Pediatr Pract Res 2023; 11(2): 53-60
DOI: 10.21765/pprjournal.1306689

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of *Staphylococcus aureus* Infections in Children

Çocuklarda *Staphylococcus aureus* Enfeksiyonlarının Değerlendirilmesi

Gulsum Alkan[1], Hatice Turk Dagı[2], Melike Emiroglu[1], Rumeysa İpteş[3], Sadiye Kubra Tuter Oz[1], Meltem Kıymaz[1], Muslu Kazım Korez[4]

[1]Selcuk University Faculty of Medicine, Department of Paediatrics, Division of Paediatric Infectious Diseases, Konya, Turkey
[2]Selcuk University Faculty of Medicine, Department of Medical Microbiology, Konya, Turkey
[3]Selcuk University Faculty of Medicine, Department of Paediatrics, Department of Medical Microbiology, Konya, Turkey
[4]Selcuk University Faculty of Medicine, Department of Statistics, Konya, Turkey

Abstract

Aim: *Staphylococcus aureus* is the most common infectious agent worldwide which leads to morbidity and mortality. Community and hospital acquired infections can range from skin infections to life-threatening infections. In our study, we evaluated demographic, clinical, and laboratory parameters and the prognosis of children with *S. aureus* infection.

Material and Method: Children infected with *S. aureus* at the Department of Paediatric Infectious Disease, Selcuk University Faculty of Medicine, from 2014 to 2022 were analysed retrospectively. Patients were evaluated for MRSA, MSSA, and community or hospital-acquired infections.

Results: A total of 116 children's detected specimens were collected; 31.9% contained MRSA and 68.1% contained MSSA. The proportion of community-acquired (CA) infections was 88.8%, while hospital-acquired (HA) infections were 11.2%. MSSA was more common in the CA-*S. aureus* group, while MRSA was more common in the HA-*S. aureus* group (p=.025). The most common clinical manifestations included soft tissue infection, lymphadenitis, cutaneous infection, osteomyelitis, and septic arthritis. Each patient was treated with antibiotics, 77.59% of patients was required hospitalization. In 62.9% of the patients, surgical intervention (drainage or debridement) was performed. Despite 86.2% of the patients were cured, infection persisted in nine patients with epidermolysis bullosa, CIPA syndrome, and bone implants. One patient with shunt meningitis died.

Conclusion: *S. aureus* cause both CA and HA superficial or invasive infections, in children. Especially in life-threatening infections, appropriate antibiotic therapy is critical for preventing mortality until an antibiogram culture result is obtained. The patient's clinical condition and regional antibiotic resistance should be considered when prescribing antibiotics empirically.

Keywords: Child, invasive infections, *Staphylococcus aureus*, skin, and soft tissue infections

Öz

Amaç: *Staphylococcus aureus*, dünya çapında morbidite ve mortaliteye yol açan en yaygın enfeksiyöz ajanlardandır. Toplumdan ve hastaneden edinilen enfeksiyonlar cilt enfeksiyonlarından hayatı tehdit eden enfeksiyonlara kadar değişebilmektedir. *S. aureus* enfeksiyonlarının tedavisi, antibiyotik direnci ve aşı eksikliği nedeniyle zordur. Çalışmamızda *S. aureus* enfeksiyonu olan çocukların demografik, klinik ve laboratuvar parametrelerini ve prognozunu değerlendirmeyi amaçladık.

Gereç ve Yöntem: Selçuk Üniversitesi Tıp Fakültesi Çocuk Enfeksiyon Hastalıkları Bölümünde 2014-2022 yılları arasında, *S. aureus* ile enfekte çocuklar retrospektif olarak analiz edildi. Hastalar MRSA, MSSA ve toplumdan veya hastane kaynaklı enfeksiyonlar açısından değerlendirildi.

Bulgular: Toplam 116 çocuk örneğinin %31,9'u MRSA ve %68,1'i MSSA idi. Toplum kökenli (TK) enfeksiyonlar %88,8 iken, hastane kaynaklı (HK) enfeksiyonların oranı %11,2 idi. MSSA, TK enfeksiyonda daha yaygınken, MRSA ise HK enfeksiyonda daha yaygındı (p=.025). En sık klinik belirtiler yumuşak doku enfeksiyonu, lenfadenit, cilt enfeksiyonu, osteomiyelit ve septik artritti. Her hastaya antibiyotik tedavisi uygulandı, hastaların %77.59'unun hastaneye yatırılması gerekti. Hastaların %62,9'una cerrahi girişim (drenaj ve debridman) uygulandı. Hastaların %86.2'sinin iyileşmesine rağmen, epidermolizis bülloza, CIPA sendromu veya kemik implantları olan dokuz hastada tekrarlayan enfeksiyonlar saptandı. Şant menenjiti olan bir hasta öldü.

Sonuç: *S. aureus*, çocuklarda hem toplumdan hem de hastane kaynaklı yüzeysel veya invaziv enfeksiyonlara neden olmaktadır. Özellikle yaşamı tehdit eden enfeksiyonlarda, antibiyogram kültür sonucu çıkıncaya kadar uygun antibiyotik tedavisi mortalitenin önlenmesi açısından kritik öneme sahiptir. Ampirik antibiyotik başlanırken hastanın klinik durumu ve bölgesel antibiyotik direnci göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Çocuk, invaziv enfeksiyonlar, *Staphylococcus aureus*, deri ve yumuşak doku enfeksiyonları

Corresponding Author: Gülsüm ALKAN
Address: Selcuk University Faculty of Medicine, Department of Paediatrics, Division of Paediatric Infectious Diseases, Konya, Turkey
E-mail: galkan-85@hotmail.com

Başvuru Tarihi/Received: 29.05.2023
Kabul Tarihi/Accepted: 15.07.2023

INTRODUCTION

Staphylococcus aureus is a Gram-positive bacterium that colonizes healthy individuals' skin and mucous membranes of the nose, throat, gastrointestinal tract, and urogenital tract without causing disease. Infections may result from injuries to the skin, mucous membranes, or invasive medical devices. When bacteria enter internal tissues and the bloodstream, they can induce a variety of severe infection. *S. aureus* is the most common invasive bacterial pathogen infecting children in many parts of the world. Both methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) strains can cause hospital- acquired (HA) or community-acquired (CA) infection (1-2).

The bacteria, depending on their strains, can induce toxin-mediated diseases or invasive infections. Toxins such as alpha-hemolysin and Panton-Valentine leucocidin (PVL), superantigens, phagocytosis inhibitors (such as polysaccharide capsule and protein A), biofilm formation, intracellular survival, and blocking the chemotaxis of leukocytes all contribute to the pathogenesis of *S. aureus* (3-5). PVL toxin is primarily associated with CA-MRSA strains, cause of the skin and soft tissues infections, and pneumonia. PVL can also induce life-threatening infections in healthy individuals (6).

Based on antibiotic sensitivity, *S. aureus* is subdivided into MSSA and MRSA. The mec-A gene, which is located on the bacterial chromosome and codes for penicillin-binding protein-2a (PBP-2a), is responsible for penicillin resistance in MRSA strains. PBP-2a is an important bacterial cell wall enzyme that catalyses the synthesis of peptidoglycan in the bacterial cell wall. Strains of *S. aureus* that produce PBP-2a are typically resistant to penicillin (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and cephalosporins (2-3,7).

The disease spectrum can range from skin infections (such as abscesses, furuncles, and cellulitis) to life-threatening invasive infections, such as bloodstream infections, endocarditis, meningitis, toxic shock syndrome, necrotic pneumonia, osteomyelitis, septic arthritis, deep neck space infections, pyomyositis, necrotizing fasciitis, lymphadenitis, orbital cellulitis, and urinary tract infections (1-2).

The infectious agent is responsible for both CA and HA infection. HA-*S. aureus* is defined as cases with a positive culture result from a normally sterile site obtained more than 48 hours following hospital admission. At the time of infection onset, the presence of an invasive device, a history of surgery, hospitalization, or dialysis are risk factors for HA-*S. aureus* infections (8).Most of HA-MRSA strains were found to be prevalent in healthcare settings, which were associated with high rates of morbidity and mortality. In addition to causing HA infections, MRSA can also result in CA infections in healthy individuals (9).

In our research, we evaluated the demographic, clinical, and laboratory characteristics and outcomes of *S. aureus* infections in children.

MATERIAL AND METHOD

We reviewed the medical records of children who were diagnosed with *S. aureus* infection at the Department of Pediatric Infectious Disease at the Selcuk University Faculty of Medicine in Konya, Turkey, between January 2014 and December 2022. The hospital's ethics committee approved the study protocols (approval number: 2023/200).

The patients were separated into categories for MRSA and MSSA infections. Demographic data of the patients, underlying diseases, source of infection (community or hospital), clinical findings, laboratory values, radiological evaluations for abscess, hospitalization rates, and treatments methods (antibiotics, surgery) were evaluated retrospectively. Antibiotic susceptibility and resistance of *S. aureus* strains were recorded. The infection was evaluated whether it was CA or HA.

Infections were categorized as bacteraemia with unknown focus, infective endocarditis, catheter-associated bacteraemia, shunt meningitidis, skin or soft tissue infection, lymphadenitis, acute (hematogenous, non-hematogenous) osteomyelitis, chronic osteomyelitis, septic arthritis (hematogenous, non-hematogenous), bursitis, and lung abscess. Patients without full records were excluded from the study.

The samples taken from the patients were processed in the microbiology laboratory with standard methods suitable for the samples. The identification and antibiotic susceptibility tests of bacteria were performed using conventional methods and VITEK 2 (bio-Mérieux, France) automated system.

Statistical Analysis

All statistical analyses were conducted utilizing R version 4.1.2 Statistical Language (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/). Shapiro-Wilk's normality test and Q-Q diagrams were used to determine the normality of the data. The homogeneity of the variances was evaluated using Levene's test. The numerical variables were presented as mean standard deviation, median with ranges (minimum to maximum), or quartiles. Additionally, categorical variables were described in terms of count (n) and percentage (%). According to the demographical and clinical characteristics of *S. aureus* infections in children, a t-test, Mann-Whitney U test, Chi-square test with Yates continuity correction, or two-proportion Z-test was conducted to determine whether there was a statistically significant difference or association between MRSA and MSSA groups.

In addition, the Two-proportion Z-test was used to determine whether there was a significant difference between MRSA and MSSA in the proportion of *S. aureus* isolates that were resistant or sensitive to antibiotics. A two-tailed p-value of 5% or less is considered statistically significant.

RESULTS

Demographic and clinical features of children:

A total 116 children's specimens were collected, 59 of which were male (50.9%). The median age of the children was 3 years (1 month-18 years). The percentage of MRSA among the isolates was 31.9% (n=37), while the percentage of MSSA was 68.1% (n=79). Epidermolysis bullosa, trauma, congenital heart disease, congenital insensitivity to pain with anhidrosis (CIPA) syndrome, malnutrition, dermoid cyst, and ventriculoperitoneal shunt were identified as predisposing factors for *S. aureus* infection in 39 patients (33.6%). Fever was present in 55 patients (47.4%) at hospital admission. No statistically significant difference about age, gender, underlying diseases and fever were determined between the MSSA and MRSA groups.

Infection with CA-*S. aureus* (88.8%) was more prevalent than infection with HA-*S. aureus* (11.2%). While there were more MSSA isolates in the CA-*S. aureus* group (93.7% vs. 78.4%, p=.025), there were more MRSA isolates in the HA-*S. aureus* group (21.6% vs. 6.3%, p=.025).

The patients presented with mostly skin or soft tissue infections, lymphadenitis and osteoarticular infections. Infection of soft tissue was more frequent in the MRSA group than in the MSSA group (37.84% vs. 18.99%, p=.029), while lymphadenitis was more frequent in the MSSA group (30.3%). The MRSA group had a higher incidence of acute osteomyelitis than the MSSA group (13.5% vs. 1.27%, p=.012), and all cases of hematogenous osteomyelitis (n=3) occurred in the CA-MRSA group. All septic arthritis were due to MSSA and, hematogenous septic arthritis accounted for 66% of cases. One patient was treated for CA-MRSA-related pulmonary abscess. Other clinical presentations demonstrated no statistically significant differences between the MSSA and MRSA groups.

Percentage of HA-*S. aureus* infections were; 30.7% soft tissue infection (n=4), 23% catheter-associated bacteraemia (n=3), 15.3 % shunt meningitidis (n=2), 7.6 % chronic osteomyelitis (n=1), 7.6 % skin infection (n=1), %7.6 bacteraemia unknown focus (n=1), %7.6 infective endocarditis (n=1).

The patient on dialysis for chronic renal failure (HA-MSSA) and the patient with ventricular septal defect (CA-MSSA) were both diagnosed with infectious endocarditis. In one patient, HA-MRSA was identified as a non-focus bacteraemia agent. The 77.59% of patients required hospitalization. The hospitalization rates of the MRSA and MSSA groups did not differ statistically significantly. **Table 1** summarizes the demographic and clinical characteristics of the patients.

II. Laboratory features of children with *S. aureus* infections (Table 2):

There was no statistically significant difference found between MRSA and MSSA acute phase reactant values, radiologic imaging findings, blood culture positivity rates. Hematogenous septic arthritis 50% (n=4), infective endocarditis 25% (n=2), shunt meningitis 12.5% (n=1), and catheter-associated bacteraemia 12.5% (n=1) comprised the percentage of patients with MSSA growth in blood cultures. Hematogenous acute osteomyelitis 60% (n=3), bacteraemia 20% (n=1), and catheter-associated bacteraemia 20% (n=1) comprise the percentage of patients with MRSA growth in blood culture.

III. Antibiogram profile of *S. aureus* isolates from children:

More than 94% of *S. aureus* isolates were resistant to penicillin G, followed by 81.7 % resistant to inducible clindamycin, 31.3 % resistant to cefoxitin, 24.3 % resistant to erythromycin, and 21.7 % resistant to clindamycin, respectively. All *S. aureus* isolates exhibited susceptibility to teicoplanin, vancomycin, and linezolid. Most of *S. aureus* strains were (%95) susceptible to daptomycin. Compared with MSSA isolates, the MRSA isolates in this study exhibited a higher resistance rate to erythromycin, ciprofloxacin, tetracycline, fusidic acid, levofloxacin, TMP-SMX, moxifloxacin, and gentamicin (**Table 3**).

IV. Management of infections and outcomes:

At study assessment, 77.5% of the patients (n=90) were received intravenous antibiotic treatment (78.3% of MRSA; %77.2 MSSA). Teicoplanin, ampicillin-sulbactam and clindamycin combination and clindamycin monotherapy were the most common used antibiotics in both groups and overall (**Table 4**). Patients received teicoplanin (n=3) despite MSSA infection due to severe infections were had hematogenous septic arthritis, catheter-associated bacteraemia, and infective endocarditis.

Twenty-six of the patients were treated orally with antibiotics and were not hospitalized. Most of these patients had skin or soft tissue infections and, less often had chronic osteomyelitis.

Seventy of the patients were discharged with oral antibiotics. Clindamycin and trimethoprim sulfamethoxazole were the most common used oral antibiotics in both groups and overall (**Table 4**). The four patients with septic arthritis or osteomyelitis were discharged with intramuscular teicoplanin.

Infections of the skin (n=8), soft tissue (n=6), septic arthritis (n=2), osteomyelitis (n=5), lymphadenitis (n=6), and bursitis (n=1) were treated orally with TMP-SMX. Oral linezolid was used to treat a patient with CA-MRSA acute osteomyelitis, while oral ciprofloxacin was used to treat a patient with a CA-MRSA skin infection.

In 62.9% (n=73) of the patients, surgical intervention was performed. While patients with osteomyelitis or septic arthritis were debrided (12.9%, n=15), patients with lymphadenitis, soft tissue infection, or lung abscess underwent drainage (50%, n=58).

Only one patient with ventriculoperitoneal shunt meningitis died. Infection persisted in patients with epidermolysis bullosa, CIPA syndrome, bone implants and culture growth was detected in fifteen of these patient's samples (%12.9).

Table 1. Demographic and Clinical Features of *Staphylococcus aureus* Infections in Children

	Overall n=116 (%)	MRSA n=37 (31.9%)	MSSA n=79 (68.1%)	p-value
Age (year), (median)	3 (1-18)	3 (1-18)	3 (1-17)	.9591
Gender (Male/Female)	59/57 (50.9/49.1)	17/20 (45.9/54.1)	42/37 (53.2/46.8)	.5992
Underlying Disease	39 (33.62)	16 (43.24)	23 (29.11)	.135
Fever on Admission	55 (47.4)	18 (48.6)	37 (46.8)	>.999
CA- *S. aureus*	103 (88.8)	29 (78.4)	74 (93.7)	**.025**
HA- *S. aureus*	13 (11.2)	8 (21.6)	5 (6.3)	**.025**
Presence of Central Catheter	4 (3.4)	1 (2.7)	3 (3.8)	>.999
Clinical Presentation				
Bacteraemia unknown focus	1 (0.86)	1 (2.7)	0 (0.0)	.319
Infective endocarditis	2 (1.72)	0 (0.0)	2 (2.53)	.331
Catheter-associated bacteraemia	3 (2.5)	2 (5.4)	1 (1.2)	.238
Shunt meningitidis	2 (1.72)	1 (2.7)	1 (1.27)	.582
Skin Infection	27 (23.28)	5 (13.51)	22 (27.85)	.089
Soft Tissue Infection	29 (25.0)	14 (37.84)	15 (18.99)	**.029**
Lymphadenitis	28 (24.14)	4 (10.81)	24 (30.38)	**.022**
Osteomyelitis	15 (12.93)	8 (21.62)	7 (8.86)	.057
*Acute Osteomyelitis	6 (5.17)	5 (13.51)	1 (1.27)	**.012**
Hematogenous	3 (2.59)	3 (0.81)	0 (0.0)	**.031**
Non-Hematogenous	3 (2.59)	2 (5.41)	1 (1.27)	.193
*Chronic Osteomyelitis	9 (7.76)	6 (16.2)	3 (3.7)	.593
Septic Arthritis	6 (5.17)	0 (0.0)	6 (7.59)	.086
Hematogenous	4 (3.45)	0 (0.0)	4 (5.06)	.165
Non-Hematogenous	2 (1.72)	0 (0.0)	2 (2.53)	.331
Bursitis	2 (1.72)	1 (2.7)	1 (1.27)	.583
Lung Abscess	1 (0.86)	1 (2.7)	0 (0.0)	.144
Treatment Management				
Hospitalization	90 (77.59)	29 (78.38)	61 (77.22)	.889
Outpatient	26 (22.41)	8 (21.62)	18 (22.78)	.889

[1]Mann-Whitney U test, [2]Chi-square test with Yates continuity correction, Abbreviations: CA-*S. aureus*, Community acquired-*Staphylococcus aureus*; HA-*S. aureus*, Hospital acquired-*Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

Table 2. Laboratory Features of Children with *Staphylococcus aureus* Infections

Initial Laboratory Values	Overall (n=116)	MRSA (n=37)	MSSA (n=79)	p-value
Total leukocyte count (K/µL)	12.800 (9.560-18.400)	13.100 (9.700-16.800)	12.550 (9.600-18.850)	.6971
Absolute neutrophil count (K/µL)	8.220 (5.100 -11.030)	8.130 (5.250-11.400)	8.325 (5.137,5-11.000)	.7601
Absolute lymphocyte count (K/µL)	3.380 (2.040- 6.080)	3.080 (2.130-5.340)	3.545 (2.000-6.355)	.6751
Haemoglobin (g/dL)	11.47 ± 1.92	11.60 ± 2.09	11.41 ± 1.84	.623
Platelet (K/µL)	403 (300-513)	391 (309.5-480)	409 (294.5-528.75)	.6681
Sedimentation (mm/h)	27 (11-53)	25 (11.75-54.5)	29 (9.5-51.5)	.8921
C-reactive protein(mg/L)	29 (9.95 -70.5)	25 (8.55 -67.5)	29 (12-70)	.7431
Procalcitonin (µg/L)	0.14 (0.07-0.43)	0.14 (0.07 - 0.30)	0.13 (0.07- 0.50)	.8851
Positive blood cultures n (%)	13 (11.2)	5 (13.5)	8 (10)	.753
Abscess formation on radiological imaging n (%)	53 (45.7)	17 (45.9)	36 (45.6)	.976
ECHO-vegetation n (%)	2 (1.7)	0 (0)	2 (2.5)	.334

[1]Mann-Whitney U test, Abbreviations: ECHO, echocardiography; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-Susceptible *Staphylococcus aureus*

Table 3. Antibiotic resistance and susceptibility profile of *Staphylococcus aureus* isolates from children

Antibiotics	Sensitivity			p-value
	Overall	MRSA	MSSA	
Penicillin G	6 (5.4)	0/37 (0.0)	6/74 (8.1)	.076
Mupirocin	92 (97.9)	26/26 (100)	66/68 (97.1)	.383
Cefoxitin	79 (68.7)	0/36 (0.0)	79/79 (100)	<.001
Erythromycin	87 (75.7)	23/37 (62.2)	64/78 (82.1)	.021
Inducible clindamycin resistance	20 (18.3)	9/34 (26.5)	11/75 (14.7)	.142
Clindamycin	90 (78.3)	25/37 (67.6)	65/78 (83.3)	.057
Fusidic acid	104 (89.7)	29/37 (78.4)	75/79 (94.9)	.007
Ciprofloxacin	77 (88.5)	20/29 (69.0)	57/58 (98.3)	.001
Levofloxacin	106 (92.2)	29/37 (78.4)	77/78 (98.7)	.002
Moxifloxacin	106 (93.8)	28/35 (80.0)	78/78 (100)	<.001
Tetracycline	97 (86.6)	25/35 (71.4)	72/77 (93.5)	.001
Gentamicin	110 (94.8)	32/37 (86.5)	78/79 (98.7)	.006
Trimethoprim-sulfamethoxazole	107 (92.2)	29/37 (78.4)	78/79 (98.7)	<.001
Teicoplanin	101 (99.0)	31/31 (100)	70/71 (98.6)	.509
Vancomycin	96 (100)	30/30 (100)	66/66 (100)	>0.999
Linezolid	116 (100)	37/37 (100)	79/79 (100)	>0.999
Daptomycin	77 (95.1)	23/25 (92)	54/56 (96.4)	.402

Table 4. Management of Children with *Staphylococcus aureus* Infections and Outcomes

	Overall n=116, (%)	MRSA n=37, (%)	MSSA n=79, (%)	p-value
Treatment				
Intravenous Antibiotic	90/116 (77.59)	29/37 (78.38)	61/79 (77.22)	.889
Cephazolin	4/90 (4.44)	0/29 (0.0)	4/61 (6.56)	.161
Ampicillin-sulbactam	9/90 (10.0)	3/29 (10.34)	6/61 (9.84)	.941
Clindamycin	15/90 (16.67)	5/29 (17.24)	10/61 (16.39)	.919
Teicoplanin	28/90 (31.11)	12/29 (41.38)	16/61 (26.23)	.149
Vancomycin	4/90 (4.44)	3/29 (10.34)	1/61 (1.64)	.062
Trimethoprim-sulfamethoxazole	4/90 (4.44)	1/29 (3.45)	3/61 (4.92)	.752
Ampicillin-sulbactam+Clindamycin	25/90 (27.78)	5/29 (17.24)	20/61 (32.79)	.126
Vancomycin+Clindamycin	1/90 (1.11)	0/29 (0.0)	1/61 (1.64)	.490
Oral Antibiotic/OPAT	96/116 (82.76)	32/37 (86.49)	64/79 (81.01)	.468
Cephalexin	2/96 (2.08)	0/32 (0.0)	2/64 (3.13)	.314
Amoxicillin	2/96 (2.08)	0/32 (0.0)	2/64 (3.13)	.314
Amoxicillin-clavulanate	10/96 (10.42)	2/32 (6.25)	8/64 (12.5)	.347
Ampicillin-sulbactam	11/96 (11.46)	1/32 (3.13)	10/64 (15.63)	.071
Clindamycin	37/96 (38.54)	14/32 (43.75)	23/64 (35.94)	.461
Trimethoprim-sulfamethoxazole	28/96 (29.17)	12/32 (37.5)	16/64 (25.0)	.206
Ciprofloxacin	1/96 (1.04)	1/32 (3.13)	0/64 (0.0)	.157
Linezolid	1/96 (1.04)	1/32 (3.13)	0/64 (0.0)	.157
Teicoplanin (Intramuscular)	4/96 (4.17)	1/32 (3.13)	3/64 (4.69)	.719
Additional treatment				
Surgery	73 (62.93)	22 (59.46)	51 (64.56)	.597
Need for debridement	15 (12.93)	4 (10.81)	11 (13.92)	.643
Need for drainage	58 (50.0)	18 (48.65)	40 (50.63)	.843
Outcome				
Cured	100 (86.21)	32 (86.49)	68 (86.08)	.952
Persistent infection	15 (12.93)	4 (10.81)	11 (13.92)	.643
Mortality	1 (0.86)	1 (2.7)	0 (0.0)	.144

Chi-square test with Yates continuity correction, Abbreviations: CA- *S. aureus*, Community acquired-*Staphylococcus aureus*; HA-*S. aureus*, Hospital acquired -*Staphylococcus aureus*; MSSA, Methicillin-Susceptible *Staphylococcus aureus* ;MRSA, methicillin-resistant *Staphylococcus aureus*; OPAT, Outpatient parenteral antimicrobial therapy

DISCUSSION

In this retrospective single-centre study, *S. aureus* infection in children was analysed. Our objective was to inform clinicians about the various clinical manifestations of *S. aureus* infections and the regional pattern of antibiotic susceptibility and resistance.

CA-MRSA infection rate has increased in recent years, healthy children are also susceptible. Infections caused by CA-MRSA are usually related to skin and soft tissues. However, CA-MRSA may associate with life-threatening infections (10-11). Skin trauma, frequent skin-to-skin contact, sharing potentially contaminated personal items or equipment that has not been cleaned, crowded conditions, restricted access to medical care, and frequent exposure to antimicrobial agents are risk factors for CA-MRSA (12).

S. aureus infection affects all ages and genders. Gomes et al. reported CA-*S. aureus* infections (n=90) in patients 20 years old over a period of 11 years. The percentage of CA-MRSA is lower than in our study (6.7% vs. 28%). The median age of the patients was two years old (66% of whom were male). In 27 cases (30%), underlying conditions were identified. The majority involved the skin (44.4%), the heart (25.9%), the respiratory tract (11.1%), and the central nervous system (3.9%). Overall, 34 (37.8%) patients had skin/soft tissue infections;56 (62.2%) patients had deep infection; pneumonia (26.8%), arthritis (17.9%), pyodermatitis (14.3%), osteomyelitis (8.9%), adenitis (5.4%), sepsis (5.4%), endocarditis (3.6%), cellulitis (1.8%), urinary tract infection (1.8%). Two (2.6%) of the four patients who were transferred to the intensive care unit died. Patients with MRSA or MSSA infections showed similar baseline features and therapeutic outcomes. The median length of stay in the hospital was 14 (1–53) days (13). In our study, we found no significant variations in the baseline characteristics or prognosis of patients infected with CA-MRSA or CA-MSSA strains.

S. aureus, colonize the skin in 20–30% of the population and is responsible for 80–90% of all skin and soft tissue infections in people worldwide (14). Although drainage is the mainstay of therapy for purulent skin and soft tissue infections antibiotics are associated with clinical improvement. 1st or 2nd generation cephalosporins are recommended for children at low risk of MRSA infection. If the rate of MRSA is high in the community, oral clindamycin, TMP-SMX and doxycycline are recommended for initial treatment. In severe infections, intravenous vancomycin and clindamycin are recommended (15). In our study, 46% of patients presented with skin soft tissue infection and 33.9% of them had MRSA. Clindamycin (28.5%), TMP-SMX (25%), and amoxicillin-clavulanate (16%) were the most common antibiotics used for treatment.

Acute bacterial lymphadenitis is a common childhood condition. Annaliese R. et al reported (2023) 148 children with lymphadenitis. In culture-positive cases, MSSA (49%) and Group A Streptococcus (43%) predominated, while MRSA was seen in a minority of cases (6%). Cephalexin, clindamycin, amoxicillin-clavulanate, was the most used antibiotics (16). In our study, 28 of the patients (24.1%) had lymphadenitis. 14.3% of the cases were identified as MRSA and 85.7% as MSSA. Of these, 75% received treatment with clindamycin.

The most common pathogenic bacteria associated with osteomyelitis in children are MSSA and MRSA.

Clinically, first- or second-generation cephalosporins are routinely used to treat of MSSA acute osteomyelitis in children (17). Oral clindamycin is commonly used to treat acute CA-MRSA osteomyelitis. Because of inducible clindamycin resistance, TMP-SMX is preferred an alternative therapy (18). In our study, there were 15 patients we followed for osteomyelitis and MRSA was detected in 8 of them. Of these, 53.3% received treatment with clindamycin, 33.3% received TMP-SMX. Arnold SR et al. reported 158 cases of acute osteoarticular infection in children. MRSA infections were associated with increased rate of subperiosteal abscess formation (71% versus 38%), therefore increased needing for surgical drainage (91 versus 62 percent) and increased median hospital stay (10 versus 7 days) (19). In our study, no significant difference was found between the two groups in terms of abscess formation, surgical requirements, or hospitalization.

Septic bursitis is an infection that typically affects the prepatellar and olecranon bursae. *S. aureus* accounts for approximately 80% of cases (20). We detected olecranon bursitis in one patient and suprapatellar bursitis in one patient.

David et al reported 313 patients with bacterial CA pneumonia. *S. aureus* was detected in 10.9% of the patients and, MRSA in 26.5% of them. Patients with *S. aureus* pneumonia had a high prevalence of complications (21). Clindamycin is recommended for MRSA pneumonia without concomitant influenza (22).

Vancomycin or clindamycin is suggested as first-line therapy for nonlife-threatening infections (eg, pneumonia, septic arthritis, osteomyelitis) without signs of sepsis thought to be caused by MRSA. Oxacillin, nafsicillin or cephazolin are recommended in patients with MSSA (22).

Vancomycin plus nafcillin or oxacillin is suggested as first-line therapy for severe infections (sepsis, meningitis, endocarditis) thought to be caused by *S. aureus* (HA/CA) (22). Patients with serious infections received vancomycin or teicoplanin treatment.

Most infective endocarditis is caused by CA-*S. aureus* bacteraemia. Children with congenital cardiac disease and/or indwelling central venous catheters are at higher risk (23-24). In our study, infective endocarditis was detected in one patient who underwent dialysis for chronic renal failure (HA-MSSA) and the one patient with ventricular septal defect (CA-MSSA).

Central nervous system (CNS) infections caused by *S. aureus* are uncommon in children. Vallejo et al reported seventy cases of *S. aureus* CNS infection. Forty-nine cases (70%) were secondary to a CNS device. Forty-seven (67.2%) were caused by MSSA and 23 (32.8%) by MRSA (25). In our study, two patients with ventriculoperitoneal shunts had meningitis. One patient with MRSA meningitidis died.

Forty to fifty percent of *S. aureus* bacteraemia in children is associated with a localized infection source such as bone and joint infections, skin and soft tissue infections, pneumonia, or an invasive device. The account of 10% bacteraemia is without a focus (26-27). Non-focal bloodstream infection detected due to HA-MRSA in one of our patients. Bacteremia was detected in 12 patients with focal infection site.

Infants are more vulnerable to invasive HA-MRSA infections. Risk factors for HA-MRSA infection are; presence of an invasive device at the time of admission, history of MRSA infection or colonization, history of surgery, hospitalization, or dialysis, prolonged hospitalization (>14 days), surgery or surgical site infection (28). In our study HA-*S. aureus* infections were skin and soft tissue infection after surgery (n=5), catheter-associated bacteraemia (n=3), shunt meningitidis (n=2), bacteraemia unknown focus(n=1), and infective endocarditis (n=1), chorionic osteomyelitis (n=1).

In the study of Şanlı et al. (2004) 210 *S. aureus* strains grown in patient cultures in different clinics were evaluated retrospectively. Of the overall strains, 48.1% were MSSA and 51.9% were MRSA; 17.6% (n=37) were CA and 82.3% (n=173) were HA. While 56.1% of MRSA were HA, 67.5% of MSSA were CA. Consistent with our study, vancomycin and teicoplanin internal resistance was not observed (29).

In MRSA strains, resistance to penicillin 100%, gentamicin 83.4%, ciprofloxacin 82.5%, levofloxacin 75.2%, clindamycin 72.4%, erythromycin 71.5% detected. In our study, antibiotic resistance rates were lower (except for penicillin); gentamicin 13.5%, ciprofloxacin 31%, levofloxacin 21.6%, clindamycin 32.4 %, erythromycin 37.8%, detected (29). In MSSA strains, resistance to penicillin 65.3%, gentamicin and ciprofloxacin 21.7%, erythromycin 19.8%, levofloxacin and clindamycin 11.8% was detected. Our research found that resistance to penicillin and clindamycin was higher 16.7% and 91.9%, respectively (29).

Our research had some limitations. This is a single center, retrospective study. Some data were missing in medical charts. Bacterial strain virulence factors were not addressed. Since, in addition to antimicrobial resistance, virulence factors affect the clinical outcome of *S. aureus* infections.

CONCLUSION

Staphylococcal infections are encountered with increasing frequency in the community and hospitals, it is one of the infections that are important in terms of mortality and morbidity. *S. aureus* infections are difficult to treat due to antibiotic resistance and a lack of vaccines. The prevalence of methicillin resistance causes significant treatment challenges. it is important to know the regional antibiotic resistance in empirical antibiotic selection. For one to effectively control *S. aureus* infections, it is essential to use preventive control methods in the community and in hospitals.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocols were approved by Selcuk University Faculty of Medicine ethics committee (approval number: 2023/200).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Outbreaks of community-associated methicillin-resistant *Staphylococcus aureus* skin infection-Los Angeles County, California, 2002-2003. MMWR Morb Mortal Wkly Rep. 2003;52(5):88.
2. Boucher HW, Corey GR. Epidemiology of methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis. 2008;46 Suppl 5: S344-9.
3. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603-61.
4. DeLeo FR, Diep BA, Otto M. Host defense and pathogenesis in *Staphylococcus aureus* infections. Infect Dis Clin North Am. 2009;23(1):17-34.
5. Foster TJ. Immune evasion by staphylococci. Nat Rev Microbiol. 2005;3(12):948-58.
6. Shallcross LJ, Fragaszy E, Johnson AM, Hayward AC. The role of the Panton Valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2013;13(1):43-54.

7. Rasigade JP, Vandenesch F. *Staphylococcus aureus*: a pathogen with still unresolved issues. Infect Genet Evol. 2014; 21:510-4.
8. 8.Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA 2007; 298:1763.
9. Charlebois, E.D., Perdreau-Remington, F., Kreiswirth, B., et al. Origins of community strains of methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis. 2004;39(1):47- 54.
10. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clinical microbiology reviews. 2010;23(3):616-87. 57.
11. DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated methicillin resistant *Staphylococcus aureus*. The Lancet. 2010;375(9725):1557-68.
12. Miller LG, Perdreau-Remington F, Bayer AS, 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.
13. 13.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(5):573-578.
14. 14.Al Kindi A, Alkahtani AM, Nalubega M, et al. *Staphylococcus aureus* Internalized by Skin Keratinocytes Evade Antibiotic Killing. Front Microbiol. 2019; 10:2242.
15. Gottlieb M, DeMott JM, Hallock M, Peksa GD. Systemic Antibiotics for the Treatment of Skin and Soft Tissue Abscesses: A Systematic Review and Meta-Analysis. Ann Emerg Med 2019; 73:8.
16. Howard-Jones AR, Al Abdali K, Britton PN. Acute bacterial lymphadenitis in children: a retrospective, cross-sectional study. Eur J Pediatr. 2023;182(5):2325-33.
17. Wen Y, Wang C, Jia H, Liu T, Yu J, Zhang M. Comparison of diagnosis and treatment of MSSA and MRSA osteomyelitis in children: a case-control study of 64 patients. J Orthop Surg Res. 2023;18(1):197.
18. Messina AF, Namtu K, Guild M, Dumois JA, Berman DM. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. Pediatr Infect Dis J. 2011;30(12):1019-21.
19. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin resistant *Staphylococcus aureus*. J Pediatr Orthop 2006; 26:703.
20. Cea-Pereiro JC, Garcia-Meijide J, Mera-Varela A, Gomez-Reino JJ. A comparison between septic bursitis caused by *Staphylococcus aureus* and those caused by other organisms. Clin Rheumatol. 2001;20(1):10-14.
21. Aguilera-Alonso D, Kirchschläger Nieto S, Ara Montojo MF, et al. *Staphylococcus aureus* Community-acquired Pneumonia in Children After 13-Valent Pneumococcal Vaccination (2008-2018): Epidemiology, Clinical Characteristics and Outcomes. Pediatr Infect Dis J. 2022;41(5): e235-e242.
22. American Academy of Pediatrics. *Staphylococcus aureus*. In: Red Book: 2021-2024 Report of the Committee on Infectious Diseases, 32 ed, Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH (Eds), American Academy of Pediatrics, Itasca, IL 2021. p.678.
23. Suryati BA, Watson M. *Staphylococcus aureus* bacteraemia in children: a 5-year retrospective review. J Paediatr Child Health 2002; 38:290.
24. McNeil JC, Ligon JA, Hulten KG, et al. *Staphylococcus aureus* Infections in Children With Congenital Heart Disease. J Pediatric Infect Dis Soc 2013; 2:337.
25. Vallejo JG, Cain AN, Mason EO, Kaplan SL, Hultén KG. *Staphylococcus aureus* Central Nervous System Infections in Children. Pediatr Infect Dis J. 2017;36(10):947-951.
26. Ligon J, Kaplan SL, Hulten KG, et al. *Staphylococcus aureus* bacteremia without a localizing source in pediatric patients. Pediatr Infect Dis J 2014; 33: e132. 14.
27. Hamdy RF, Dona D, Jacobs MB, Gerber JS. Risk Factors for Complications in Children with *Staphylococcus aureus* Bacteremia. J Pediatr 2019; 208:214.
28. Paintsil E. Pediatric community-acquired methicillin-resistant *Staphylococcus aureus* infection and colonization: trends and management. Curr Opin Pediatr 2007; 19:75.
29. Şanlı K. Susceptibility Patterns of Community-acquired and Hospital-acquired *Staphylococcus aureus* Strains Against Various Antimicrobials. İKSSTD 2020;12(2):188-93