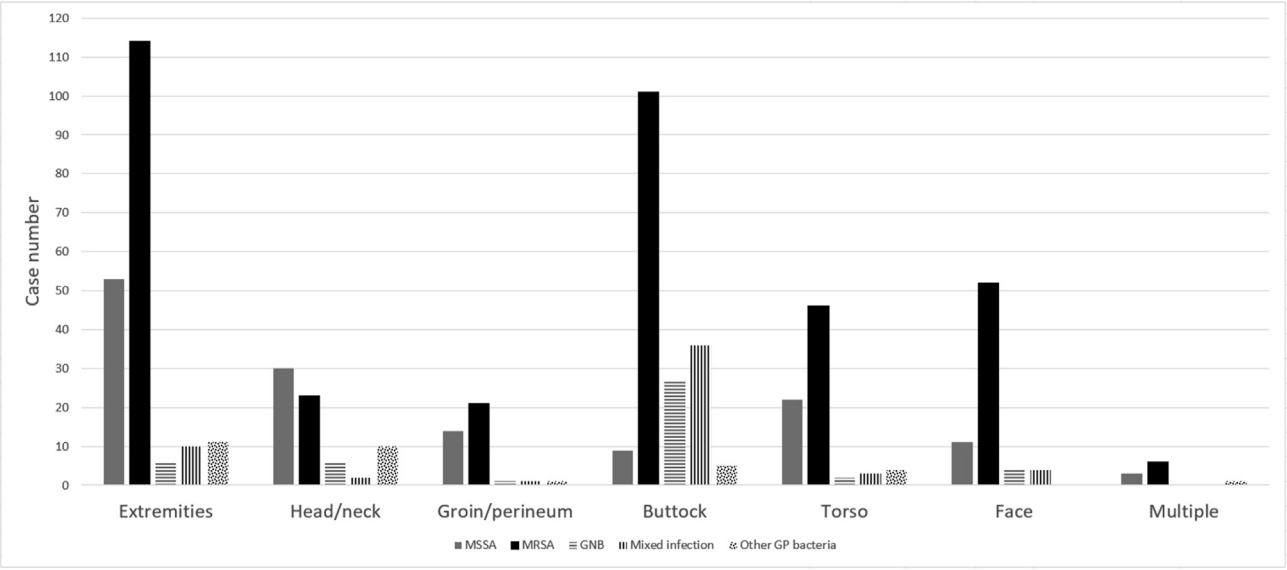


**Figure 2.** Distribution of pus culture results by location.

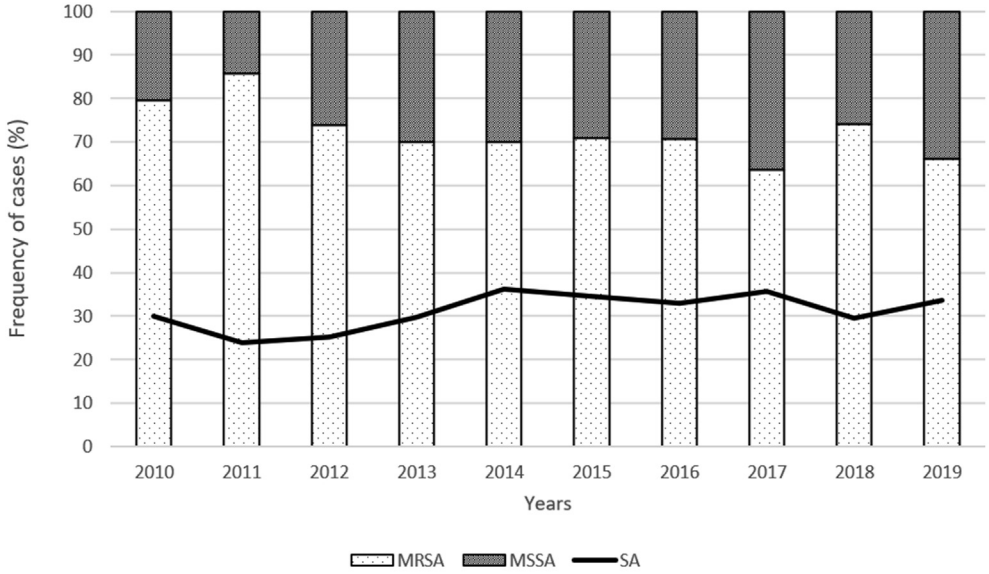


**Figure 3.** Frequency of *S. aureus* (included proportions of MRSA and MSSA) isolates from 2010 to 2019.

bloodstream. The *S. aureus* makes coagulases and quickly is walled off from the host through the formation of abscesses. This action may allow *S. aureus* to make exotoxin needed for spread and disease production and protect from the human immune system.[26] In our study, patient with higher hemoglobin values had more possibilities for CA-MRSA SSTIs. The virulence factor of CA-MRSA might partially explain it for the acquisition of iron from hemoglobin.[27,28] Further studies are needed to validate the associations between hemoglobin value and *S. aureus* SSTIs.

Some animal studies have proposed that PVL is a major virulence determinant.[29] Presence of PVL genes is primarily associated with skin infections such as furunculosis and skin abscesses and is not limited to MRSA strain.[5] Although clinicians are concerned primarily with CA-MRSA infections, MSSA infections can also present similar epidemiologic and clinical features.[30] Some studies even point out that MSSA strains may cause more severe infections, related to the higher prevalence of virulence genes in MSSA.[31] The precise epidemiology of PVL-positive MSSA is not well known. According to previous studies in Taiwan, the proportion of MSSA strains containing the PVL gene has been reported to range from 8.4% to 19.7%.[32,33] However, there was no PVL PCR testing in our hospital microbiologic laboratory. We could not know the precise proportion of the PVL gene in our *S. aureus* isolates. In our study, the CA-MSSA group was generally younger and had more comorbidities than the CA-MRSA group. The reasons why the CA-MSSA group needed surgery more in our study might be explained by the inexperience immune system due to younger age, more

**Table 4** Antibiotic susceptibility of *Staphylococcus aureus* isolates from hospitalized children with SSTIs.

| Antibiotics | MSSA Susceptibility (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **2010** (N = 11) | **2011** (N = 6) | **2012** (N = 11) | **2013** (N = 15) | **2014** (N = 15) | **2015** (N = 14) | **2016** (N = 15) | **2017** (N = 24) | **2018** (N = 14) | **2019** (N = 17) |
| Penicillin | 0 | 16.7 | 9.1 | 46.7 | 33.3 | 0 | 13.3 | 16.7 | 14.3 | 17.6 |
| Oxacillin | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Erythromycin | 36.4 | 50 | 54.5 | 53.3 | 60 | 85.7 | 467 | 45.8 | 42.9 | 82.4 |
| Clindamycin | 45.5 | 83.3 | 72.7 | 66.7 | 60 | 100 | 73.3 | 83.3 | 92.9 | 94.1 |
| Ampicillin /Sulbactam | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| TMP-SMX | 100 | 100 | 100 | 100 | 100 | 92.8 | 93.3 | 100 | 100 | 94.1 |
| Cefazolin | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | MRSA Susceptibility (%) | | | | | | | | | |
| | 2010 (N = 35) | 2011 (N = 35) | 2012 (N = 32) | 2013 (N = 35) | 2014 (N = 35) | 2015 (N = 34) | 2016 (N = 37) | 2017 (N = 43) | 2018 (N = 41) | 2019 (N = 36) |
| Oxacillin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Clindamycin | 22.9 | 17.1 | 9.4 | 5.7 | 17.1 | 35.3 | 43.2 | 53.5 | 63.4 | 61.1 |
| TMP-SMX | 100 | 94.3 | 96.9 | 100 | 100 | 100 | 100 | 100 | 100 | 94.4 |
| Rifampicin | 100 | 100 | 96.9 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Vancomycin | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Linezolid | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Tigecycline | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Fusidic acid | 100 | 100 | 96.9 | 100 | 97.1 | 97.1 | 100 | 100 | 100 | 97.2 |
| Teicoplanin | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Daptomycin[a] | — | — | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

| | MSSA Susceptibility (N = 142), N (%) | MRSA Susceptibility (N = 363), N (%) | *P* value |
|---|---|---|---|
| Oxacillin | 142 (100%) | 0 (0%) | <0.001* |
| Clindamycin | 111 (78.2%) | 124 (34.2%) | <0.001* |
| TMP-SMX | 139 (97.9%) | 358 (98.6%) | 0.552 |

[a] Daptomycin was only used in 2012—2019.

**Abbreviations:** MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, Trimethoprim-sulfamethoxazole.

—, Not applicable.

*$P < 0.05$.

comorbidities, and possibly more PVL genes than in the CA-MRSA group. Further studies are needed to elucidate the precise PVL prevalence in CA-MSSA more clearly.

In the literature, as many as 70% of patients with a primary SSTI, especially for MRSA infection, develop a recurrent SSTI within one year.[34] A previous study demonstrated that those who received IDSA guideline-recommended systemic antibiotics were significantly less likely to remain *S. aureus* colonized at follow-up one month in pediatric patients with *S. aureus* SSTI and concurrent *S. aureus* colonization.[35] Basically, incision and drainage of purulent lesions combined with systemic antibiotic use seemed to yield optimal clinical outcomes. The appropriate therapies for recurrent infections in our study were performing incision and drainage for purulent lesions and considering adjusting empiric antibiotics according to the antimicrobial susceptibility result and clinical response.

In the past, antimicrobial susceptibility patterns have been used to discriminate between CA-MRSA and HA-MRSA strains. However, this approach is now unreliable because CA-MRSA may also acquire resistance to non-β-lactam antibiotics.[36] Clindamycin is an option for staphylococcal SSTIs due to its good distribution in the skin and wound exudates in the USA.[37] However, a different scenario was noted in Taiwan, where most CA-MRSA was resistant to clindamycin and erythromycin. The antibiotic susceptibility patterns of CA-MRSA in our study were also compatible with it. Clindamycin alone is no longer appropriate for children with severe diseases possibly caused by *S. aureus* infection in Taiwan. Empiric glycopeptides (vancomycin or teicoplanin) or linezolid use should be considered.[4]

## Limitations

This study had several limitations. First, given the retrospective, single-center design of the study, the data sources are not standardized, and documentation may be inconsistent or unavailable, which may limit the generalizability of our findings. Incorrect ICD-9/ICD-10 coding may have resulted in the exclusion of some patients from the analysis, and misclassification of exposures and outcomes is

a potential source of bias. To minimize this, we performed a structured chart review using a standard data collection form, with predefined definitions for each variable. Due to variability in the laboratory assessment of children with SSTIs presenting to different divisions, there is potential for ascertainment bias in our results concerning laboratory values. Another limitation is that we could not perform molecular genotyping for the isolates in the hospital laboratory, as most of these isolates were not available for analysis.

In addition, our study population was limited to children. The epidemiologic and clinical characteristics may differ in adults due to different colonization patterns and immunity compared with children. Last but not least, whether microbiological studies accurately determine the responsible pathogens for SSTIs or not in unclear. Most cases of SSTIs are non-culturable as reported by previous studies, and our study was no exception.[12,38] Among culturable cases, the specificity of isolated pathogens (especially from swab cultures) is doubtful. *S. aureus* is often co-cultured with beta-hemolytic streptococci in swab cultures.[13,14] In one of those studies, most patients from which *S. aureus* was cultured had confirmed or probable streptococcal infections. Several patients with swab cultures positive for penicillin-resistant *S. aureus* responded to penicillin monotherapy.[13] Some studies using polymerase chain reaction (PCR) and pyrosequencing techniques have questioned the general principle that streptococci and *S. aureus* are the main bacterial etiologies of cellulitis.[39,40] One of those two studies showed that *S. aureus* was detected by PCR via skin biopsies taken from both infected and uninfected skin. Furthermore, the pyrosequencing technique was used and identified abundant atypical bacteria in addition to streptococci and staphylococci. Both streptococci and *S. aureus* were detected with a similar frequency in infected and uninfected skin tissues.[39] According to pyrosequencing data in those studies, neither streptococci nor *S. aureus* are the most abundant pathogens detected. This therefore supports the theory that immune response to atypical bacteria may partly explain the pathology of cellulitis, which is a hypothesis supported by the low yield of cultures.[39,40]

## Conclusions

In conclusion, *S. aureus* is the leading pathogen of SSTIs in hospitalized children. Age <1 month and local lymph node reaction, appear to be factors associated with CA-MSSA, but no variables were independently associated with CA-MRSA. More local epidemiologic data are needed to elucidate and identify the predictors for CA-MRSA SSTIs. We found that MRSA is increasing as a cause of skin and soft tissue infections, but MSSA might remain a more common cause of invasive infections. Determining the optimal empirical antibiotic choice in community-acquired *S. aureus* SSTIs is still a challenge to clinicians. Clinicians might consider oxacillin in combination with an anti-MRSA antibiotic as empiric therapy in critically ill patients with suspected invasive staphylococcal infections. Continued surveillance is warranted, as the epidemiology of SSTIs can change constantly.

## Declaration of competing interest

None.

## Acknowledgements

None.

## References

1. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo Jr CA. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant Staphylococcus aureus. *Ann Emerg Med* 2008;**51**:291—8.
2. Chen FJ, Lauderdale TL, Huang IW, Lo HJ, Lai JF, Wang HY, et al. Methicillin-resistant Staphylococcus aureus in Taiwan. *Emerg Infect Dis* 2005;**11**:1760—3.
3. Fritz SA, Shapiro DJ, Hersh AL. National trends in incidence of purulent skin and soft tissue infections in patients presenting to ambulatory and emergency department settings, 2000-2015. *Clin Infect Dis* 2020;**70**:2715—8.
4. Huang YC, Ho CF, Chen CJ, Su LH, Lin TY. Comparative molecular analysis of community-associated and healthcare-associated methicillin-resistant Staphylococcus aureus isolates from children in northern Taiwan. *Clin Microbiol Infect* 2008;**14**(12):1167—72.
5. Nurjadi D, Friedrich-Jänicke B, Schäfer J, Van Genderen PJ, Goorhuis A, Perignon A, et al. Skin and soft tissue infections in intercontinental travellers and the import of multi-resistant Staphylococcus aureus to Europe. *Clin Microbiol Infect* 2015; **21**(6).
6. Folden DV, Machayya JA, Sahmoun AE, Beal JR, Holzman GS, Helgerson SD, et al. Estimating the proportion of community-associated methicillin-resistant Staphylococcus aureus: two definitions used in the USA yield dramatically different estimates. *J Hosp Infect* 2005 Aug;**60**(4):329—32.
7. Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;**6**:2—8.
8. Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, et al. Use of a structured panel process to define quality metrics for antimicrobial stewardship programs. *Infect Control Hosp Epidemiol* 2012;**33**:500—6.
9. Salazar-Ospina L, Jimenez JN. High frequency of methicillin-susceptible and methicillin-resistant Staphylococcus aureus in children under 1 year old with skin and soft tissue infections. *J Pediatr* 2018;**94**:380—9.
10. Gomes RT, Lyra TG, Alves NN, Caldas RM, Barberino MG, Nascimento-Carvalho CM. Methicillin-resistant and methicillin-susceptible community-acquired Staphylococcus aureus infection among children. *Braz J Infect Dis* 2013;**17**:573—8.
11. Rodriguez EA, Correa MM, Ospina S, Atehortua SL, Jimenez JN. Differences in epidemiological and molecular characteristics of nasal colonization with Staphylococcus aureus (MSSA-MRSA) in children from a university hospital and day care centers. *PLoS One* 2014;**9**:e101417.
12. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect* 2010;**138**:313—7.
13. Bruun T, Oppegaard O, Kittang BR, Mylvaganam H, Langeland N, Skrede S. Etiology of cellulitis and clinical

prediction of streptococcal disease: a prospective study. *Open Forum Infect Dis* 2016;**3**:ofv181.
14. Lazzarini L, Conti E, Tositti G, de Lalla F. Erysipelas and cellulitis: clinical and microbiological spectrum in an Italian tertiary care hospital. *J Infect* 2005;**51**:383—9.
15. Sattler CA, Mason Jr EO, Kaplan SL. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible Staphylococcus aureus infection in children. *Pediatr Infect Dis J* 2002;**21**:910—7.
16. Miller LG, Remington FP, Bayer AS, Diep B, Tan N, Bharadwa K, et al. Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant Staphylococcus aureus infection from methicillin-susceptible S. aureus infection: a prospective investigation. *Clin Infect Dis* 2007;**44**:471—82.
17. Lee GC, Hall RG, Boyd NK, Dallas SD, Du LC, Trevino LB, et al. Predictors of community-associated Staphylococcus aureus, methicillin-resistant and methicillin-susceptible Staphylococcus aureus skin and soft tissue infections in primary-care settings. *Epidemiol Infect* 2016;**144**:3198—204.
18. Khawcharoenporn T, Tice AD, Grandinetti A, Chow D. Risk factors for community-associated methicillin-resistant Staphylococcus aureus cellulitis-and the value of recognition. *Hawaii Med J* 2010;**69**:232—6.
19. Shinefield H. Staphylococcal infections. In: Remington J, Klein J, editors. *Infectious diseases of the fetus and newborn infant*. 4th ed. Philadelphia: W. B. Saunders; 1995. p. 1111—2.
20. Gooch J, Britt E. Staphylococcus aureus colonization and infection in newborn nursery patients. *Am J Dis Child* 1978;**132**:893—6.
21. Leshem E, Maayan-Metzger A, Rahav G, Dolitzki M, Kuint J, Roytman Y, et al. Transmission of Staphylococcus aureus from mothers to newborns. *Pediatr Infect Dis J* 2012;**31**:360—3.
22. Huang YC, Chao AS, Chang SD, Chen YJ, Peng MT, Sung JH, et al. Association of Staphylococcus aureus colonization in parturient mothers and their babies. *Pediatr Infect Dis J* 2009 Aug;**28**(8):742—4.
23. Bar-Meir M, Tan TQ. Staphylococcus aureus skin and soft tissue infections: can we anticipate the culture result? *Clin Pediatr* 2010;**49**:432—8.
24. Guss J, Kazahaya K. Antibiotic-resistant Staphylococcus aureus in community-acquired pediatric neck abscesses. *Int J Pediatr Otorhinolaryngol* 2007 Jun;**71**(6):943—8.
25. Torres VJ, Pishchany G, Humayun M, Schneewind O, Skaar EP. Staphylococcus aureus IsdB is a hemoglobin receptor required for heme iron utilization. *J Bacteriol* 2006;**188**(24):8421—9.
26. Schlievert PM, Case LC, Nemeth KA, Davis CC, Sun Y, Qin W, et al. Alpha and beta chains of hemoglobin inhibit production of Staphylococcus aureus exotoxins. *Biochemistry* 2007;**46**(50):14349—58.
27. Gianquinto E, Moscetti I, De Bei O, Campanini B, Marchetti M, Luque FJ, et al. Interaction of human hemoglobin and semihemoglobins with the Staphylococcus aureus hemophore IsdB: a kinetic and mechanistic insight. *Sci Rep* 2019 Dec 9;**9**(1):18629.
28. Waryah CB, Gogoi-Tiwari J, Wells K, Eto KY, Masoumi E, Costantino P, et al. Diversity of virulence factors associated with west Australian methicillin-sensitive Staphylococcus aureus isolates of human origin. *BioMed Res Int* 2016;**2016**:8651918.
29. Brown EL, Dumitrescu O, Thomas D, Badiou C, Koers EM, Choudhury P, et al. The Panton-Valentine leukocidin vaccine protects mice against lung and skin infections caused by Staphylococcus aureus USA300. *Clin Microbiol Infect* 2009;**15**:156—64.
30. Lina G, Piemont Y, Godail-Gamot F, Bes M, Peter M, Gauduchon V, et al. Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia. *Clin Infect Dis* 1999;**29**:1128—32. https://doi.org/10.1086/313461.
31. Mongkolrattanothai K, Boyle S, Kahana MD, Daum RS. Severe Staphylococcus aureus infections caused by clonally related community-acquired methicillin-susceptible and methicillin-resistant isolates. *Clin Infect Dis* 2003;**37**:1050—8. https://doi.org/10.1086/378277.
32. Chen YJ, Chen PA, Chen CJ, Huang YC. Molecular characteristics and clinical features of pediatric methicillin-susceptible Staphylococcus aureus infection in a medical center in northern Taiwan. *BMC Infect Dis* 2019 May 10;**19**(1):402.
33. Chiu YK, Lo WT, Wang CC. Risk factors and molecular analysis of Panton-Valentine leukocidin-positive methicillin-susceptible Staphylococcus aureus colonization and infection in children. *J Microbiol Immunol Infect* 2012 Jun;**45**(3):208—13.
34. Fritz SA, Hogan PG, Hayek G, Eisenstein KA, Rodriguez M, Epplin EK, et al. Household versus individual approaches to eradication of community-associated Staphylococcus aureus in children: a randomized trial. *Clin Infect Dis* 2012 Mar;**54**(6):743—51.
35. Hogan PG, Rodriguez M, Spenner AM, Brenneisen JM, Boyle MG, Sullivan ML, et al. Impact of systemic antibiotics on Staphylococcus aureus colonization and recurrent skin infection. *Clin Infect Dis* 2018 Jan 6;**66**(2):191—7.
36. Okuma K, Iwakawa K, Turnidge JD, Grubb WB, Bell JM, O'Brien FG, et al. Dissemination of new methicillin-resistant Staphylococcus aureus clones in the community. *J Clin Microbiol* 2002;**40**(11):4289—94.
37. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis: Off Publ Infect Dis Soc Am* 2005;**41**(10):1373—406.
38. Patel Wylie F, Kaplan SL, Mason EO, Allen CH. Needle aspiration for the etiologic diagnosis of children with cellulitis in the era of community-acquired methicillin-resistant Staphylococcus aureus. *Clin Pediatr* 2011;**50**:503—7.
39. Johnson RC, Ellis MW, Schlett CD, Millar EV, LaBreck PT, Mor D, et al. Bacterial etiology and risk factors associated with cellulitis and purulent skin abscesses in military trainees. *PLoS One* 2016;**11**:e0165491.
40. Crisp JG, Takhar SS, Moran GJ, Krishnadasan A, Dowd SE, Finegold SM, et al. Inability of polymerase chain reaction, pyrosequencing, and culture of infected and uninfected site skin biopsy specimens to identify the cause of cellulitis. *Clin Infect Dis* 2015;**61**:1679—87.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.01.007.